NCT# 01555541

University of California, San Francisco
Consent to Participate in a Research Study

CC# 112525: A phase II study of intensive consolidation and stem cell mobilization therapy with ofatumumab, etoposide, and high-dose ara-C (OVA), followed by autologous stem cell transplantation in high-risk patients with relapsed/refractory Diffuse Large B-Cell Lymphoma

Introduction

This is a clinical trial, a type of research study. Dr. Charalambos Andreadis and his associates in the Adult Lymphoma and Stem Cell Transplantation Program at UCSF Medical Center will explain the trial to you. This trial is being supported by a Grant and study medication from the pharmaceutical company Novartis.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being considered for this clinical trial because you have relapsed or progressive diffuse large B-Cell Lymphoma (DLBCL) and you are undergoing "Salvage Therapy" (standard second-line chemotherapy treatment) followed by an autologous stem cell transplantation (autoSCT), which is the appropriate therapy for you.

Why is this study being done?

Patients with relapsed or progressive DLBCL can be potentially cured with autoSCT. However, patients who have received prior therapy containing rituximab and who have either never achieved a complete response, or who progressed within 12 months of achieving a complete response, are at higher risk of treatment failure and have a lower likelihood of cure with traditional autoSCT.

At UCSF, we have developed an 'augmented' form of chemotherapy given prior to autoSCT. This therapy is given following standard salvage therapy and consists of etoposide (VP-16) and high-dose ara-C. In this study, we are combining it with ofatumumab in a regimen abbreviated as OVA. The aim of using this additional course of chemotherapy (OVA) is to decrease the amount of residual disease in your body (small amount of cancer cells that might remain after salvage therapy) and to eliminate any contaminating cancer cells from being collected with your stem cells for autoSCT.

The basis for this approach to treatment is that a similar augmented therapy (consisting of rituximab, etoposide, and ara-C), has been used at UCSF for over 10 years with good results. Like rituximab, ofatumumab is an antibody (a substance that can bind to proteins such as those found on cancer cells). We will now try combining etoposide and ara-C with ofatumumab,

which binds to cancer cells at a different location than rituximab, and may potentially overcome the cancer cell's resistance to rituximab.

You are being asked to participate in this study because based on the specific characteristics of your disease, the study doctors feel that you may benefit from this augmented chemotherapy.

Etoposide, and ara-C are FDA approved therapies for lymphoma. However, they are not approved for use in this combination (OVA). All other treatments, including salvage therapy, stem cell collections and stem cell infusions are part of standard therapy for lymphoma.

Ofatumumab (Arzerra®) is FDA approved for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

The goal of this clinical trial is to show that OVA is successful in collecting autologous stem cells for use in autoSCT and to examine its effectiveness in eliminating residual DLBCL in patients with your risk factors. If this clinical trial is successful it will lead to a larger trial in the future to study this treatment regimen in many institutions across the United States.

Novartis, the company that is providing ofatumumab, is also providing financial support to UCSF to conduct this study.

How many people will take part in this study?

About 24 patients will be involved in this study at UCSF Medical Center.

What will happen if I take part in this research study?

Before you begin the main part of the study . . .

You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. This is done to help determine whether or not you may benefit from the study and if you will able to undergo further intensive treatment. If any of these tests are found to be abnormal, you may not be allowed to participate in this study.

The following procedures are part of your normal care and would be done even if you did not join the study:

- Medical history and physical examination
- Laboratory/Blood tests (about 2 teaspoons of blood will be taken to look at your blood counts, organ function, and your immune function)

The following procedures are <u>not</u> part of your normal care and are being done solely for this study:

- Blood sample for Hepatitis B and C testing (about 1 teaspoon):
  Your blood will be tested for hepatitis B and C. Patients who test positive for Hepatitis B will be tested for ongoing infection with a test called Hepatitis B viral load. Patients with a positive viral load will not be allowed to participate. If the results of Hepatitis B viral load testing do not suggest ongoing infection, you will need to have Hepatitis B viral load testing every 2 months while on the study. If your results are later found to be positive, you will obtain appropriate therapy for hepatitis and you may not be allowed to continue on study treatment. Based on your baseline risk, your doctor may prescribe antiviral medication for Hepatitis to prevent you from developing active, ongoing infection. Patients who test positive for Hepatitis C will be excluded from the study.

  All Hepatitis testing done throughout the study will be done solely for the study (it is not part of normal care)

- Tissue samples:
  As part of your regular care, you had a blood and/or tissue sample taken to diagnose your cancer. If there is any sample left over that is no longer needed for your care, the study doctor will keep some of it for research tests to look for differences in DLBCL cancer cells. Some of your sample will also be kept for residual disease testing (to compare them to samples that may be taken later in the study).

<u>Salvage Therapy:</u>
Salvage therapy (standard second-line chemotherapy treatment) is not part of this study; it is part of your regular care. However you will need to have responded to salvage therapy before being able to continue on to the main part of the study. After undergoing salvage therapy, you will have the following procedures to see if you responded to salvage therapy and if you are still eligible for the study:

The following procedures are part of your normal care:

- Medical history and physical examination

- Laboratory/Blood tests

- Echocardiogram or MUGA scan:
  You will have one of these exams to determine how well your heart squeezes blood.
  - Echocardiogram: For this exam, you will be asked to lie on your left side while a technician places a probe with gel on your chest to create images of your heart. This procedure will take about 45-60 minutes.
  - MUGA scan: For this exam, a small blood sample will be taken, mixed with a radioactive substance, and injected back into your body. You will then wait for about 60 minutes for the radioactive substance to circulate throughout your body. After this time, you will lie flat on a scanning bed while the scanner takes images of your heart. You will need to lie still for about 10-20 minutes so that the images are clear. The procedure will take about 90 minutes.

