Coversheet

Informed Consent Form

Official Study Title:	PHASE I STUDY OF THE ADMINISTRATION OF PERIPHERAL ACTIVATED T-CELLS AND EBV SPECIFIC CTLS EXPRESSING CD19 CHIMERIC RECEPTORS FOR ADVANCED B-CELL NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA
NCT number	**NCT** 00709033
Document Date	**05/15/2013**

H-22899- ATECRAB -- PHASE I STUDY OF THE ADMINISTRATION OF PERIPHERAL ACTIVATED T-CELLS AND EBV SPECIFIC CTLS EXPRESSING CD19 CHIMERIC RECEPTORS FOR ADVANCED B-CELL NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

Background

In this consent form, "you" signifies you or your child.

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 lymph gland cancer called non-Hodgkin Lymphoma or chronic Lymphocytic Leukemia (throughout the rest of this consent these 2 diseases will be referred to as "lymphoma" or "CLL"). Your lymphoma or CLL has come back or has not gone away after treatment (including the best treatment we know for these cancers). Because there is no standard treatment for your cancer at this time or because the currently used treatments do not work fully in all cases, 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. 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 disease: 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 blood cells 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-CD19. This antibody sticks to lymphoma cells because of a substance on the outside of these cells called CD19. CD19 antibodies have been used to treat people with lymphoma and CLL. For this study, the anti-CD19 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 receptor. These chimeric receptor-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.

We found that T cells work better if we also attach a protein called CD28 to the T cells. This protein makes the T cells more active and survive longer. By joining the anti-CD19 antibody to the T cells and adding the CD28, we expect to be able to make cells that will last for a longer time in the body and recognize and kill the lymphoma cells.

We also found that T cells that are also trained to recognize the virus that causes infectious mononucleosis (called Epstein Barr Virus or EBV) can stay in the blood stream for many years. By joining the anti-CD19 antibody to the cytotoxic T lymphocytes (CTLs) that recognize EBV, we believe that we will also be able to make a cell that can last a long time in the body and recognize and kill lymphoma cells.

In this study we are going to see which of these methods of prolonging T cell activity is better. Half of your cells will have the CD19 chimeric receptor with CD28 put on them. The other half will be selected and expanded based on their ability to recognize EBV and will have the CD19 chimeric receptor without CD28 put on them. Both cell populations will be reinfused in your body and, by analyzing your blood periodically, we will be able to see if there is a difference in how long they last. These CD19-CD28 chimeric receptor T cells and CD19 chimeric-EBV specific T cells are investigational products not approved by the Food and Drug Administration.

This research study is sponsored by Baylor College of Medicine.This research study is funded by the NIH and NCI

Purpose
The purpose of this study is to find the biggest dose of chimeric T cells that is safe to administer, to see how long each of the T cell populations (CD19-CD28 and CD19-EBV-specific) last, to assess what the side effects are, and to evaluate whether this therapy might help people with lymphoma or CLL.

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

Approximately 18 subjects may be treated on this study.

Earlier, you or your donor gave us blood to make CD19-CD28 chimeric receptor T cells and CD19 chimeric-EBV specific T cells in the laboratory. These cells were grown and frozen for you. To get the CD19 antibody (and the CD28) to attach to the surface of the T cell, we inserted the antibody gene into the T cell. 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. The two viruses (CD19 only and CD19 with CD28) can be told apart by a special laboratory test. Because you will have received cells with a new gene in them you will be followed for a total of 15 years to see if there are any long term side effects of gene transfer. In the event of death, we will request permission to perform an autopsy to learn more about the effects of this intervention on your disease.

When you enroll on this study, you will be assigned a dose of CD19-CD28 chimeric receptor-T cells and CD19 chimeric receptor-EBV specific T cells. Several studies suggest that the infused T cells need room to be able to proliferate and accomplish their functions and that this may not happen if there are too many other T cells in circulation. Because of that, if your level of circulating T cells is relatively high, you will receive one treatment of cyclophosphamide. This drug will decrease the numbers of your own T cells before we infuse the CD19 chimeric receptor T cells. Although we do not expect any effect on your tumor with the dose that you will receive, this drug is part of many

regimens that are used to treat lymphoma or CLL. If you are already receiving chemotherapy, this may not be needed. We would prefer that you not receive other chemotherapy until 6 weeks after your cell infusion but you can do so if your doctor thinks it is medically necessary.

You will be given an injection of cells into the vein through an IV line at the assigned dose. Before you receive the injection, you may be given a dose of Benadryl (Diphenhydramine) and Tylenol (Acetaminophen). The injection will take about 20 minutes. We will follow you in the clinic after the injection for up to 3 hours. If after a 4-6 week evaluation period after your infusion, you seem to be experiencing a benefit (confirmed by radiological studies, physical exam and/or symptoms), you may be able to receive up to three additional doses of the T cells if you wish. These additional infusions would be at least 4-6 weeks apart and at the same dose level you received the first time or a lower dose. The treatment will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or The Methodist Hospital.

