UNIVERSITY OF CALIFORNIA, LOS ANGELES

CONSENT TO PARTICIPATE IN RESEARCH

TITLE: **Adoptive Transfer of MART-1 F5 TCR Engineered Peripheral Blood Mononuclear Cells (PBMC) after a Nonmyeloablative Conditioning Regimen, with Administration of MART-1$_{26:35}$-Pulsed Dendritic Cells and Interleukin-2, in Patients with Advanced Melanoma**

Lay Title: A Phase 2 Study of Gene Modified Immune Cells in Patients with Advanced Melanoma

You are being invited to participate in a research study conducted by Antoni Ribas, M.D., Bartosz Chmielowski, M.D., Ph.D., Arun Singh, M.D., Siwen Hu-Lieskovan, M.D., Ph.D. and Deborah Wong, M.D., Ph.D. and John A. Glaspy, M.D., M.P.H. from Division of Hematology/Oncology; James S. Economou, M.D., Ph.D. from the Division of Surgical Oncology; Johannes Czernin, M.D., from the Division of Nuclear Medicine; Akira Ishiyama, M.D. from the Division of Head and Neck Surgery, and Tara McCannel, M.D., Ph.D. from the Jules Stein Eye Institute at the University of California, Los Angeles (UCLA). The study is sponsored in part by the National Institutes of Health (NIH), the Melanoma Research Foundation, the Melanoma Research Alliance, the Caltech-UCLA Joint Center for Translational Medicine and the California Institute for Regenerative Medicine (CIRM), and the Eli & Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. You are being asked to take part in this research study because you have melanoma that has spread to other areas of your body. This research study uses a new approach in treatment of cancer, i.e. gene-modified cells will be given intravenously to attempt to fight melanoma. The risks of participation are currently not entirely defined.

Your participation in this study is entirely voluntary. Between 8 and 22 patients at UCLA will be enrolled in this research study. If you agree, you will be asked to participate in this protocol for at least 3 months, and the study investigators will follow you indefinitely. You should read all the information given to you in this consent form and ask questions about anything that you do not understand before you decide to participate or not. A copy will be given to you to take home.

Disclosure Statement:

Your health care provider may be an investigator of this research protocol. As an investigator, he or she is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor(s) not associated with this project. You are not under any obligation to participate in any research project offered by your physician.

- **PURPOSE**

The purpose of this phase 2 study is to find the best way to give this new experimental regimen and determine if it can treat metastatic melanoma in humans. In this phase 2 study, the experimental products are given initially to a group of 8 people. If safe and found to have a significant antitumor activity, it will be given to up to 14 other people, for a total of 22 people in this study. Physicians watch

subjects carefully for any harmful side effects. Although the experimental regimen has been well tested in laboratory and animal studies, and a similar regimen has been given to a group of patients at the National Cancer Institute in Bethesda, MD, the side effects in people cannot be completely known ahead of time. This protocol is offered only to people whose condition cannot be helped by other known treatments.

The study investigators' main aim is to obtain sufficient information about the effects of gene-modified cells in humans. The gene modification of cells is an attempt to direct your own immune cells to kill melanoma cancer cells. The gene-modified cells studied in this experimental protocol are your own white blood cells from your blood that will be modified in the laboratory using genetic techniques to express a specific receptor against melanoma cells.

Gene modification of cells involves the transfer of foreign genetic material (DNA) into a cell, in this case your immune system cells, using a form of a crippled virus that has been modified to express the melanoma specific receptor called MART-1 T cell receptor (or TCR).

Study Drugs. This clinical trial has two main study agents:

- The first study agent is called **gene modified MART-1 TCR T cells**. T cells are a special type of white blood cells that have the ability to kill cancer cells. They are also called cytotoxic T lymphocytes (or CTL), which means that they can kill other cells. The CTLs will be obtained from your body and taken to the laboratory to grow them and modify their genes. The CTL cells will be gene modified with a virus vector similar to the HIV virus called a retrovirus vector. This retrovirus is called a vector because it has been extensively modified to make sure that it cannot make copies of itself or induce AIDS in patients. The retrovirus vector will allow expression of a protein called the T cell receptor (or TCR). This TCR is specific for a marker on the surface of melanoma cells called the MART-1 tumor antigen. The investigators expect that the insertion of the TCR specific for the MART-1 melanoma marker will allow the CTLs to be redirected to recognize and attack melanoma cancer cells.

- The second study agent is called a **dendritic cell vaccine loaded with the MART-1** melanoma protein. Dendritic cells are a type of blood cells that specialize in stimulating the immune system, and will be grown in the laboratory from your own blood cells. The dendritic cells do not directly fight cancer cells. Instead, they teach other cells in the body to look for cancer cells with the MART-1 protein and destroy them. Therefore they function as an "on switch" for the immune system and it is called a tumor antigen. MART-1 is a protein produced by your cancer, which may be recognized by cells of the immune system. The goal of giving the dendritic cell vaccines to you will be to further help the ability of the gene modified MART-1 TCR CTLs to attack melanoma lesions in your body.

Study Design. The study participants in this phase 2 clinical trial will be divided into two groups, an initial group of 8 patients and a second group of 14 patients, to allow the study investigators to assess the safety and antitumor activity of this combination. If the first group of 8 patients does not show favorable outcomes in terms of safety and antitumor activity, the second group of patients will not be enrolled. If there is a favorable outcome in the first group of patients, the study will proceed to enroll a total of 22 patients with melanoma. No random assignment to a particular group is used in this trial;

both groups will receive the same treatment. Therefore, all subjects in this study will receive both the same dose of gene modified immune system cells and the dendritic cell vaccines.

- **OVERVIEW OF THE STUDY PROCEDURES**

The study procedures will start with the collection of white blood cells through apheresis (a procedure in which blood is drawn from a patient and separated into its components, some of which are retained, such as white blood cells, and the remainder returned by transfusion to the patient.). You will be asked to undergo two aphereses, one to make the gene-modified MART-1 TCR CTLs and the dendritic cell vaccines, and a second one after you have received the gene modified cells to later study them in your blood.

On the day of the first apheresis, you will be admitted to the hospital and will receive chemotherapy over the next five days that decreases the risk of rejection of the transferred cells by your immune system and facilitates their expansion and attack of the melanoma lesions. During this time, the gene-modified MART-1 TCR CTLs and the dendritic cells will be manufactured in the laboratory from the apheresis product and will be extensively tested to assure that they express the appropriate TCR and that they do not contain any contaminating bacteria or virus.

Then the gene-modified MART-1 TCR CTLs will be given back to you through a vein in your arm. It will be followed by vaccination with the dendritic cells under the skin. During the next 7days you will also receive interleukin 2 (IL-2), which is a standard treatment for patients with metastatic melanoma. During the next 2 to 3 weeks you will stay in the hospital until the study investigators determine that you have fully recovered from all of the procedures and it is safe for you to go home. Chemotherapy frequently causes a decrease in the platelet or red blood cells, and therefore you may require platelet and/or red blood cells transfusions.

In the event the treating physicians determine that you are not clinically fit to receive the gene-modified MART-1 TCR CTL infusion within 24 hours of the scheduled day, the cells will be cryopreserved on the harvest day for later use. It is possible that the cells are manufactured but they do not meet the pre-specified criteria for safe re-administration to you. In that case the study investigators will not be able to administer the cells to you despite you having received the conditioning chemotherapy to be prepared to receive the MART-1 TCR CTL infusion.

During this clinical trial we will perform imaging studies, called PET (or Positron-Emission-Tomography) scans. They will allow the study investigators to analyze if the gene-modified MART-1 TCR CTLs travel to the tumor. Additionally, several biopsies of your tumor lesions will be performed.