- DLCO (diffusing capacity of the lung for carbon monoxide) test:
  This exam determines how well oxygen passes into your blood from the lungs and how well carbon dioxide passes from your blood into your lungs. This exam is done to see how well your lungs are working. For this exam, a clip will be put on your nose and you will be asked to inhale (breath in) a small amount of "tracer" gas (carbon monoxide) through a mouthpiece. After inhaling the tracer gas, you will hold your breath for 10 seconds, and then blow it out (exhale). The exhaled gas will be tested to see how much of it was absorbed from your lungs. The procedure will take about 30 minutes. If you are a smoker, you will be asked to not smoke for 4 to 6 hours before this exam.

- Lumbar puncture:
  This exam (commonly referred to as a "spinal tap") involves using a needle to take a sample of cerebrospinal fluid (the fluid surrounding your brain and spinal cord). It is done to see if your cancer has spread to your brain and/or spinal cord. For this exam, you will lie down sideways and a local anesthetic will be given through a small needle into the skin. You will be asked to lie still and breathe slowly, as a large needle for the lumbar puncture is pushed into the spinal canal and the cerebrospinal fluid is withdrawn into a syringe. After the needle is removed, you will have to lie still for a short while to prevent headaches (a common side effect of this procedure). For the rest of the day, you should lie down for several hours, drink plenty of fluids, and report any symptoms of headache or dizziness to your doctor. This procedure will take about 30 minutes.

  This procedure will only be done on patients who have a history of cancer in the brain or spinal cord, or if the doctor suspects it may have spread there.

- Bone marrow aspiration and biopsy:
  A bone marrow aspiration involves using a needle to remove a sample of fluid from your bone marrow; a bone marrow biopsy involves using a needle to remove a piece of your bone marrow. These procedures are done to evaluate the cancer in your bones. The doctor will insert the needles into your hip bone to remove the fluid and marrow samples (about 2 teaspoons). You will receive medicine to numb the surface of your skin where the needles will be inserted. This procedure will take about 15-30 minutes.

  Samples of your tissue will be kept for research studies to look for differences in DLBCL cancer cells and to compare to samples which may be taken later (to see if there is any residual disease present in your body).

- FDG-PET scan and CT scan or PET/CT scan:
  The FDG-PET scan is done to show how the organs and cells work in your body and to show activity of the cells in your tumor. The exam will begin with an injection of a radioactive substance. You will then wait for about 30 minutes for the radioactive substance to circulate throughout your body. After this time you will lie down on a scanning bed, which will move you into the scanner (a large ring, similar to a big doughnut hole). The scanner will take images of your body. You will need to remain very still so that the images are clear. This procedure will take about 1 hour. You will

need to fast (not eat) for 6 hours before your exam, and you will need to drink at least 2 large glasses of water before the exam.

The CT or PET/CT scan makes detailed pictures of your body tissue and organs and is done to see if your cancer has spread. In order to get clearer pictures, you may be given "contrast material" (a special dye that makes it easier to see your organs and tissues). The contrast material may be given orally (by mouth), intravenously (by needle into a vein), or rectally (into your lower bowels; this is less likely). For the exam, you will lie flat on a scanning bed that will move you into the scanner. You will need to lie still and may be asked to hold your breath for a few seconds so that the images are clear. This procedure will take about 30 minutes.

The following procedures are <u>not</u> part of your normal care and are being done solely for this study:

- Blood sample for research tests:
  About 2 teaspoons of blood will be drawn and used for residual disease testing.

- Pregnancy test:
  If you are a woman who is able to have children, you will have a serum pregnancy test (women who are pregnant or breastfeeding are not eligible for this study)

- EKG:
  This exam shows the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. This procedure will take about 15-30 minutes.

After undergoing all these procedures, it is possible that you may not be able to participate in the study. If this happens, the study doctor will discuss other treatment options with you.

During the main part of the study...

If the exams, tests and procedures above show that you can be in the main part of the study, and you choose to take part, then you will undergo the following tests and procedures.

Treatment will consist of two sequential steps: initial chemotherapy (OVA augmented therapy) with stem cell collection, followed by high dose chemotherapy and stem cell re-infusion or transplantation. A summary (schema) showing the parts of the study can be found on the last page of this consent form.

<u>Step 1 - Chemotherapy and Stem Cell Collection</u>
For the first step, you will be admitted to the hospital for approximately four weeks.

Because you will be having many blood draws, infusions of medication, and transfusions during this study, you will have an intravenous catheter (called a central venous catheter) placed into

one of the large veins in your neck or arm.

You will receive therapy with ofatumumab on the first day of treatment (and weekly thereafter, for a total of 4 doses). Ofatumumab is given as an intravenous (IV) infusion over several hours. Before each infusion of ofatumumab, you will be given medication to help to reduce any infusion reactions. These may include anti-histamines, steroids and pain relievers. You will be checked closely, and if you do have any infusion reactions these will be treated.