Medical tests before treatment—
Before being treated, you will receive a series of standard medical tests:
Physical exam
Blood tests to measure blood cells, kidney and liver function
Measurements of your tumor by scans and/or bone marrow studies

Medical tests during and after treatment—
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 scans and/or bone marrow studies 6 weeks after the infusion

To learn more about the way the CD19-CD28 chimeric receptor T cells and CD19 chimeric receptor-EBV specific T cells are working and how long they last in the body, extra blood will be drawn. The total amount on any day is about 10 teaspoons (or less than half a teaspoon per pound of weight for children). This volume is considered safe, but may be decreased if you are anemic.

This blood may be drawn from a central line if you have one. On the day you receive the cells, blood will be taken before the cells are given and several hours afterwards. Other blood will be drawn one week after the infusion, 2 weeks, 4 weeks and 6 weeks after the infusion, every 3 months for 1 year, every 6 months for 4 years, then yearly for a total of 15 years. The total blood drawn during your participation in this study will not exceed 280 teaspoons.

If you have a biopsy of your tumor or bone marrow studies in the future after completing this study, we may ask to have a piece of tumor or bone marrow to look for CD19-CD28 chimeric receptor T cells and CD19 chimeric receptor-EBV specific T cells.

These specimens and information about your circumstances may be used in other research being conducted in immune therapy. Although there will be a record identifying under what circumstances

these specimens were obtained, under all circumstances your identity will be kept confidential. There is a small risk for the loss of confidentiality. However, study personnel will make every effort to minimize this risk.

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 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.

You can see and get a copy of your research related health information. Your research doctor may be able to provide you with part of your information while the study is in progress and the rest of your information at the end of the study.

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. Many side effects will go away shortly after treatment is stopped, but in some cases, side effects may be long lasting or permanent. Some side effects may be life threatening.

Patients are watched carefully and treatment is stopped if serious side effects develop.

Side Effects of the CD19 Antibody
There are several antibodies that are similar to CD19 and 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. One other side effect is that the antibody may react with normal cells, such as normal immune system cells called B cells that have CD19 on their surface, as well as the cancer cells. If the CD19-CD28 chimeric receptor T cells and CD19 chimeric receptor-EBV specific T cells worked very well they could kill your normal B cells as well as the lymphoma and CLL cells. In that case you would not have B cells to make antibodies, which help you fight infection and may have a higher risk of some types of infection. We will check your antibody levels and, if these are low, we will replace with a product called IVIG, which contains antibodies. You would need to get IVIG every 6-8 weeks as long as you have low levels of antibodies and recurrent infections.

Side Effects of the T cells
Similar types of T cells have been given to patients with cancers and infections. Usually the patients 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 patients with large tumors, the cells have caused inflammation leading to 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.

Another possible side effect from the EBV specific T cells is that some of the EBV-infected B cells or the B95 EBV virus will be injected with the T cells into your body. We think this is unlikely because the B cells are treated with radiation to stop them from growing and an antiviral drug that prevents release of EBV is added to the cultures.

If you are receiving donor T cells after a stem cell transplant from a related or unrelated donor there is also the possibility that these donor T cells might try to attack other parts of your body and cause graft versus host disease (GVHD). This is exceedingly rare when the donor is an identical twin. GVHD occurs when cells from your bone marrow donor (graft) recognizes that your body tissues (host) are different from those of the donor. When this happens, cells in the graft may attack the host's skin, liver and intestines. If you have GVHD after the transplant you may not be able to get the cells. If you have GVHD after the T cells have been given, we will treat you appropriately.

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 for 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.

More recently in experimental studies, 5 cases of cancer have been reported in children who received a retroviral vector with a gene to treat X-linked Severe Combined Immunodeficiency (SCID) (like the "boy in the bubble"). While most of the children who participated in the SCID studies appear to have been cured of their disease, one child developed leukemia (a form of cancer of the blood) approximately 30 months after receiving the gene therapy treatment; this child appeared to be responding to treatment for leukemia, but later died. A second child developed leukemia 34 months after receiving the gene therapy treatment. A group of experts in the field of gene therapy looked at the test results and concluded that gene therapy caused the leukemia in the first two children. There are now a total of five children that are known to have developed leukemia in these trials.