- **STUDY PROCEDURES**

1. Screening Tests and Procedures. If you volunteer and are eligible to participate in this study, you will need to be seen by one of the participating study investigators. The study investigators will explain the study to you and if you agree to participate, you will need to give your written consent. Before you are enrolled in this study, you will be asked questions and tests will be done to see if you are eligible to enroll. This will include:

- Medical history.
- Physical exam, including ECOG performance status (checks how you are functioning in your day to day living), weight, height, and vital signs (temperature, blood pressure while sitting, heart rate).
- CT, PET or MRI scans of your brain, chest, abdomen, and pelvis. These tests will either be reviewed if they have been performed recently, or will need to be repeated if older than one month.
- If you have visible melanoma lesions on your skin, photographs may be taken.
- Discussion about birth control. If you or your partner are able to have children and are sexually active, you will be asked to follow birth control measures during the participation in this study.
- MART-1 protein testing. You will have your tissue sample tested through immunohistochemistry (IHC) or genetic analysis of melanoma (this can be done in archived tissue, in a new tumor biopsy or may already be available from prior analysis) to know whether you are MART-1 antigen positive to be eligible for the study. If we are able to obtain a tissue sample from a pre-existing biopsy that was performed within 60 days of your screening visit, then an additional biopsy may not be required. In the event that a screening biopsy is required to be performed, the study will cover this cost.
- Blood tests:
    - The blood tests will require about 6 teaspoonfuls drawn from a vein in your arm. The blood tests will include a complete blood count, which checks for anemia and bone marrow function; clotting tests of the blood; and blood chemistries, which check for liver, kidney, and thyroid function.
    - You will be checked for antibodies to viruses including the human immunodeficiency virus (HIV), hepatitis B and C viruses, cytomegalovirus, and Epstein-Barr virus. You will be asked to sign a separate consent for the HIV testing. The reason for this testing is that a positive infection with any of these viruses would make it too risky to give you the chemotherapy included in this protocol, and therefore it would not be safe for you to participate. The California State Health Department requests that positive results of these tests be reported to them. Therefore, in the case that your tests are positive the study investigators will have to report them to the State Health Department, and this reporting will include your personal identifying information. In the case of positive tests, you will be referred for counseling to the appropriate infectious disease specialist designated by your insurance.
    - We will study if you have any evidence of your immune system being activated against your normal organs (that is, to rule out an “autoimmune condition”). The reason for this testing is that a positive test would make it too risky for you to receive the immune activating treatments in this protocol, and therefore it would not be safe for you to participate.
    - Unless tested on you before, blood will be sent for determination of your type of immune system (HLA testing). The reason for this testing is that this protocol can only have a chance of working if you have a particular HLA type called HLA-A2.1 (or HLA-A*0201).

All of these tests need to be done within 60 days prior to receiving the study drug. These tests will help the study investigators to decide if you will be eligible and if it is safe for you to receive the experimental drugs.

If you decide that you want to participate in the study and the study investigators determine that you are eligible, you will then be enrolled. It is possible that you may finish all of the screening tests but not be eligible to participate in this study.

2. Procedures in Preparation for Your Participation in the Study. You will then be asked to undergo several tests before you have the first infusion of the study drugs.

Tumor Biopsies. This protocol attempts to study the safety of administering the study drugs, and the ability of the gene modified MART-1 TCR CTLs to find melanoma lesions in humans, which requires the collection of samples from your tumor whenever feasible. Therefore, a surgeon or dermatologist will see you in the office, while in the hospital, or you will be asked to go to the outpatient surgery center (usually on the 1st or 6th floor of the 200 UCLA Medical Plaza). A biopsy is the removal of solid tissue by cutting. This involves the following steps: First cleaning the skin around the sites of the biopsy, then injecting numbing medicine (a local anesthetic) applied with a needle and a syringe. Following that, the surgeon will cut the skin, and take out a piece of your tumor. The surgeon will then stitch back the skin over this area. The stitches will be taken out one week later. Only tumor lesions in the skin or that can be felt under the skin will be eligible for biopsy. The biopsy of your tumor will help the study investigators determine how the investigational agents find your tumor deposits. Another way to obtain a biopsy would be by image-guided biopsy, most frequently locating a lesion by ultrasound or CT scan imaging and placing a thick needle into the lesion to obtain a piece of tissue from it. The biopsies performed during the study will be billed to you or your insurance. In the event that a screening biopsy is required to be performed, the study will cover this cost.

Maintenance of the Tumor Biopsy and Leukapheresis Tissue Banks. The samples will be processed and maintained in a dedicated laboratory space at the UCLA Factor building. The laboratory has restricted access. Only investigators specifically trained are allowed entry to that area. Your samples will be stored frozen in a freezer equipped with a centralized monitoring system that immediately notifies the investigators if the temperature changes to above or below the optimal range of temperatures. Your samples will be coded, and the samples will not contain personal information that allows directly identifying you. The code linking your sample with your personal information will be maintained in a secured cabinet under the care of the Principal Investigator of this study. The samples will be maintained in this tissue bank as long as the study investigators require tumor samples or blood samples for the study of immune responses to cancer and understand the mechanisms of action of the study drugs.

Baseline PET/CT Scans. The study investigators want to determine if PET/CT scans using markers of tumor sugar consumption and tumor cell aggressiveness can help determine whether your immune system is activated after the administration of the study drug. The PET probe FDG measures tumor sugar use, and is labeled with a small amount of radioactive fluorine (^{18}F radioactive compound), making them visible by PET scanning.

PET/CT combines a PET scanner and a CT scanner into one device. The PET/CT device is in clinical use in more than 1000 hospitals worldwide. If you have undergone a recent (less than 30 days) CT scan or complete PET/CT scan, then the research PET/CT scans will be done with a limited set of CT images to avoid excessive exposure to irradiation. Otherwise, the research PET/CT scans will include a complete CT to allow the study investigators to adequately find which organs are involved with melanoma in your body.

PET is an established scanning technique that utilizes small amounts of radioactivity that are attached to a sugar. This sugar is called fluorodeoxyglucose (shortened as FDG). FDG serves as a "contrast agent" for PET and is injected in one of your hand or arm veins. The PET scan helps identify the sugar consumption of cancer tissue as well as activated immune cells, as compared to that of other normal tissues.

Eye Exam. A thorough eye exam will be conducted by an ophthalmologist at the UCLA Jules Stein Eye Institute. The purpose of this eye exam is to detect if the immune system activation by the study drugs has any adverse effects on the eyes. This eye exam will include dilatation of your pupils, taking pictures of your eye, and may include injecting a dye through a vein in your arm.

Ear Exam. A thorough ear exam will be conducted by an ear-nose-throat (ENT) specialist at the UCLA outpatient clinics. The purpose of this ear exam is to detect if the immune system activation by the study drugs has any adverse effects on the ears. This will include a history of ear-related problems and an examination of the ear function.

Heart Test. Prior to enrolling in this study, you will undergo an electrocardiogram (ECG). This will be done to ensure that there are no conduction abnormalities in your heart and that there are no signs of ischemic heart disease, which could put you at risk with the therapies employed in this study.

Cardiac Function Test. A baseline MUGA scan or echocardiogram will be performed prior to enrolling in the trial. An LVEF<45% or severe diastolic dysfunction will preclude patients from enrolling in the trial.

Pulmonary Function Test. The administration of IL-2 within this protocol may result in leakage of liquid into the lung resulting in breathing problems. In two patients these problems were severe enough to require intubation (putting a breathing tube down the patient's throat and hooking it into a breathing machine). Given this serious risk you will be asked to undergo breathing tests to analyze the function of your lungs. If these breathing tests are not within normal range then it will not be safe for you to participate in this protocol.

Pregnancy Test. If you or your partner can be or become pregnant, you should discuss this with the study coordinators. The gene transfer approach used in this protocol may put a fetus at risk. Therefore, if you are a female with potential to become pregnant, a pregnancy test will be performed within 2 weeks of being admitted for the administration of the gene modified study cells.

Need to Place a Temporary Catheter in Your Veins for the Hospital Admission. All patients need to have access of treatments delivered to big veins during the hospital admission. Some patients may already have a temporary or permanent catheter (a flexible tube) that allows nurses and study investigators to infuse treatments through a large vein, called Central Venous Catheter or CVC. Common examples of such catheters are tunneled catheters placed in a neck vein (Hickman type catheter) or a PICC (which stands for "peripherally inserted central catheter") that is placed in an arm vein. A catheter is placed in a large vein in your arm or neck area by an experienced physician. This can be done at the bedside or in a surgical room. It is anticipated that the most

common catheter placed will be a PICC catheter in an arm vein. This catheter may be placed before being admitted to the hospital or after being admitted.