On the first day of treatment, you will also have the following procedures:

- Medical history and physical examination
- Laboratory/Blood tests daily (about 2 teaspoons)
- Research blood test (about 2 teaspoons) to look at differences in your cancer cells

You will receive chemotherapy with etoposide and ara-c for the next four days of the hospitalization. The drug etoposide is given as an IV injection continuously over 24 hours for four days (96 hours). The drug ara-C (cytarabine) is given intravenously over 2 hours twice a day for four days (for a total of 8 doses). You will be given medications to prevent nausea and vomiting, fevers, rashes, pain or any other side effects from the chemotherapy. Because chemotherapy will lower your blood cell counts, you may be given antibiotics, blood/platelet transfusions, and nutritional support as needed.

After 2 weeks of hospitalization you will receive G-CSF (also called neupogen) injections to help the white blood cells recover more quickly and to stimulate the release of "stem cells" from the bone marrow into the blood. G-CSF will be given daily by subcutaneous (under the skin) injection. After approximately 7 days of G-CSF injections, the blood cell counts will begin to rise. Once the white blood cell count reaches an adequate level, you will begin the stem cell collection process. This process, called "leukapheresis", and is performed daily until adequate stem cells are collected. The process requires that an additional catheter (called a “Quinton” catheter) be placed into one of the large blood veins in the neck. The Quinton catheter is attached to an apheresis machine. The machine draws some of your blood into the machine, spins the blood and separates the blood into various components (white blood cells, red blood cells and platelets). The white blood cells, including the circulating stem cells, will be collected into a bag while the remainder of the blood cells are returned to you through the catheter. Each collection procedure takes 3 to 4 hours. The leukapheresis procedure will be repeated daily until enough stem cells have been collected and saved for the second phase of treatment. A small amount of these stem cells (less than 5% of the total) will be saved and stored at a UCSF Laboratory for research studies (the stem cells will be analyzed to see if any leftover cancer cells can be found)

During treatment with OVA (about 4 weeks), you will also have the following procedures:

- Laboratory/Blood tests (about 2 teaspoons daily)
- Research blood test (day 21or later)
    - To see how the drug is absorbed by your body (about 2 teaspoons)
    - For residual disease testing (1 teaspoon)

Once the stem cells have been collected and you have recovered from the side effects of chemotherapy you will be discharged from the hospital. This completes Step 1. In order to

proceed to Step 2, you must have recovered completely from the effects of Step 1 and must have no evidence of active infection. If there are any signs of organ dysfunction or recurrent lymphoma, you may not be able to continue with this study.

Six weeks after starting the first step of treatment, you will be evaluated to make sure you are still in remission and to make sure that your internal organs (heart, liver, kidney and lungs) are in satisfactory condition to proceed with further intensive treatment. Your evaluation will include the following:

- Medical history and physical examination
- Laboratory/blood tests (2 teaspoons)
- Research blood tests:
  - To see how the drug is absorbed by your body (2 teaspoons)
  - To look at differences in your cancer cells (2 teaspoons)
  - For residual disease testing (2 teaspoons)
- Blood sample for Hepatitis B testing
- FDG-PET scan and CT or PET/CT scan
- Bone marrow biopsy (if your bone marrow was previously affected by lymphoma)

While on Step 1, if your disease progresses after starting OVA treatment and the intention of your treatment team is to proceed with autologous stem cell transplantation in the future, you will still be followed at regular intervals starting at month 3 of the schedule listed in "after you have completed treatment" section below. If you do not intend to have a transplant, you will be followed by Dr. Andreadis or his staff during the first two years after treatment. They will continue to obtain your records from your local doctor or contact you every 3 months for 2 years to see how you are doing.

Step 2 - Autologous Stem Cell Transplantation

If you are able to continue with treatment, you will then be admitted to the hospital to proceed with the second step in the treatment, the autologous stem cell transplant. You will be hospitalized continuously for 3-5 weeks. As with the first hospitalization, you will have a central venous catheter placed into one of the large veins in your neck or arm.

Stem cell transplant will take place on "Day 0". Before this happens, you will receive chemotherapy 6 days, 4 days, and 2 days before day 0 (designated as day -6, day -4, and day -2).

You will have routine laboratory/blood tests on each day of chemotherapy.

You will receive high-dose 'CBV' chemotherapy, which consists of 3 drugs (Cyclophosphamide, BCNU, and VP-16). BCNU (carmustine) will be administered intravenously over 2 hours (day -6). After 1 day of rest, you will receive VP-16 (etoposide) intravenously over 4 hours (day -4). After another day of rest, you will receive cyclophosphamide (Cytoxan®) intravenously over 1 hour (day -2).

After a day of rest from the CBV chemotherapy, you will receive an IV infusion of your stem cells (day 0), which were saved in Step 1 of treatment. The stem cell infusion is given through

your IV catheter like a transfusion.

During the remainder of your time in the hospital you will be given blood/platelet transfusions, antibiotics, and nutritional support to prevent or treat the side effects of treatment (similar to that during Step 1). Six days after starting the stem cell infusion, you will receive daily subcutaneous injections of G-CSF to help your white blood cells recover more quickly; G-CSF injections will continue until your white blood cells have recovered. After your body has healed from the effects of the high-dose chemotherapy, you will be discharged from the hospital.

While on Step 2, if your disease progresses after starting CBV treatment, you will still be followed by Dr. Andreadis or his staff. They will review continue to obtain your records from your local doctor or contact you every 3 months during the first two years after treatment to see how you are doing.

After you have completed treatment . . .