The risk of this problem occurring in this study should be very low because many genes need to be

changed for a cell to turn cancerous. Moreover, the gene we plan to use is different from the gene used in the SCID study. Furthermore, over the past 12 years we and others have treated several hundred patients with genes to mark cells (the integrated gene marks the cells and allow the cells to be identified from unmarked cells). None have developed any signs of cancer related to the treatment. But even though gene marking has not caused any patients any problems to date we do not know for certain what the risk is that this treatment will contribute to getting another cancer. For this reason, we will need to follow you for 15 years.

Side Effects of Cyclophosphamide (Cytoxan) - only for patients who receive this as discussed in Procedures:
Lowered white blood cell count (cells that fight infection) that may lead to fever and infection needing hospitalization and/or treatment with IV antibiotics, lowered platelet count (cells that help the blood to clot) which may lead to bruising or bleeding, lowered red blood cell count (cells that carry oxygen)(anemia) which could cause tiredness or shortness of breath. You may need a red blood cell and/or platelet transfusion if your blood counts are too low. You could also experience one or more of the following: fatigue, nausea, vomiting, hair loss, loss of appetite, a metal like taste in the mouth, irritation of the bladder that could cause bleeding and blood in the urine, and gonadal dysfunction (trouble with reproductive organs that produces mature sex cells -- ova or spermatozoa) or sterility.

Risks to Unborn Children from Cyclophosphamide - only for patients who receive this as discussed in Procedures:
Toxicities or defects in a developing fetus have been noted in humans receiving cyclophosphamide (alone or in combination with other anticancer agents). These toxicities may include chromosome abnormalities, multiple anomalies, and low birth weight. Cyclophosphamide is also excreted into breast milk and may cause potential adverse effects, to infants who breast-feed, related to immune suppression, growth problems, and carcinogenesis.

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.

Benadryl: Drowsiness, dizziness, headache, irritability, stomach upset, vision changes (e.g., blurred vision), decreased coordination, or dry mouth/nose/throat may occur

There are no known risks of CD28.

Because of potential or unknown effects of the study on a fetus, if you are a woman of childbearing potential, you must have a negative serum pregnancy test prior to entry into this study.

Since this is a research study, there may be risks that are currently unknown. 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.

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. 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 therapy. You may also choose to receive no further treatment 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 CD19-CD28 chimeric receptor T cells and CD19 chimeric receptor-EBV specific 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. You or your insurance company may be charged for some reserach related costs including the infusion of the product. You or your insurance company are responsible for medical services that are part of the standard of care for your cancer.

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.

Women of Childbearing Potential

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 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.

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.

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.

Your Health Information

We may be collecting health information that could be linked to you (protected health information). This protected health information might have your name, address, social security number or something else that identifies you attached to it. Federal law wants us to get your permission to use your protected health information for this study. Your signature on this form means that you give us permission to use your protected health information for this research study.

If you decide to take part in the study, your protected health information will not be given out except as allowed by law or as described in this form. Everyone working with your protected health information will work to keep this information private. The results of the data from the study may be published. However, you will not be identified by name.

People who give medical care and ensure quality from the institutions where the research is being done, the sponsor(s) listed in the sections above, representatives of the sponsor, agents of the Food and Drug Administration, and regulatory agencies such as the U.S. Department of Health and Human Services will be allowed to look at sections of your medical and research records related to this study. Because of the need for the investigator and study staff to release information to these parties, complete privacy cannot be guaranteed.

The people listed above will be able to access your information for as long as they need to, even after the study is completed.

If you decide to stop taking part in the study or if you are removed from the study, you may decide that you no longer allow protected health information that identifies you to be used in this research study. Contact the study staff to tell them of this decision, and they will give you an address so that you can inform the investigator in writing. The investigator will honor your decision unless not being able to use your identifiable health information would affect the safety or quality of the research study.

The investigator, CARLOS ALMEIDA RAMOS, 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: CARLOS ALMEIDA RAMOS at 713-441-6256 during the day and 832-822-4242 (TCH) or 713-441-1450 (TMH) 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. Coded information may be provided to the NIH/NCI such as Patient ID, Patient Zip code, Patient country code and Patient Birth date (month/year). However, in the event of an audit NIH/NCI might have access to more information that is part of your research record.

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.

H-22899- ATECRAB -- PHASE I STUDY OF THE ADMINISTRATION OF PERIPHERAL ACTIVATED T-CELLS AND EBV SPECIFIC CTLS EXPRESSING CD19 CHIMERIC RECEPTORS FOR ADVANCED B-CELL NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

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 _____

H-22899- ATECRAB -- PHASE I STUDY OF THE ADMINISTRATION OF PERIPHERAL ACTIVATED T-CELLS AND EBV SPECIFIC CTLS EXPRESSING CD19 CHIMERIC RECEPTORS FOR ADVANCED B-CELL NON-HODGKIN'S LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA

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
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date