If there are problems with the making of the gene modified MART-1 TCR CTLs, it is possible that you could undergo all of these procedures and the study investigators then tell you that you cannot receive the study drugs. This may happen if the gene modified MART-1 TCR CTLs do not meet the standards set up by the study investigators before they are given to you.

3. Hospital Stay for Leukapheresis and Study Drug Administrations. The following procedures will require that you be admitted to the UCLA hospital. The procedures are counted from the day when you will receive the gene modified MART-1 TCR CTLs, which is designed as day 0.

Day -6. Leukapheresis. The leukapheresis will be planned on the day of admission to the hospital and will be done early in the morning before you are admitted. This protocol attempts to generate two study agents that are made up of cells collected from your body. The study investigators determined that they would require more blood cells than can safely be obtained by a regular blood draw. Therefore, you will be asked to undergo a procedure called apheresis (in this case, a leukapheresis, since only white blood cells are collected) once or twice. The apheresis will be used to collect cells to make the MART-1 TCR CTL and the dendritic cell vaccines. During the apheresis procedure, white blood cells are collected using a medical device called a blood cell separator. Blood will be drawn from a needle in your arm, and attached to the blood tubing set in the blood cell separator. The blood is then mixed with a blood thinner called citrate, and it is drawn into the machine. The purpose of this is to keep your blood from making blood clumps (clots) during processing in the blood cell separator machine. The white blood cells are separated in a centrifuge and pumped into a collection bag. The total amount of white blood cells collected is about ½ – 1 cup. The remainder of your blood is returned to you through a needle placed in the other arm. The amount of blood outside your body at any one time is about 1-½ cups. Normal saline (salt water) will be used to fill the tubing, help return the red cells at the end of the procedure, and keep the needle or catheter from clotting. Additionally, a sample of the liquid part of the blood called plasma (10 teaspoonfuls) will also be drawn at the time of the leukapheresis procedure. This procedure usually takes 3-4 hours and will be done at the UCLA Hemapheresis Unit, on the 6th floor of the 200 Medical Plaza building.

Potential Need to Place a Temporary Catheter in Your Veins for the Leukapheresis Procedure. If the veins in your arm are too small or the blood flow is inadequate for the leukapheresis procedure, which is fairly common, a temporary catheter (a flexible tube) will be surgically placed in a large vein in your groin or neck area by an experienced physician. This can be done at the bedside or in a surgical room. If you need this procedure, you will be asked to sign a separate consent form for the procedure.

Laboratory Culture of Gene-Modified Immune System Cells. The CTLs are grown from your white blood cells obtained from the first apheresis procedure. Two days later the CTLs will be isolated and gene modified with the retrovirus vector expressing the melanoma-specific MART-1 TCR. These cells will be tested extensively to make sure that they are not contaminated with bacteria or other organisms, and that they express the appropriate TCR and function properly.

Laboratory Culture of Dendritic Cells. The dendritic cells will be grown in the laboratory from your white blood cells obtained from the leukapheresis procedure. It takes one week to grow them.

The MART-1 melanoma antigen will be added to these dendritic cells. You will receive three injections of dendritic cells expressing MART-1, one on the following day after the gene modified CTL infusion and then at two weeks interval. On each occasion, the dendritic cells expressing MART-1 will be injected into the skin close to where your lymph glands drain, usually in your lower belly.

Day -6. Admission to the Hospital. After the leukapheresis, you will be admitted to the Hematology/Oncology unit at the Ronald Regan UCLA Medical Center. This unit is located on the 6th floor of the hospital building. This is so that any complications that might occur will be detected and cared for. The following will occur:

- You will be asked about illnesses, injuries, side effects, and any medications you have taken or medical procedures that have been done to you since the prior visit.
- Physical exam, including ECOG performance status (checks how you are functioning in your day to day living), weight, height, and vital signs (temperature, blood pressure while sitting, heart rate).
- You will have a catheter placed in a vein through which you will receive liquids in preparation for the chemotherapy regimen.
- You will have blood drawn to check your health. Tests include complete blood counts, which check for anemia and bone marrow function; the ability of your blood to clot; blood chemistries, which check for liver and kidney. Most of these blood tests will be repeated daily or every other day while you are in the hospital.
- You will start to receive one or two drugs to prevent complications with infections, the antibiotic Bactrim to decrease the risk of a rare form of pneumonia called Pneumocistis carinii pneumonia (or PCP), and the drug ganciclovir to decrease the risk of activation of a virus called cytomegalovirus (or CMV). Gancyclovir will only be given to patients who have evidence of prior exposure to the CMV virus. Both of these drugs will be stopped before administering the gene-modified MART-1 TCR CTLs, since both drugs would interfere with their function in your body.

Day –5 to –4: Administration of High Dose Cyclophosphamide. You will receive two daily doses of the chemotherapy agent cyclophosphamide (also called Cytoxan) through a vein in your arm, together with medications to prevent nausea and vomiting. You will have frequent vital sign evaluations, daily blood tests taken from a vein in your arm, and daily analysis of your urine.

Day –4 to –1: Administration of High Dose Fludarabine. You will receive four daily doses of the chemotherapy agent fludarabine (also called Fludara) through a vein in your arm, together with medications to prevent nausea and vomiting. You will have frequent vital sign evaluations and daily blood tests taken from a vein in your arm.

After High Dose Chemotherapy Administration. You will require very close observation in the hospital for the 2 to 3 weeks after receiving the chemotherapy.

- Throughout the period after the chemotherapy and before you go home, you will be evaluated by your nurses and treating physicians frequently to detect any complication. During this time, you will have frequent evaluations of your vital signs, at least daily blood tests taken from a vein in your arm, and periodical urine analysis.

- You will receive a medication to treat low white blood cell counts called Neupogen or G-CSF. This medication is usually given as a daily injection under the skin, and its goal is to help your white blood cells recover faster after the chemotherapy.
- If you develop fevers during the period in the hospital, you may require receiving treatment with antibiotics or drugs that fight fungal infections.
- You may require receiving blood or platelet transfusions, since the chemotherapy given in this protocol is likely to lower your red cells and platelets (blood cells that help in clotting) in the blood.

Day 0: Administration of the Gene-Modified MART-1 TCR CTLs. The cells will be harvested fresh on the day of infusion and sealed in an infusion bag. After the clearance of the quality control tests, you will receive the gene-modified cells through a vein in your arm or a central venous catheter. While they are being given, you will have your vital signs checked constantly to make sure that you do not have a reaction to the cells.

Days 1-7: Administration of Interleukin-2 (IL-2). You will receive IL-2 as an injection under the skin (subcutaneous) twice a day for 7 days. Before each dose, a nurse will assess how you are tolerating the treatment; you will have vital signs checked continuously and blood tests drawn. This information will be evaluated by one of your treating physicians, who will make an assessment of the safety of giving the next dose of IL-2. Doses of IL-2 will be given or skipped based on how your body is tolerating them. You will be given medications to prevent nausea and vomiting, medications for chills and for fever, as required by you. You will likely receive antibiotics during this period, since fevers are frequent with IL-2 administration, and the study investigators cannot differentiate fevers caused by IL-2 from those caused by an infection.

Day 1, 14 and 30: Dendritic Cell Vaccine Administrations. On each one of these days you will receive an injection of the dendritic cells expressing MART-1 under the skin, close to a lymph node gland that is not known to be involved with melanoma (in most cases, these injections are given in the lower belly). The last dendritic cell administration may occur after you have been discharged from the hospital, depending on how rapidly your body recovers from the chemotherapy.

Day 14 to 30: Discharge Home. You will be discharged from the hospital when your white blood cells and platelets have recovered from the chemotherapy given to you before administering the gene-modified MART-1 TCR CTLs. This usually takes 3 to 4 weeks, and it varies depending on each patient. Therefore, the date of release from the hospital cannot be fully predicted before initiating the study.

4. Procedures after Receiving the Experimental Drugs.

Days 14, 30, 45, 60, 75 and 90: On each of these days (or a day close to this day), the study investigators will draw approximately 7 tablespoons (100 ml) of blood from one of your veins. This blood will be used to analyze how your immune system has been repopulated with the gene-modified MART-1 TCR CTLs.