After being discharged from the hospital you will continue to require close observation and outpatient treatment. You will be required to return to UCSF for the following tests and procedures:

<u>At 1 and 2 months:</u>

- Medical history and physical examination
- Laboratory/blood tests (2 teaspoons)
- Blood sample for Hepatitis B testing (1 teaspoon)

<u>At 3 months:</u>

- Medical history and physical examination
- Blood test for routine safety tests (2 teaspoons)
- Research blood tests:
  - To see how the drug is absorbed by your body (2 teaspoons)
  - To look at differences in your cancer cells (2 teaspoons)
  - For residual disease testing (2 teaspoons)
- Blood sample for Hepatitis B testing
- FDG-PET scan and CT or PET/CT scan
- Bone marrow biopsy (if your bone marrow was previously affected by lymphoma)
- DLCO test (this is a study procedure)

<u>At 6, 12, and 24 months:</u>

- Medical history and physical examination
- Laboratory/blood tests (2 teaspoons)
- Research blood tests:
  - To see how the drug is absorbed by your body (2 teaspoons)
  - To look at differences in your cancer cells (2 teaspoons)
  - For residual disease testing (2 teaspoons)
- Blood sample for Hepatitis B testing (1 teaspoon)

- FDG-PET scan (this is a study procedure. It will be done at 6 months only if the previous scan done at 3 months showed evidence of your disease) CT or PET/CT scan

If the study doctor suspects that you cancer has returned, you will be asked to come in for the following tests and procedures:

- Medical history and physical examination
- Laboratory/blood tests
- FDG-PET and CT or PET/CT scan
- Bone marrow biopsy (if your bone marrow was previously affected by lymphoma). Samples of your tissue will be kept for research studies to look for differences in DLBCL cancer cells. (this is a study procedure)

After the follow-up procedures above, you may be contacted by Dr. Andreadis or his staff during the first five years after treatment to see how you are doing. The UCSF staff will also continue to obtain your records from your local doctor for 5 years.

How long will I be in the study?

Treatment and post-treatment procedures will last approximately 26 months. Afterwards, the researchers would like to check up on you for 5 years after your treatment to see how well you are doing.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the transplant treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

All cancer treatments are associated with risks. Side effects may be mild, moderate, or severe. This research study may involve risks we don't know about yet. Everyone taking part in the study will be watched carefully for any side effects. AutoSCT is a difficult and risky procedure. All possible attempts will be made to keep you as safe and comfortable as possible but there will be periods during the treatments and hospitalizations when you will be uncomfortable. Many

side effects go away soon after you complete the treatment and hospitalizations. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death (depending on the state of your lymphoma and your general health, the risk of dying due to treatment is believed to be less than 4 %). The treatment you receive may prove to have more side effects than other treatments. *This will not be known until after the study is completed and the data has been analyzed*.

If you experience any side effects, you must tell your doctor, who may give you other drugs to ease any discomfort you may experience. In addition, if a severe reaction to the drug occurs, your doctor may need to stop the study treatment.

STEP 1: (Consolidation chemotherapy)
During the first chemotherapy treatment with **ofatumumab**, etoposide and ara-c, you will likely experience the following side effects:

Risks and side effects related to ofatumumab (Ofatumumab has been given to patients with arthritis, leukemia, multiple sclerosis and certain other types of blood cancer) include those which are:

Likely
- skin rash
- allergic reactions, sometimes severe with swelling of face or mouth
- difficulty breathing, shortness of breath, chest tightness, cough
- low blood pressure (can cause light-headedness when you stand up
- flushing, high temperature
- excessive sweating
- shaking or shivering
- rapid heart beat
- nausea
- diarrhea
- back pain
- high blood pressure
- itchy, bumpy rash (hives)
- throat pain or irritation
- lack of energy
- stuffy nose
- low levels of white blood cells (which may increase risk of infection and fever)
- low levels of red blood cells (anemia)
- low levels of platelets in the blood (which may cause wound healing problems or bleeding)
- cold sores

Less Likely
- infections of the lungs or airways (*respiratory tract*) such as pneumonia

- infections of the ear, nose or throat
- blood infections
- urinary tract infections
- shingles
- increase in potassium, phosphate and uric acid in the blood that can cause kidney problems (*tumor lysis syndrome*)
- problems with blood clotting
- the bone marrow failing to produce enough red or white blood cells
- rash or darkening of the skin

Rare but serious

- A condition called "progressive multifocal leukoencephalopathy" (PML). PML is a rare but serious and life threatening brain condition, that has been reported with medicines similar to ofatumumab, including rituximab. PML may include memory loss, trouble thinking, difficulty walking, or loss of vision. If any of these symptoms develop, you will be evaluated immediately with appropriate tests and a neurological consultation. Any further therapy with ofatumumab will be discontinued.
- Severe skin reactions such as toxic epidermal necrolysis (serious and life threatening reaction which causes large areas of peeling skin and blisters to form on the mucous membranes lining the mouth, throat, anus, genitals, and eyes) may be observed with monoclonal antibodies and may also be observed in association with ofatumumab. In some cases this reaction may be fatal
- Sudden and severe Hepatitis B virus (HBV) infection can occur in patients newly exposed to HBV following treatment with ofatumumab, which can be fatal. Your study doctor will discuss with you whether or not vaccination for hepatitis B infection should be considered. If you have had hepatitis B, ofatumumab could cause your hepatitis B to become active again. Your blood will be monitored regularly for this condition. Additionally, your doctor may treat you with a suitable anti-viral medicine to help prevent this.
- Blockage of the small intestine, which can cause abdominal pain, nausea, vomiting, or decreased appetite
- Cytokine-related infusion reactions or post injection systemic reactions: Cytokines are substances in your blood that allow cells to talk to each other. These can be released and cause infusion reactions or post injection systemic reactions, particularly during or following the first dose of ofatumumab. Infusion reactions tend to decrease with subsequent doses of ofatumumab. Most of the infusion / injection site reactions reported with ofatumumab have been mild or moderate; however, infusion reactions may be severe or even lead to death. You will receive medicines before the infusion / injection to reduce the risk of these reactions on your treatment days.
- In the setting of an infusion reaction these events can rarely occur: Fluid collection in the lungs and change in heart rhythm. Patients with decreased lung function may be at greater risk of side effects that affect the lungs. Change in heart rhythm may be associated with decreased blood flow to the heart which may lead to chest pain and heart attack.