Day 20-40. You will be scheduled to undergo procedures to determine the fate of the gene-modified MART-1 TCR CTLs after they were given to you. Each one of these procedures may be done at a

different site, and the study investigators or study coordinators will be able to direct you to where they are being scheduled. It will include the following:

- **Research PET/CT Scan.** A PET/CT scan will be done for research purposes between study days 20 and 40 (although it can also be performed two weeks or up to one month after this period of time).
- **Tumor Biopsy.** If feasible, a tumor lesion will be removed for research purposes following the same procedure as described in the Screening biopsy. This will help the study investigators determine if the gene-modified MART-1 TCR CTLs are able to find your melanoma lesions throughout your body.
- **Partial Leukapheresis.** A partial leukapheresis to collect white blood cells and plasma (3.5 tablespoons) will be performed that will take half as much time as the one described in the Screening procedures. The purpose of this leukapheresis is to collect blood cells for future research. It will take less time because the study investigator will plan to process half the amount of blood compared to the initial leukapheresis. This procedure will take approximately 2 hours and will be done at the hospital bed or at the UCLA Hemapheresis Unit, on the 6th floor of the 200 Medical Plaza building. This will help the study investigators determine if the gene-modified MART-1 TCR CTLs are able to expand in your blood.

Days 30, 45, 60 and 75. You will be asked to go to the UCLA oncology outpatient clinic, either in the 100 or 200 Medical Plaza for follow up study visits.

- You will be asked about illnesses, injuries, side effects, and any medications you have taken or medical procedures that have been done to you since the prior visit.
- Physical exam, including ECOG performance status (checks how you are functioning in your day to day living), weight, height, and vital signs (temperature, blood pressure while sitting, heart rate).
- About 4 teaspoonfuls of blood will be drawn to check your health.

Between Days 75 and 90. You will be asked to undergo the following:

- CT, PET and MRI scans of your brain, chest, abdomen, and pelvis to determine the potential effects of the study drugs on your melanoma tumors.
- If you have visible melanoma lesions on your skin, photographs will be taken.
- Eye Exam. This eye exam will be conducted by an ophthalmologist at the UCLA Jules Stein Eye Institute, and may include dilatation of your pupils, taking pictures of your eye, injecting a dye through your vein and placing a contact lens in your eye.
- Ear Exam. This exam will be conducted by an ear-nose-throat (ENT) specialist at the UCLA outpatient clinics. It will include a history of ear-related problems and an examination of the ear function.

Day 90. This will be the last visit during the most intensive part of the study protocol. The main goal of this visit is to determine if the study drugs had an effect against your melanoma, and if you have any side effect from your participation in the study.

- You will be asked about illnesses, injuries, side effects, and any medications you have taken or medical procedures that have been done to you since the prior visit.

- Physical exam, including ECOG performance status (checks how you are functioning in your day to day living), weight, height, and vital signs (temperature, blood pressure while sitting, heart rate).
- About 5 teaspoonfuls of blood will be drawn to check your health.
- The study investigators will go over the results of the tests to evaluate your melanoma, including CT, PET or MRI scan of your chest, abdomen and pelvis.
- If you have visible skin tumors, these tumors will be photographed and may be biopsied.

5. Follow-Up (or Post Study) Procedures. The federal agencies require that all patients that have received experimental gene transfer products be followed for up to 15 years. Therefore, the study investigators will want to see or contact you at least every 3 months during the first 2 years, and every 6 months during the next 3 years, and then at least once a year up to 15 years thereafter. You will be asked about your melanoma and whether you have received new therapy for melanoma. At those time points, blood will be taken from your vein to study how they persist and the potential long term effects of the gene modified cells given to you. If you die during this time, your family members or physician will be asked about the date and cause of death. If your melanoma has not progressed, your tumors will continue to be evaluated until they progress. If you have treatment-related health problems, the study investigators will continue to follow them to make sure that you have recovered appropriately. Additional procedures and laboratory tests may be needed.

- **AUTOPSY REQUEST**

If you die, no matter what the cause is, the study investigators will ask for permission to perform an autopsy. The reason is to perform a thorough evaluation of all your organs due to your participation in this experimental gene transfer protocol. You should discuss this option with your family members and discuss with the study investigators at any time if you have questions or concerns about the future request for an autopsy procedure.

Chart of Study Procedures

The chart below shows what will happen to you as explained above. The left-hand column shows the day of the study and the right-hand column tells you what will happen on that day. Day 0 is the day that the gene-modified cells are infused.

Day	What will happen
Day -6 (6 days before infusion of cells)	• Get routine blood tests • Leukapheresis • Get admitted to the hospital • Physcial exam • Bacterim administration • Gancyclovir administration (if prior exposure to CMV)
Days -5 to -4	• Get routine blood tests • Cyclophosphamide treatment (chemotherapy administration)
Days -4 to -1	• Get routine blood tests • Fludarabine treatment (chemotherapy administration)
Day 0	• Get routine blood tests • Infusion of gene-modified MART-1 F5 TCR
Day 1	• Dendritic cell vaccine administration
Days 1 to 7	• Twice daily IL-2 administration • Get blood to test cytokine profile
Day 14	• Get blood to test gene-modified cells and cytokine profile • Dendritic cell vaccine administration
Days 20 to 40	• Leukapheresis • Biopsy of tumor • PET/CT scan
Day 30	• Get blood to test gene-modified cells • Get routine blood tests • Physical exam • Dendritic cell vaccine administration
Day 45	• Get blood to test gene-modified cells • Get routine blood tests • Physical exam
Day 60	• Get blood to test gene-modified cells • Get routine blood tests • Physical exam
Day 75	• Physical exam • Get blood to test gene-modified cells
Day 75-90	• Get routine blood tests • MRI or CT scan of the brain • Eye exam • Ear exam

Day 90	• Physical exam • Get blood to test gene-modified cells
Every 2-3 months for two years	• Physical exam • Get blood to test gene-modified cells
Every 6 months up to five years	• Physical exam • Get blood to test gene-modified cells
Every 12 months up to fifteen years	• Physical exam • Get blood to test gene-modified cells

- **POTENTIAL RISKS AND DISCOMFORTS**

You must tell the study investigators immediately if you have side effects, injuries or new symptoms or complaints, even if you do not think they are related to the study medication. Any medicine may have side-effects. As with any investigational drug, there may be risks or side effects with gene-modified cells that are currently unknown. These may possibly be serious, permanent or even life-threatening. It is particularly important that you tell the study investigators immediately if you experience new symptoms that may be related to your participation in this research protocol.

A) Serious Risks Observed in Prior Subjects in this Protocol and in Similar Protocols at UCLA.

1. Prolonged Drop in Blood Cells. One patient out of 14 in this protocol required two months of hospital stay due to a delayed recovery of blood cell counts. During this time the patient required being in an isolation room to prevent from infections, and had to receive frequent transfusions of red blood cells and platelets. The patient also received immune dampening medications like corticosteroids. The blood cell counts recovered approximately two months after starting in the protocol.

2. Pneumonia Requiring Extended Hospital Stay. Two patients in this protocol experienced serious complications and died due to a lung infection (pneumonia) requiring mechanical ventilation and intensive care support. These patients experienced severe trouble breathing, impaired kidney function, and low blood pressure during these episodes leading to a prolonged hospital stay. Due to these complications the study protocol was amended to require a baseline lung function test within the normal range, the number of cells infused was decreased and the dosing of IL-2 was changed from high dose to low dose since it was felt it was a very likely cause of these severe complications.

3. Tumor Related Bleeding. One patient in this protocol died after serious complications. The melanoma did not respond and as it got worse, it led to massive intra-abdominal bleeding while the patient was on a blood thinner.

4. Visual Loss. One patient in a related trial (NY-ESO-1 protocol using a different tumor marker than MART-1 F5) developed visual loss in both eyes. On the second day of chemotherapy, the patient noted some blurry vision that improved and had a normal examination of the patient's visual system. Three weeks later, this patient noted worsening of the vision with a severe decrement of the visual acuity which progressed to a complete loss of vision.