Risks and side effects related to the **cytarabine** include those which are:

Likely
- Nausea, vomiting and decreased appetite
- Fever/chills
- Rash or darkening of the skin
- Low Blood Counts (low white blood cells, red blood cells and platelets)
- Complete hair loss
- Mouth sores and difficulty swallowing
- Diarrhea

Less Likely
- Eye irritation with redness or pain on the surface of the eye
- Damage to the liver, usually reversible
- Damage to the lungs, usually reversible
- Inflammation around the heart causing pain
- Inflammation of the pancreas
- Numbness or burning in the feet or hands
- Infection
- Headache or dizziness

Rare but serious
- Brain damage resulting in slurred speech, difficulty with coordination and walking. This usually consists of a temporary (2-5 days) loss of coordination and temporary difficulty in speech or thinking. However in rare cases (less than 2%) these changes may be permanent, disabling or even fatal.
- Allergic reactions causing swelling around the face, low blood pressure or difficulty breathing
- Kidney dysfunction requiring dialysis
- Bladder dysfunction possibly requiring placement of a catheter in the bladder

Risks and side effects related to the **etoposide** include those which are:

Likely
- Nausea and vomiting
- Fevers/chills
- Rash
- Low Blood Counts (low white blood cells, red blood cells and platelets)
- Weakness or tiredness (malaise)
- Mouth sores
- Abdominal cramps
- Diarrhea
- Low blood pressure (may be serious)
- Sterility (unable to have children)

Less Likely
- Liver dysfunction
- Kidney damage
- Nerve damage
- Fluid buildup in the lungs or legs
- Infection

Rare but serious
- Secondary cancer
- Abnormal heart rhythm
- Numbness or burning in the feet or hands
- Severe allergic reaction causing severe skin rash with blistering
- Toxic reaction in the tissues surrounding the IV catheter
- Inflammation of the lungs with chronic damage to the lungs
- Visual changes
- Severe high blood pressure

STEP 2: (Transplant Chemotherapy)
During the transplant chemotherapy treatment with BCNU, etoposide, and cyclophosphamide, you may experience the following side effects:

(Risks and side effects related to **etoposide** are listed above)

Risks and side effects related to the **BCNU (Carmustine)** include those which are:

Likely
- Low blood pressure, fast heartbeat, chest pain and headache during infusion
- Disorientation, dizziness
- Nausea, anorexia and vomiting
- Transient eye flushing, blurry vision
- Mouth sores, crampy abdominal pain and diarrhea
- Low Blood Counts
- Malaise
- Complete hair loss

Less Likely
- Chest pain
- Facial Flushing
- Abdominal pain
- Mouth irritation
- Infection

Rare but serious
- BCNU lung injury. This can develop anytime between drug administration and as late as

4 years afterwards. It presents as shortness of breath, cough, fever, and chest pain. Additional testing such as lung function tests and CT scans may be needed to diagnose this condition. If treated early it is largely reversible but it can rarely progress to pulmonary fibrosis, which is permanent lung damage that can be fatal.
- Liver damage, most often reversible
- Kidney dysfunction, rarely requiring dialysis
- Allergic reaction

Risks and side effects related to the **Cyclophosphamide** include those which are:

Likely
- Nausea, anorexia and vomiting
- Mouth sores, crampy abdominal pain and diarrhea
- Low Blood Counts
- Malaise
- Hair loss
- May cause sterility

Less Likely
- Facial flushing
- Headache
- Skin Rash
- Nasal and sinus congestion during infusion

Rare but serious
- Lung damage, causing shortness of breath
- Heart damage, sometimes irreversible causing fatigue and shortness of breath
- Bladder damage, rarely leading to permanent scarring or even death. Frequent urination, pain with urination, blood with urination, or bladder spasms can occur. Catheterization of the bladder (insertion of a tube into the bladder) and medications to help with bladder function may be needed.
- SIADH, a condition that affects electrolyte balance in your body and results in water retention. It is temporary and treatable with restriction of water intake.
- Can cause secondary cancers

General Side Effects from this high-dose chemotherapy:

The high dose chemotherapy combination is expected to cause damage to hair, skin and the lining of the mouth and intestines. Hair loss will be complete but is usually temporary. In some cases the hair will not grow back completely or at all. During the first 1 to 2 weeks after stem cell transplantation there will be severe sores in the mouth. These may be painful enough to require morphine or other narcotics for pain control. In addition to causing mouth sores, the combination chemotherapy affects the entire intestine. This may lead to long periods of nausea or vomiting, diarrhea or crampy abdominal pain and inability to eat for several weeks. In time,

the body will naturally heal from all or most of these high dose chemotherapy related toxicities and this recovery will take approximately 1 to 3 weeks.