5. Tumor Related Bleeding. One patient in a related protocol died after serious complications. The patient had melanoma (an aggressive form of skin cancer), and this cancer did not respond to the treatment. As it got worse, the melanoma growth in the abdomen led to massive bleeding which

happened while the patient was on a blood thinner.

6. Arrhythmia. One patient in the NY-ESO-1 protocol developed serious irregular heart beats called unsustained ventricular tachycardia that required intravenous medication to control the rhythm after 18 doses of IL-2. This is a known complication of IL-2 and the symptoms were resolved after IL-2 was discontinued. The number of doses of IL-2 have been reduced to no more than 14 doses for all similar trials.

B) Potential Risks Related to this Protocol.

1. Risks of Gene Transfer. The HIV-like virus used in this protocol is called a retroviral vector used for gene transfer. There is limited experience in using retroviral vectors in humans, so the potential for short-term and long-term side effects are not fully known. Below we describe the risks associated with two gene therapy vectors, one that is not part of this protocol (adenoviral vectors) and one that is part of this protocol (retroviral vectors), to inform you of the type of risks that may be associated with gene therapy in general.

- **Risk of Cancer with Retroviral Vectors.** The vectors used to perform the gene transfer may cause cancer. When retroviral vectors enter a normal cell, the vector inserts itself into the normal genes in that cell in a process that is called integration. Most integrations cause no harm to the cells or to the subject. But, there is a chance that there may be some places of the normal human genes where integration of the viral vector may result in activation of nearby genes.

  If one of the genes that are activated by viral vector integration has the role of controlling cell growth, integration near it may result in cancer. This has occurred in animal studies in mice and monkeys using retroviral vectors. The retroviral vector integration seems related to cancer development in these animals.

  The development of cancer has also happened in human clinical trials using retroviral vectors. Twelve children with a severe form of immune deficiency received blood stem cells gene modified using a retroviral vector. Most of the children who participated in that clinical trial appear to have been cured of their immune deficiency disease. However, 3 children developed a form of cancer of the blood called leukemia approximately 3 years after receiving the gene transfer. One of the children died from leukemia. A group of experts looked at all the study test results, and found that the gene transfer caused the leukemia cancer.

  The retroviral vector used to make the gene modified MART-1 TCR CTLs is related but different from the retroviral vectors that caused the leukemia cancers. In animal models, there is little evidence that the type of retroviral vector used in the current protocol induces cancer from integration. Therefore, it is unlikely that you would be exposed to the same risks. However, the long-term risks of any form of gene transfer approach in humans are currently unknown.

- **Risk Associated with Replication Competent Retrovirus (or RCR) with Retroviral Vectors.** The retroviral vector used to make the gene modified MART-1 TCR CTLs is related to (but different from) HIV, the virus that causes AIDS. To make it as safe as possible, this retrovirus vector does not have the parts that would allow it to behave like an HIV virus in your body. In

particular, the genes that allow the HIV virus to make new virus and infect new cells are not present in the retroviral vector. However, there is the risk that the retroviral vector may mutate (change its genes) and grow as a virus after it has been inserted in your CD8+ cells. This would be called a replication competent retrovirus (or RCR).

The risks of RCR are currently unknown, but it is possible that it may make you sicker than you are now. It is theoretically possible that you may develop a disease similar to HIV infection. To date, no patient has developed an RCR from retrovirus vectors.

To minimize the risks of you receiving an RCR, the gene modified MART-1 TCR CTLs will be tested for RCR before they are administered to you. You will be monitored for the appearance of RCR in your blood during many of the follow up visits included in this protocol. If one of the tests for RCR is positive at any time, you will be contacted and asked to return to the clinic within 2 weeks to provide more blood to confirm the test results. A positive test result does not mean that you have really developed RCR. Should your repeated tests show that you have RCR, there is no approved treatment for an RCR. Medical and research experts will work with you to define the best care available to attempt to treat the RCR, which most likely may include the type of drugs that lead to control of HIV infection.

2. Risks of Turning the Immune System against Melanoma. This protocol is intended to turn on the immune system against melanoma cancer cells by guiding it to attack cells that express the MART-1 marker. This melanoma marker MART-1 is not only expressed in melanoma cancer cells and may be expressed also in normal pigmented cells in the body.

- **Risk of Skin Toxicities.** Turning on the immune system against MART-1 may result in loss of color of moles or large areas of the skin. This may result in increased sensitivity to sunlight and predispose to sunburns. Patients treated with a similar regimen at the National Cancer Institute, Bethesda, MD, have developed skin rashes that feel like sunburns throughout the body, and normal pigmented cells have disappeared from large parts of their body. These toxicities are likely to happen to you if you participate in this research.

- **Risk of Eye Toxicities.** A serious toxicity would be if the immune system starts attacking MART-1 positive pigmented cells in the eye. This may result in blindness. Therefore, we request that you comply with the visits with the eye doctors scheduled in this study to allow the study investigators to detect any adverse effect in your eyes and start a treatment for it.

- **Risk of Ear Toxicities.** Some patients treated with a similar regimen at the National Cancer Institute, Bethesda, MD, have developed problems in the ear and equilibrium. This has presented as problems keeping the balance and sensation that things around the person are moving when they are not. This condition is known as autoimmune vestibular toxicity and it is due to an attack of the gene modified MART-1 TCR CTLs against MART-1 positive cells in the middle and inner ear. These toxicities may happen to you if you participate in this research. If this happens to you, you should contact the study investigator immediately and you would likely receive injections of corticosteroids into your ear.

- **Risk Associated with Autoimmune Toxicity from Mispairing of TCRs**. The chains of the receptor on the transgenic lymphocytes could mispair with the chains on your own lymphocytic

cells, which could result in conditions such as loss of weight, muscle atrophy, fatigue, weakness, significant loss of appetite, bone marrow failure, lymphocytic depletion, pancreatitis, and colitis, etc.. If any of the above occurs or there is evidence of other autoimmunity development, you would receive immune suppressive therapy as clinically indicated based on the severity of symptoms, using medications like corticosteroids, cyclosporin-A, mycophenolate mofetil, anti-TNF-alpha antibodies or anti-thymocite globulin (ATG).

3. Risks of Dendritic Cell Administration: Vaccination with dendritic cells expressing MART-1 could potentially result in an allergic reaction, which could include redness and swelling at the injection site, itching, hives, low blood pressure, difficulty breathing, or in the most extreme situation, death. Receiving acetaminophen (Tylenol®) and diphenhydramine (Benadryl®) before each injection of the vaccine reduces the possibility of these reactions occurring. In addition, if your immune system becomes overly stimulated, you might develop pain, redness and swelling at the injection site over the course of several days. However, the only harmful effects noted in other studies where dendritic cells were administered to human subjects with cancer were occasional mild fever or swelling at the injection site, lasting for 1-2 days, and loss of color of moles and skin.

A serious complication may arise if the vaccine preparation is contaminated with bacteria. This can happen since this vaccine is cultured in the laboratory for one week in a medium where bacteria may grow. This may lead to fever, chills and lowering of the blood pressure, and may require hospitalization. The vaccine is tested for the presence of bacteria during the culture and at the time of injection in an attempt to prevent this complication, with results reported and verified before administering the vaccine to you. However, final results of this testing may not be available for up to two weeks, and may show that the vaccine is contaminated with bacteria. If this should occur, you will be contacted to begin treatment with antibiotics.

4. Risks of High Dose Chemotherapy with Cyclophosphamide and Fludarabine. Below are the major toxicities associated with high doses of chemotherapy, describing the common side effects of the combined chemotherapy, and then listing some of the unique toxicities associated with each of the two chemotherapy drugs being administered in preparation for the administration of the gene modified cells:

- **Risks of High Dose Chemotherapy.**
  - A common side effect of high dose chemotherapy is nausea and vomiting. Your treating physicians will try to prevent this side effect by giving you modern antinausea medications, like a drug called Zofran.
  - We expect to see moderate to severe decreases of white blood cells, red blood cells and platelets. If serious decreases occur, you may have to be given blood cells or platelets.
  - Fever may be a result of infection that develops when white blood cells are low after chemotherapy. This will require treatment with antibiotics and medications to fight fungal or viral infections.
  - Some patients may develop headache and insomnia, which would be treated with medication, if needed.
  - A universal side effect of high dose chemotherapy is complete disappearance of the hair (or alopecia) within one month of receiving the chemotherapy. The hair usually reappears over the next several months.
  - Other side effects may include diarrhea (lasting up to 3 weeks), and abnormal function of liver,

which may be mild, moderate or potentially life threatening.
- It is possible that chemotherapy drugs may cause sterility and you may not be able to bear or father a child.
- A rare but potential side effect of high dose chemotherapy is an increased risk of developing cancer several years later.
- In rare cases, bone marrow failure may result following high-dose chemotherapy indicated by drop in the number of white blood cells and platelets.
- There also could be life-threatening infection and/or respiratory failure requiring mechanical ventilation. These risks could happen to you.
- During the immuno-compromised status after chemotherapy, any kind of infection may flare up giving rise to unexpected complications.

- **Risks of High Dose Chemotherapy with Cyclophosphamide.**
  - Common risks:
    - Cyclophosphamide (or Cytoxan) can lead to bleeding in the urine. You will receive a medication called Mesna to prevent this potential side effect, and your urine will be checked daily for the presence of blood while you receive this chemotherapy drug.
    - Weakness and muscle pain.
    - Fatigue.
  - Uncommon risks (less than 1%):
    - Seldom, cyclophosphamide can induce serious cough and shortness of breath within a condition known as interstitial pulmonary fibrosis.
    - Seldom, cyclophosphamide can induce serious loss of salt from the blood resulting in serious accumulation of liquid in the body, which is a resultant of a condition known as syndrome of inappropriate antidiuretic hormone secretion (SIADH). This condition is due to an effect of this drug on a gland in the brain.
    - Seldom, cyclophosphamide can induce serious problems in the heart, which can be inflammation (myopericarditis), death of heart cells (diffuse hemorrhagic myocardial necrosis) and inflammation of the lining of the heart (pericarditis).

- **Risks of High Dose Chemotherapy with Fludarabine.**
  - Common risks:
    - Weakness and muscle pain.
    - Fatigue.
    - Tingling in hands or feet (paresthesias).
    - Transient visual or hearing disturbances.
    - Transient sleep disorders.
  - Uncommon risks (less than 1%):
    - Seldom, fludarabine can induce break down of red blood cells resultant from an immune response, which is called hemolytic anemia. If this happens, patients feel extreme fatigue and become very pale, and require immediate medical attention and treatment with corticosteroids to decrease immune responses.
    - Seldom, fludarabine can induce serious cough and shortness of breath with a condition known as idiopathic interstitial pneumonitis.
    - Seldom, fludarabine can induce a reaction in the place where blood cells are made, the bone marrow, known as bone marrow fibrosis. This would lead to severe decrease in cells in the blood resulting in fatigue, propensity to bleeding and propensity to

infections.
- Seldom, fludarabine can induce severe changes in the brain known as progressive encephalopathy, which may lead to blindness and coma.

5. Risks of Low Dose Interleukin-2 (IL-2). High dose IL-2 has been approved by the Food and Drug Administration (FDA) for the treatment of melanoma and kidney cancer since it results in long term disappearance of metastatic melanoma in a small percentage of patients. In the current protocol you will receive low dose IL-2 (approximately 15 times less IL-2 in total than the FDA approved regimen for melanoma and kidney cancer, over a longer time period.). Injection site reactions have been noted with the subcutaneous form of IL-2, including transient injection site nodules and induration. Furthermore, some patients develop a rash, itching and dermatitis. This treatment can result in moderate nausea and vomiting, and moderate fevers and chills in most of the patients. Some patients develop moderate to severe pain in the joints that requires treatment with morphine-like drugs. It has the potential to induce moderate to severe heart, lung, kidney and liver problems. These side effects improve rapidly (within days) after the treatment is stopped, and it is very infrequent that it may result in long-term problems. There are reports of patient deaths due to IL-2 toxicities.

Due to these potential toxicities, patients that receive IL-2 need to be checked if their heart and lungs can stand the stress imposed by this treatment by performing heart tests. You will be asked to undergo such testing before you are allowed to participate in this study. Despite these known toxicities and risks, the great majority of patients are able to safely receive low dose IL-2, including it as an adjunct in stem cell transplant settings, and permanent problems are extremely rare.

6. Risks of Leukapheresis: The most common side effect from white blood cell collection is caused by the medication (called citrate) used to prevent clumping of the blood. Citrate binds to calcium in the body and may temporarily lower the calcium level. The first symptoms of this occurring are tingling, vibrating, or a numb feeling of the face, lips, teeth, hands, or feet. You will be instructed to tell the nurse immediately if you have any of these symptoms. All patients are continuously observed during the procedure. The nurse will give you calcium replacement to prevent or treat these symptoms, and when necessary slow down the speed at which the anticoagulant is given. Most patients are very comfortable throughout the procedure. There are rarely serious complications resulting from use of the blood cell separator. However, as in any medical procedure, there are certain risks involved. These include but are not limited to air entry into the blood stream, infection, shock, irregular heartbeat or heart failure. These complications are rare. Also, as in any donation of blood, there are a variety of minor reactions, which may occur such as fainting, dizziness, nausea, and bruising/swelling around the needle site. In rare instances, the small amount of blood remaining in the tubing cannot be returned to the patient. Any feeling of discomfort experienced during or after should be brought to the attention of the Hemapheresis Unit staff. If any complications arise, the Hemapheresis nurse and medical staff will provide immediate treatment.

It is possible that you require the placement of a catheter in a neck vein (central line) if the veins in your arms do not allow to correctly perform the leukapheresis procedure. This will be evaluated by an experienced leukapheresis nurse. Complications of placing a central line in a neck vein include pain, bruising and rarely, infection, at the site where blood is drawn. It is also possible to feel lightheaded or faint. A rare complication is puncturing your lung resulting in shortening of breath, which would require that you are admitted to the hospital for the placement of a tube in your chest to drain the air and allow your lung to re-expand.

7. Risks of Tumor Biopsies: A biopsy may result in local bruising, swelling or bleeding at the site where the skin is opened, lightheadedness, and fainting. Rarely, an infection may develop. These risks are reduced by having the biopsy performed in a clean environment by an experienced surgeon, and by close monitoring of the stitched wound after the procedure.

8. Risks of Research PET/CT Scans.

- **Intravenous Injection:** Administration of PET dyes through the vein can cause some slight discomfort when the needle is inserted into the arm vein. However, this is no more than the discomfort encountered when the blood samples are taken during a periodical medical examination or when blood is donated at the blood bank. The potential side effects of placing an intravenous line may include momentary discomfort during the puncture, lightheadedness, fainting, soreness and/or bruising for several days. In very rare circumstances, either bleeding or infection can develop at the needle puncture site. However, since the procedure is performed using sterile and standard medical practices, the chance of that occurring is very unlikely.

- **Confinement:** Being in the PET/CT scanner can cause claustrophobia (anxiety), in about 5% of patients. If you develop this feeling of claustrophobia, you should tell the study doctor or the technologist who is in the room that you cannot continue the study, and it will be terminated. The scanning procedure takes place in a quiet room. The scanner itself does not make any noise.

- **Radiation Exposure:** We are exposed to radiation on a daily basis, both from natural (sun and earth) and man made sources. In addition to the radiation that you may be exposed to as part of your clinical care (if you are receiving clinical care), you may receive one PET/CT scan while participating in this research study. The estimated radiation dose that you will receive as a result of this additional scan is 1436 millirem, or 29% of the 5,000 millirem annual limit allowed radiation workers

  If you participate again within 12 months in another study involving radioactivity or x-rays, you should inform the person ordering the scans that you were a participant in this study. The investigator will ensure through accurate record keeping at UCLA that the total amount of radioactivity administered for research purposes will remain small, and again, is not expected to cause any adverse effects.

- **For Women of Childbearing Potential:** Current knowledge indicates no confirmed detrimental effects to a developing fetus of radiation doses below 1000 mSv. The radiation dose that you will receive from the study procedure is very small in comparison. However, the study doctors wish to minimize any potential for exposure of a fetus to even these low levels of radioactivity. Because of exposure to radiation, it is important for you to practice effective methods of birth control, as discussed in the section below entitled "Risk to the Unborn Child (Men and Women)**"**. You should indicate to the study doctors any possibility that you are pregnant or that you have not used an effective and medically acceptable method of birth control in the recent past.