During the re-infusion of blood stem cells you will experience a number of side effects related to the chemical DMSO which is mixed with the stem cells in order to allow it to be safely frozen and thawed. The stem cell infusion takes place over 30-60 minutes. Typical side effects are nausea, vomiting, headache, flushing, chest tightness and pressure and abdominal cramps. You will receive anti-nausea medicines to try to minimize these effects and they should be gone within several hours after the infusion is completed.

Complications from Low Blood Counts
Most of the danger associated with high dose chemotherapy is due to the complications associated with low blood counts. During both treatment steps you are expected to have low blood counts. These treatments will temporarily stop your own bone marrow from producing normal blood cells. There will be a period of approximately 2 to 3 weeks when the blood counts will be low. Low white blood counts can lead to problems with infections. You will receive antibiotics to prevent infection and additional medications to treat an infection if it occurs. Despite aggressive treatment, occasionally an infection can become overwhelming and you could even die from infection. You will require transfusions of red blood cells because of anemia. You will also require transfusions of platelets to prevent bruising and bleeding. In cases where your body does not accept platelet transfusions from other people, there may be a risk of serious or even fatal bleeding.

Damage to Internal Organs
There are certain inherent risks in receiving very high dose chemotherapy of this type. Damage to internal organs can occur as a direct toxicity of this treatment. If this damage occurs, it may be disabling or even fatal. Usually, no specific treatment for these complications is available. This high dose therapy is also damaging to the reproductive system and there is a high likelihood (more than 95% chance) that you will be permanently sterile. Damage to the nerves may occur causing burning or tingling and rarely pain in the hands and feet.

Failure to Engraft
The high dose chemotherapy that you will receive will permanently damage the bone marrow so that it will never grow back. Restoration of your bone marrow function and blood counts will require the growth (engraftment) of your own infused stem cells. The engraftment rate with autologous transplantation is approximately 99%. If engraftment fails, there will be insufficient platelets, white cells and red cells to prevent bleeding and infection. If uncorrected this condition could be fatal. Initial therapy for this problem includes the use of bone marrow growth factors. Re-transplantation may or may not be possible and you could potentially die of this complication.

Failure to Control Malignant Disease
Despite the intensity of this treatment program there is still a chance that it will not completely control your cancer or that the disease may recur after some period of control.

If your cancer is in remission but recurs after the transplant, further treatment may be available. Should the cancer recur your doctor will describe the options of further therapy.

Risk of Second Cancers
Patients who receive treatment with high-dose chemotherapy have an increased risk of getting second cancers, including leukemia or lymphoma after the transplant procedure. The risk may be as high as 5-10% of developing a second cancer within 20 years of the procedure. You should receive routine screening for cancer if you receive this treatment.

Side Effects of Supportive Care Medications
You will receive medicine before the infusion/injection to reduce the risk of infusion/injection reactions on your treatment days. Overall, these medicines given before the infusion/injection are well tolerated.

Voriconazole is used to prevent fungal infections. Voriconazole can cause side effects including those which are:

Likely
- Nausea and vomiting
- Diarrhea and abdominal cramps
- Visual changes with color changes and difficulty with bright light
- hallucinations
- Headache
- Fever/Chills
- Rash

Less Likely
- Low white blood cell count
- Swelling in the feet
- Fast heart beat
- Liver inflammation with elevated liver tests

Severe
- Severe allergic reaction with low blood pressure and difficulty breathing
- Severe skin rash with blistering
- Abnormal heart rhythm with possible death
- Kidney failure, possibly requiring dialysis

Fluconazole is used to prevent fungal infections. Fluconazole can cause side effects including those which are:

Likely
- Nausea and vomiting
- Diarrhea

- Headache
- Rash

Less Likely
- Liver inflammation with elevated liver tests
- Abdominal cramps with pain
- Dizziness
- Taste changes

Rare but Serious
- Allergic reaction causing low blood pressure or shortness of breath
- Seizures
- Low white blood cells with infection
- Low blood platelets with possible bleeding
- Severe rash with possible blistering
- Abnormal heart rhythm with possible death
- Swelling due to allergic reaction

Moxifloxacin is used to prevent bacterial infections. Moxifloxacin can cause side effects including those which are:

Likely
- Nausea and vomiting
- Diarrhea and crampy abdominal pain
- Headache
- Dizziness

Less Likely
- Liver inflammation with elevated liver tests
- Rash
- Joint aches
- Infection in the colon called pseudo-membranous colitis causing severe diarrhea and cramps

Rare but Serious
- Seizures
- Abnormal heart beating
- Allergic reaction causing low blood pressure or shortness of breath
- Psychosis and depression
- Low white blood cells with infection
- Low blood platelets with possible bleeding
- Reversible kidney failure possibly requiring dialysis
- Severe rash with possible blistering

Acyclovir is used to prevent viral infection including lip and mouth ulcers from herpes simplex and shingle infections from varicella zoster (the chicken pox virus). Acyclovir can cause side effects including those which are:

Likely
- Nausea and vomiting
- Diarrhea and crampy abdominal pain
- Headache
- Dizziness

Less Likely
- Malaise or fatigue
- Rash
- Joint aches
- Lightheadedness
- Confusion

Rare but Serious
- Seizures or coma
- Kidney problems
- Low white blood cell counts with infection
- Low blood platelets with bleeding

Neupogen (G-CSF) is a growth factor used to stimulate the growth of white blood cells. Neupogen can cause side effects including those which are:

Likely
- Nausea and vomiting
- Fever or chills
- Headache
- Chest and sternal pain
- Elevated white blood cells
- Bone pain
- Bruising and pain at the injection site

Less Likely
- Liver inflammation with elevated liver tests
- Kidney problems
- Diarrhea and/or abdominal/flank pain
- Elevated uric acid levels with possible gout
- Enlarged spleen
- Fatigue with or without anemia
- Low blood platelets with possible bleeding
- Low blood pressure

Rare but Serious

- Rupture of the spleen requiring surgery
- Severe pneumonia/inflammation of the lungs
- The side effects of Neupogen can often be controlled with acetaminophen (Tylenol) or other pain medication, but occasionally Neupogen must be discontinued due to side effects.

Corticosteroids: The following side effects may occur with short term use of corticosteroids: fluid retention, acne, constipation, mood swings, sleeping problems, sweating, headache, dizziness, feeling sick to your stomach, stomach pain, bloating, and blurry vision.

Antihistamines: An antihistamine, such as cetirizine, will be given to you in this study. Use caution when driving a car or operating potentially dangerous machinery because sleepiness may occur. Also avoid alcohol or other drugs that can further decrease alertness. The most common side effect is sleepiness. Dizziness, fainting, headache, confusion, nausea, flushing, fatigue, rash, and dry mouth may also occur. Short-term increases in liver tests that suggest possible liver damage have occurred infrequently.

Acetaminophen/Paracetamol: Acetaminophen/paracetamol will be given to you in this study. Side effects from acetaminophen are rare. Your doctor will instruct you on the maximum daily dose of acetaminophen. Taking more than the recommended amount may cause liver damage. You should not take two or more products that contain acetaminophen at the same time unless directed by a physician. Your doctor should be informed about blood thinners, isoniazid (INH), and medications for pain, fever, and coughs. Tell your doctor if you drink three or more alcoholic beverages every day. Notify your doctor if any rash, hives, swelling of the face and throat, or difficulty breathing or swallowing occurs.

Procedure Risks

Risks of Blood Draw

If you have a blood draw from your arm, you may feel some discomfort when the needle is placed in the vein. Sometimes a bruise may develop where the blood was drawn or the needle was placed for treatment, and occasionally infection, clotting, or bleeding may develop at the puncture site.

Risks of Intravenous Access (central catheter placement)

You will have several catheters placed into your vein. Likely complications include discomfort, pain, bruising, and/or bleeding at the catheter insertion site. Occasional complications of the central venous catheter include blood clot formation, a punctured lung and infection. Rare complications include air embolus and death.

Risks of Bone Marrow Aspiration and Biopsy

There may be some temporary pain or discomfort associated with these procedures. While complications are extremely rare, excessive bleeding and infections at the site of the biopsy can

occur.

Risks of Lumbar Puncture
Can cause a headache approximately 20% of the time. This headache tends to be worse when you sit up as opposed to when you lay flat. This headache can be treated with pain medicines as well as increasing your intake of fluids especially caffeinated fluids. There can be some local pain in the lower back where the needle entered your skin. Infection of the spinal fluid is extremely rare. Bleeding into the lower back area which might affect your spinal nerves is also very rare.

Risks of Radiology Tests
The amount of radiation you will be exposed to is relatively small. These doses of radiation could be potentially harmful, but the risks are so small that they are difficult to measure. If you have had a lot of x-ray already, you should discuss this with your study doctor.

Risks of FDG-PET scan
This scan involves the risks of radiation (see above). The contrast material (radioactive form of glucose) is used. This substance can be easily eliminated from the body either through radioactive decomposition or excreted through urine.

Risks of CT scan
This scan involves the risks of radiation (see above). If contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). Rarely, the contrast material may cause nausea, vomiting or a headache. The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan with contrast. If you are taking metformin (or similar drugs by mouth to treat high blood sugar), such treatment will be stopped for 2-3 days around the time a scan is planned in order to avoid kidney side effects.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected by vein. You may feel warm and flushed and get a metallic taste in your mouth.

Risks of EKG
You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

Risks of Echocardiogram
This exam might cause you to be uncomfortable from the pressure of the probe on your chest or lying still for the examination.

Risks of MUGA scan
This scan involves the risks of radiation (see above). You may develop bruising where the needle is placed in your veins to administer the radioactive substance. You may be uncomfortable lying flat. You may have an allergic reaction to the radioactive substance.

Risks of DLCO
You may feel uncomfortable when your nose is clipped shut or when the mouthpiece is placed in your mouth.

Risk to an Unborn Child
Females:
It is possible that these chemotherapy agents may cause unknown side effects to an unborn child now or in the future due to exposure in the womb. There may also be a risk to the child if he/she is breastfeeding.

If you are a woman who is able to become pregnant, you will need to have a negative pregnancy test before starting treatment. You will not be able to participate in this research study if you are pregnant, or if you are breastfeeding. Your participation in this study requires that you use an acceptable means of birth control throughout the study and for one year after completing treatment. Examples of effective birth control are: a condom or a diaphragm with spermicidal jelly, oral, injectable, or implanted birth control, or abstinence.

If you are a man you must agree to use condoms during intercourse or to remain abstinent during the study and for one year after completing treatment. This is to prevent the possibility of a pregnancy from sperm that might have been damaged by treatment.

If you become pregnant while participating in this study or father a child, you must contact your doctor immediately. Your doctor will advise you of the possible risks to the unborn child and discuss options for managing the pregnancy. Because of possible risks to an unborn child, the study drug will be stopped permanently for pregnant participants.