  You will be asked for a urine specimen to have a pregnancy test done before the research PET CT scans are done. If your pregnancy test is positive you cannot participate in this research study.

9. Risks of Regular PET/CT Scans and MUGA Scans. The amount of radiation received by you during these scans is the same as that for similar patients who are not on protocol; therefore, there is no increased risk of radiation exposure by participating in the study. You will be asked not to move during the test, but relax and breathe normally.

A liquid solution known as a contrast, given through a vein, is frequently used during CT scans. The contrast is a solution used to make certain organs, blood vessels and tissues stand out in greater contrast to better image your disease. You may experience nausea, flushing, warmth and a salty taste.

Intravenous contrast can cause allergic reactions. Allergic reactions to contrast may include itching, rash or hives. These usually disappear quickly. If needed, antihistamines can be given to help relieve the symptoms. Please inform the study physician about any bad previous experience with intravenous contrast administration.

Anaphylactic reaction is a severe allergic reaction. When this occurs, you may experience severe hives and/or difficulty in breathing. This reaction is quite rare, but is potentially life-threatening if not treated. Medications that may reverse this adverse reaction include corticosteroids, antihistamines, and epinephrine.

Toxicity to the kidneys that can result in kidney failure is an extremely rare complication of the intravenous contrast used in CT scans. Patients who already have impaired kidney function are most prone to this reaction.

It is estimated that the overall frequency of adverse reactions is 5 to 10 percent. Thus, 5 to 10 of 100 patients experience allergic reactions. Most of these are very mild and may consist of only a few hives. However, in one of every 1,000 to 2,000 examinations, a moderate or severe reaction can occur. The risk of death from a contrast agent is estimated to be 0.3 to 2.6 per 100,000 uses (comparable in magnitude to the risk of death from receiving a dose of penicillin).

10. Risks of MRI. An MRI uses magnetic energy and radio waves rather than x-ray radiation. A few patients may experience anxiety due to claustrophobia, or an inability to be in a confined space without being given a sedative (a drug used to calm them). In addition, you will hear loud, knocking noises. Occasionally, subjects will report a mild headache from the "knocking" sound. There are no other reported side effects. If you have any metal implants within the body (cardiac pacemaker, orthopedic pins, plates, or screws) you will not be able to undergo an MRI since metal implants interfere with the MRI system's magnetic field. You will still be able to participate in this study, but would have a CT scan instead of an MRI.

Recently, it has been reported that a rare but serious adverse reaction called nephrogenic systemic fibrosis (NSF) may occur after exposure to the gadolinium-based contrast agent gadodiamide (Omniscan®, GE Health Diagnostic, Amersham, United Kingdom). Nephrogenic systemic fibrosis is a condition wherein patients develop large areas of hardened skin with lesions called plaques and papules with or without skin discoloration. In some cases, NSF could lead to physical disability and may involve not only the skin, but also the liver, lungs, muscles and heart. The typical patient in whom this has occurred is middleaged and has end-stage kidney disease."

11. Risks of Ophthalmologic Eye Exam: Dilatation of your pupils may result in sensitivity to daylight requiring wearing sunglasses for several hours after the visit. Taking pictures of your eye may also result in sensibility to the light and local pain. Injecting a dye through a vein in your arm may result in local pain, a burning sensation in the arm and in extreme cases an allergic reaction. Placing a contact lens in your eye may result in local pain in the eye. A rare risk associated with pupil dilatation during the eye exam is the development of a condition known as acute angle closure glaucoma, which would manifest as severe eye pain due to sudden increase in pressure in the eye. This would require treatment to reduce the pressure in the eye.

12. Risk to the Unborn Child (Men and Women). The study drug used in this study may involve currently unforeseeable risks to pregnant women, the embryo or fetus, or to breast-feeding infants, and for this reason you must not become pregnant or father a baby while on this study, or for six months following your participation in the study. If you are sexually active, you must use a medically acceptable method of birth control while on this study. Examples of accepted birth control measures are: birth control pills, a condom with spermicidal jelly, a diaphragm with spermicidal jelly, or abstinence. You must continue using birth control for six months after your last dose of study drug. The study investigators must approve the form of birth control.

If you are a woman of childbearing potential (not surgically sterile or post-menopausal), you must have a negative pregnancy test before beginning treatment. Additionally, you must not be nursing an infant during this study.

If you or your partner miss a period or become pregnant while you are on this study, you must tell the study investigators immediately. You or your partner will be referred to counseling about the options available to you. The study investigators will not be part of any decision resulting from this counseling. If you become pregnant, the study treatments will be stopped and we will request to follow you for the pregnancy outcome.

13. Risks of Central Venous Catheter Insertion. The most common risks of placement of CVC catheters in an arm vein like a PICC line are local pain and redness in the area where the catheter goes through the skin and reaches the vein. Other problems may be bleeding or oozing from the site where the catheter is placed. These risks are minimized by their placement by specially trained nurses called PICC nurses, or by their placement under radiology guidance to correctly find a vein. Central line insertion in a neck vein may additional serious complications like a pneumothorax (rupture of a lung), which would be experienced as an immediate feeling of shortness of breath. This risk is minimized by the placement of this type of catheters by highly trained physicians that are specifically approved to do place this type of catheters. If the tip of either a PICC or neck catheter reaches the heart and comes in contact with the heart wall it may induce changes in heart rate called arrhythmia, which you may feel as palpitations. This would be managed by pulling out the catheter a bit. Another complication may be if the tip of the catheter goes towards the neck veins as opposed to going to the large vessels in the heart area. In this case there would also be a need to pull out the catheter a bit. The site where the catheter tip is located is checked with an X-ray of the chest after the catheter has been placed, and the catheter is not used until a Doctor has confirmed that this tip is in a good location. With both types of catheters there may be complications of infection, which would be due to introducing bacteria into the blood with the use of the catheter. If you develop fevers or other signs of infection while having a catheter in place, blood cultures will likely be taken from both the catheter and from a vein elsewhere in the body. If the culture from the central line grows bacteria, the line is the likely source of the infection. In this case, the Doctors

may consider pulling this line out and placing another one later, or treating it with antibiotics without pulling the line out.

14. Risks of Blood Draws. The most common side effects of drawing blood that have been seen in humans or animals are pain, bruising and rarely, infection, at the site where blood is drawn. It is also possible to feel lightheaded or faint. Please tell the study investigators or study staff if you do not feel well after having your blood drawn. Some patients may require the insertion of a device into your vein in order to minimize the amount of discomfort and trauma to your veins.

15. Risks of HIV Testing. Testing for the HIV virus, which is the cause of AIDS, may include anxiety while waiting for the test results, emotional distress upon learning of the test results, risks of social stigmatization and discrimination in employment, housing and insurance.

16. Risks of Electrocardiogram (ECG) Test. You may feel some discomfort similar to pulling off an adhesive bandage when the technician removes the electrodes placed on your chest during the procedure.

17. Risks of Pulmoanry Function Test (PFT). Side effects from PFT testing are extremely rare and have usually occurred in patients with severe underlying cardiac disease. Some potential complications include:

- Potential for syncope with breathing in deeply (valsalva)
- Extremely rare but possibility of myocardial infarction (heart attack) with the valsalva maneuver (bearing down)
- Pain and low risk of infection from arterial blood gas drawing

18. Risks of Echocardiogram (ECHO) or MUGA scan. Echocardiography testing is very safe and it does not involve radiation. There is a small risk of dermatologic irritation from the gel used during the procedure. Another method of acquiring the LVEF is called a MUGA scan – this scan involves the injection of tin and Technetium-99 – but these are given at very low doses so the side effects are minimal. There is an extremely small amount of radioactivity with the test. For all patients, an ECHO will be preferentially ordered.

19. Unknown Risks. The study treatments and procedures may involve risks that are currently unforeseeable.

- **ANTICIPATED BENEFIT TO SUBJECTS**

Taking part in this study may or may not improve your health. While doctors hope the MART-1 TCR CTLs will be more useful against cancer compared to the usual treatment, there is no proof of this yet. You have the option to refuse to participate in this study.