Some males (ask your study doctor if this applies to you):
You should not father a baby while you are on this study. If you are engaging in sexual intercourse with a woman of childbearing potential, you should use a highly effective method of birth control. Check with the study doctor about what kind of birth control methods to use and for how long to use them. Some methods may not be approved for use during this study. You must tell the doctor right away if your partner gets pregnant. If your partner gets pregnant during the study, you may be asked questions about the pregnancy and the baby.

Unknown Risks
For studies involving experimental treatments, there may be unknown risks associated with the treatment. If you believe you have been injured, or if you have any unusual symptoms, you should report them to the study doctor. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope therapy with OVA will be more useful against your cancer compared to the usual treatment, there is no proof of this. We do know that the information from this study will help doctors learn more about autologous transplantation using OVA as a treatment for lymphoma. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study. This may include autologous transplantation and/or chemotherapy such as RICE (rituximab, ifosfamide, carboplatin, etoposide) or rituximab plus cyclophosphamide. Your study doctor will discuss any available treatment options with you.
- To not receive any therapy at all. You would still be able to receive supportive care or comfort care. This type of care helps reduce pain, tiredness and tries to improve the way you feel without directly treating the lymphoma. You may be able to receive specific lymphoma therapy in the future if desired.
- You may be able to receive other experimental lymphoma treatments either at UCSF or at another facility.

Please talk to your doctor about your choices before deciding if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research and data analysis include:

- Novartis Pharmaceuticals Corporation (the drug supplier) and its authorized agents.
- The U.S. Food and Drug Administration (FDA), National Cancer Institute (NCI), and other government agencies in the United States and other countries, which are involved in keeping research safe for people.
- The Committee on Human Research (UCSF's institutional review board, which is

involved in protecting your rights as a participant in this study)
- The UCSF Helen Diller Family Comprehensive Cancer Center
- The Bone Marrow Transplant Registry, and their representatives
- The University of California

A UCSF medical record will be created as a result of your participation in this study. This consent form, and some of the results from your research tests, will be included in your medical record. Information from your records will be entered in a database. Therefore, your other UCSF doctors may become aware of your participation

California regulations require laboratories to report new cases of HIV, hepatitis B, and hepatitis C infection to the county public health department. The reports include the patient's name, social security number, and other identifying information. Information about these new infections is used to track these diseases statewide and nationwide. Other than this required reporting, your results will be treated confidentially by the study staff. Personally identifying information will not be reported to other departments or agencies

What are the costs of taking part in this study?

Treatments and tests, not standard of care, that are performed strictly because of study participation will be funded by Novartis This will include EKGs, certain FDG-PET and CT scans, biopsy samples for research, DLCO tests, and certain blood tests. The study drug, ofatumumab, will also be provided free of charge by Novartis.

The doctors and hospital will bill you or your insurance company for tests and procedures that are considered part of your usual care, just as they would if you were not participating in this study. This includes chemotherapy infusions and supportive care medications.

It is possible that your insurance company will refuse to pay for these tests and procedures even after you have already received treatment, and you will have to pay for your care. Every attempt will be made to obtain insurance approval for treatment before the study investigations and treatments are administered. You will be given the opportunity to meet with a financial advisor from the hospital to determine the maximum dollar amount that you will be expected to pay.

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

Will I be paid for taking part in this study?

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

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, Dr. Charalambos Andreadis, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her [redacted].

Treatment and Compensation for Injury: If you are injured as a result of this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending upon a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this you may call the office of the Committee on Human Research at (415) 476-1814 or write: Committee on Human Research, UCSF, Box 0962, San Francisco, CA 94143.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, Dr. Charalambos Andreadis, or one of his associates [redacted].

For questions about your rights while taking part in this study, call the office of the Committee on Human Research, UCSF's Institutional Review Board (a group of people who review the research to protect your rights) at **415-476-1814**.

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

CONSENT

You have been given copies of this consent form and the Experimental Subject'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.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled If you wish to participate in this study, you should sign below.

_____	_____
Signature of Patient	Date
_____	_____
Name of Patient	Date
_____	_____
Signature of Person Obtaining Consent	Date
_____	_____
Name of Person Obtaining Consent	Date
_____	_____
Witness (only required if the participant is a non-English speaker)	Date

STUDY SCHEMA

Determination of Eligibility to Enter Study

Step 1: Consolidation chemotherapy/Intensive Mobilization (3-5 weeks)

Ofatumumab (days 0,7,14,21) + Ara-C (days 1-4) + Etoposide (days 1-4)
Neupogen starts day +14
Stem cells collected when WBC >10,000/uL

Interim Assessment at 6 weeks from start of Step 1
If study continuation criteria met, proceed to next step (at least 2 weeks after discharge from step 1)
If disease progresses and

Intent is to proceed to transplantation in the future, proceed to follow-up period starting at three months
No intention for transplantation, follow-up will occur every 3 months by study team for up to 2 years

Step 2: Transplantation (3-5 weeks)

Day -6: Enter hospital, receive BCNU
Day -2: Receive etoposide
Day -2: Receive cyclophosphamide
Day 0: Receive infusion of own stem cells
Day +6: Start Neupogen (G-CSF), until count recovery
Approximately Day 14-21: discharged from hospital

If disease progresses, follow-up will occur every 3 months by study team for up to 2 years

Follow-up period

First month following discharge: “House arrest”, limited contact with people
Monthly (at least) clinic visits
Three months: Response Assessment
Months 6, 12, 24: Clinic visit and response assessment
Telephone or chart review every 6 months for up to 5 years