• ANTICIPATED BENEFITS TO SOCIETY

This study may lead to a better understanding of how the immune system fights cancer. Such an understanding may lead to the development of improved methods for treating human cancer. Therefore, the knowledge gained may benefit others.

• ALTERNATIVES TO PARTICIPATION

Your participation is voluntary and you may choose not to participate in this study. The study investigators are very willing to discuss the benefits and side effects of alternative treatments.

There are seven treatments approved by the FDA for metastatic melanoma:

- The anti-PD-1 antibody pembrolizumab (or Kytruda®)
- The anti-Pd-1 antibody nivolumab (or Opdivo®)
- The anti-CTLA4 antibody ipilimumab (or Yervoy ®)
- BRAF V600E inhibitors vemurafenib (or Zelboraf ®) or dabrafenib (or Tafinlar ®)
- MEK inhibitor trametinib (or Mekinist ®)
- The chemotherapy agent DTIC (or Dacarbazine)
- The chemotherapy agent hydroxyurea
- The immunotherapy agent Interleukin-2 (or IL-2 or Proleukin ®)

Pembrolizumab (Kytruda) has recently demonstrated an improvement in survival compared to other standard of care therapies in two randomized clinical trials. Vemurafenib, dabrafenib, and trametinib showed an effect on melanoma patients with BRAF V600E mutation. Neither DTIC, hydroxyurea, nor IL-2 has demonstrated an improvement in survival for patients with metastatic melanoma. IL-2 is part of this protocol. You should be aware that you have the option of receiving these treatments without participating in this protocol.

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study with chemotherapy, radiation therapy or experimental anticancer agents
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

You also have the option to receive no treatment at this time. Other investigational protocols with chemotherapy, radiation therapy, or experimental anticancer agents may be available for your disease. The study investigators can provide you with detailed information about your disease and the risks and benefits of different treatment options. At any time, you may freely discuss your participation with the study investigators or doctors not involved in this research.

- **COST OF PARTICIPATION**

The study will pay for research-related items and/or services that are provided only because you are participating in the study. These research-related items and/or services are explained in other areas of this consent form.

You or your health plan may be responsible to pay for all the types of items listed below:

- Items and services that would have been provided to you even if you were not in the study
- Health care given during the study as part of your regular care
- Items and services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items and/or services

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

- **EMERGENCY CARE AND COMPENSATION FOR INJURY**

It is important that you promptly tell the study doctors if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the number(s) listed below.

If you are injured as a result of being in this study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California or the study sponsor or billed to you or your insurer just like other medical costs, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For more information about this, you may call the UCLA Office of the Human Research Protection Program at 310-825-5344 or send an email to mirb@research.ucla.edu.

- **PRIVACY AND CONFIDENTIALITY**

The study doctors will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security

You will be asked to sign a separate form called the **University of California Permission to Use Personal Health Information for Research** that will allow UCLA to share information from your medical records with the study doctor so they can use your information as part of this study.

Coding of Specimens and Medical Information.

Your tissues, cells from your blood and medical information will be labeled with a code. Only the researchers conducting this study will have the information that matches the code to traditional identifying information, such as your name, address, phone number, or social security number. The information that matches the code to your identifying information will be kept in a safeguarded database. Only very few, authorized people, who have specifically agreed to protect your identity, will have access to this database. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of this identifying information about you.

The research team, authorized UCLA personnel and regulatory agencies such as the FDA, may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

If photographs of you are taken, they may be used for educational purposes. Your identity will be protected by showing the minimum amount of your body that includes the lesion or reaction being pictured, and by disguising your eyes, birth marks or anything else that may make it easy for others to recognize that it is a picture of you.

How information about you will be stored.

All research data and records will be stored electronically on a secure network with encryption and password protection.

How long information from the study will be kept.

The researchers intend to keep the research data and records indefinitely for future research.

BIOPSY TISSUE SAMPLE OR BLOOD CELLS REMAINING AT THE END OF THE STUDY

You will be asked to consider whether you would permit part of this sample to be shared with other researchers. You will be asked to sign an additional consent form for this. If you agree to have your sample shared with other researchers and later decide to withdraw, we may not be able to retrieve any or all of your sample from other researchers. The researcher is not required to store your sample(s) indefinitely.

Use of My Specimens.

Any specimens (e.g., tissue, blood, urine) obtained for the purposes of this study will become the property of the University of California. Once you provide the specimens you will not have access to them. The University may share your specimens in the future with other researchers or outside institutions. Information that identifies you will not be shared with anyone outside of UCLA. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed

by the University. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens.

Researcher Financial Interests in this Study.

The researchers in this study have no financial interests in this study.

- **PARTICIPATION AND WITHDRAWAL**

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from UCLA.
- If you decide to take part, you can leave the study at anytime.
- If you decide to stop being in this study, you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
- If you decide not to take part, you can still get medical care from UCLA.

- **IDENTIFICATION OF INVESTIGATORS**

In the event of a research related injury or if you experience a bad reaction, please contact:

Antoni Ribas, M.D. Professor of Medicine Division of Hematology-Oncology [redacted]	John A. Glaspy, M.D., M.P.H. Professor of Medicine Division of Hematology-Oncology [redacted]
James S. Economou, M.D., Ph.D. Professor of Surgery Chief, Division of Surgical Oncology [redacted]	Bartosz Chmielowski, M.D., Ph.D. Assistant Professor of Medicine Division of Hematology-Oncology [redacted]
Arun Singh, M.D. Clinical Instructor in Medicine Division of Hematology-Oncology [redacted]	Siwen Hu-Lieskovan, M.D., Ph.D. Clinical Instructor in Medicine Division of Hematology-Oncology [redacted]
Deborah Wong, M.D., Ph.D. Clinical Instructor in Medicine Division of Hematology-Oncology [redacted]	

In the event of eye problems you should contact the following Eye doctors that are study investigators and know about the potential effects of the study drug in the eye and vision:

Tara McCannel, M.D., Ph.D.
Assistant Professor of Ophthalmology
[redacted]

In the event of ear or nose problems you should contact the following Ear and Nose doctor, who is a study investigators and knows about the potential effects of the study drug in the ear and nose:

Akira Ishiyama, M.D.
Professor of Surgery
Division of Head and Neck Surgery
[redacted]

The following doctor is in charge of the research PET/CT scans:

Johannes Czernin, M.D.
Professor of Pharmacology
Division of Nuclear Medicine
[redacted]

These doctors are available to you for any questions about the study or in the event of an emergency 24 hours a day, 7 days a week. You can have him/her paged through the UCLA operator at (310) 825-6301.

UCLA Office of the Human Research Protection Program (OHRPP):

If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: (310) 825-5344; by email: mirb@research.ucla.edu or U.S. mail: UCLA OHRPP, 11000 Kinross Ave., Suite 211, Box 951694, Los Angeles, CA 90095-1694.

WHERE CAN I GET MORE INFORMATION ABOUT PARTICIPATING IN CLINICAL TRIALS?

National Cancer Institute (NCI) Information:
You may call the NCI's Cancer Information Service at:

- 1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

Public Information about this Study:

- *ClinicalTrials.gov* is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

- The National Cancer Institute's (NCI) Clinical Trials Reporting Program (CTRP) is a comprehensive database of information about all NCI-supported clinical trials. The goal of this comprehensive database is to help NCI identify areas that need more clinical research and to help NCI decide which studies are most important to do first. The NCI requires that cancer clinical trials report information about how many subjects are enrolled in the trials and the outcome of the trials. Specific information about you as a subject will be included in the database. This information will include information about your cancer, your study identification number, the month and year of your birth, as well as your gender, country of origin, race, ethnicity, and zip code. This information will be maintained in a secure and confidential manner by the NCI CTRP in their electronic database. The NCI CTRP has many safeguards in place for privacy, security, and limited authorized access.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?

If you want to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

SIGNATURE OF RESEARCH SUBJECT

I have read the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form, as well as a copy of the Research Participant's Bill of Rights.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

_____ _____

Signature of Subject date

_____

Name of Subject (Printed)

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____ _____

Signature of Investigator date (must be the same as subject's)

_____ _____

Name of Investigator (Printed) Contact Number