

MEDICAL RECORD	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY <ul style="list-style-type: none"> • Adult Patient or • Parent, for Minor Patient
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INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0130 PRINCIPAL INVESTIGATOR: Robert Yarchoan, M.D.

STUDY TITLE: Pilot Study of Liposomal Doxorubicin Combined with Bevacizumab Followed by Bevacizumab Monotherapy in Adults with Advanced Kaposi's Sarcoma

Continuing Review Approved by the IRB on 03/13/17

Amendment Approved by the IRB on 06/17/14 (G)

Date posted to web: 04/20/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

This is a research study to gain information on the use of two anti-cancer medications when used in combination to treat advanced Kaposi's sarcoma (KS). The objectives are to gather preliminary information on how well the combination works, and to evaluate the safety of this combination. The first medication is a chemotherapy drug liposomal doxorubicin (brand name Doxil), which is already approved by the US Food and Drug Administration (FDA) for the treatment of KS. The second drug, bevacizumab (brand name Avastin), is a biologic agent that was developed to stop abnormal blood supply to tumors. It is approved by the FDA, in combination with other drugs, for the treatment of breast cancer, colon cancer and lung cancer. However, its use in people with KS is experimental. We are evaluating this combination as a

PATIENT IDENTIFICATION	CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY <ul style="list-style-type: none"> • Adult Patient or • Parent, for Minor Patient NIH-2514-1 (07-09) P.A.: 09-25-0099 File in Section 4: Protocol Consent (1)
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novel approach to the treatment of advanced KS. We will be measuring KS tumor responses to this combination, in an attempt to determine whether the drug might have anti-KS activity that should be explored in further research.

Why are you being asked to take part in this study?

Individuals may be eligible to participate in the research study if they have relatively severe AIDS-related Kaposi's sarcoma, or if they have Kaposi's sarcoma unrelated to AIDS or HIV infection. To be eligible for the trial, patient-volunteers must have KS that can be evaluated for potential response to therapy, and meet a number of other criteria. If you meet these criteria, you are being asked to take part in this study so that we may evaluate this novel combination of liposomal doxorubicin with bevacizumab in people, like yourself, with advanced KS.

How many people will take part in this study?

We plan to enroll 20-26 patient-volunteers in this study.

Description of Research Study

If you consent to participate in this study, you will receive therapy through a vein (IV), starting with an initial dose, followed one week later by therapy every 3 weeks for one year. We will continue to follow you for up to 2 additional years to make sure that your KS does not worsen once therapy is stopped. If your KS worsens during the course of your participation in the study, you may be eligible for additional liposomal doxorubicin and/or bevacizumab within this study.

The treatment for KS in this study will consist of two phases, an induction phase and a maintenance phase. The goal of the induction phase is to rapidly reduce your KS. During the induction phase, you will receive a single dose of bevacizumab followed by 6 cycles of the combination of liposomal doxorubicin and bevacizumab every 3 weeks. The goal of the maintenance phase is to attain further tumor shrinkage and prevent recurrences of KS, while minimizing the amount of liposomal doxorubicin used. In the maintenance phase, you will not receive liposomal doxorubicin, but will continue to receive bevacizumab every 3 weeks for a total of 1 year of therapy. If, during the first phase, you have no evidence of KS after fewer than 6 cycles, we will discontinue the liposomal doxorubicin, and proceed to the second phase of the study.

During the study, we will also be collecting blood and saliva, performing non-invasive imaging studies of your KS for research purposes, and performing 1-3 biopsies both for routine purposes as well as special research into the biology of KS and the effect of the research medications on your body and on the KS tumors (biopsies for research alone are optional). A description of

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what will happen if you take part in this study, as well as a list of potential risks and discomforts associated with participation in the study are listed below.

Due to a shortage of liposomal doxorubicin (brand name Doxil) in the United States, you may receive an alternate imported brand of liposomal doxorubicin (Lipodox). The FDA has approved the temporary use of Lipodox during the national shortage of Doxil.

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

Before you begin the study, you will be evaluated by a physician investigator, as well as other members of the research team for eligibility in the study. We will discuss your medical history in detail and draw blood from a vein and collect a urine sample to determine your eligibility to participate in the study. A biopsy is required for participation. If you have already had a biopsy, we will work with you to have the biopsy sent to pathologists at the NCI for review. If you have not had a biopsy, we will arrange for a biopsy to confirm the diagnosis of KS. You will also undergo special tests of your heart as well as a chest X-ray to make sure that you are eligible to participate and to document whether KS affects your lungs. Additional studies may be required to document the extent of KS, depending on your symptoms.

During the study, you will receive a single dose of bevacizumab followed one week later by both liposomal doxorubicin and bevacizumab every 3 weeks for 6 cycles. Patients with HIV will be required to be taking combination antiretroviral medications. All patients will be required to take a daily baby aspirin to prevent blood clots. During the first cycle, you will be evaluated by a physician prior to therapy, as well as one week later, to answer any questions you may have and to ensure that you are tolerating the therapy. On subsequent cycles, a physician will evaluate you on the day you receive therapy. After the first 6 cycles, you will receive bevacizumab alone. During each cycle, approximately 10 teaspoons of blood will be collected from a vein to be used for laboratory studies that are part of routine care for patients receiving therapy, as well as special research studies. Saliva will be collected during the first cycle, then every 3 cycles afterwards. We will also collect a urine sample every cycle to make sure that the therapy is not damaging your kidneys. If your KS completely disappears, you will be asked to repeat any abnormal tests that you had when you entered the study, including a biopsy. Optional tests will include an additional biopsy for special studies evaluating the effect of therapy on your KS tumor. Part of the evaluation will include measurement of your blood pressure. If your blood pressure is greater than 140/90 on two consecutive visits, you will be started on oral medications to control your blood pressure. After completing the 6 cycles of the combination of liposomal doxorubicin and bevacizumab, you will have a repeat evaluation of your heart.

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On this protocol, you will have periodic conventional photographs made of your lesions. Additionally, three experimental imaging methods will be performed. The three methods are called: 1) laser Doppler imaging, 2) multi-spectral imaging and, 3) infrared thermal imaging. Laser Doppler imaging takes about 3 minutes to perform on each lesion. It uses a low power laser beam that scans across the skin lesion being measured. The instrument does not touch your skin. You may be asked to have a blood pressure cuff put on your arm and have laser Doppler imaging performed before and after the cuff is inflated for a short time (generally less than thirty seconds). We do not believe that this instrument will harm your skin: in standard practice a similar machine is used to measure how deeply severe burns affect the skin. If you stare at a laser light it could harm your eyes, but precautions will be taken so that you will not stare at it. It is also used to assess allergic responses in the skin. However, its use in Kaposi's sarcoma is experimental. The purpose of this experimental use is to attempt to measure the amount of blood flow through the blood vessels in the Kaposi's sarcoma lesions. It will not have a therapeutic effect on the lesions. The multi-spectral imaging exam should take about 2 minutes to perform on each lesion. It uses principles of the way hemoglobin absorbs light. Hemoglobin is a protein in the blood that carries oxygen to your tissues. The light on the multi-spectral imaging instrument is absorbed differently depending on whether the hemoglobin has oxygen attached to it or not. This will allow an estimate to be made regarding the total blood volume, and how much of it is carrying oxygen or not. We do not believe that the instrument will harm you. The technique will not make your Kaposi's sarcoma improve. The thermal imaging takes about a minute to perform on each lesion. It uses a special camera to take digital infrared pictures of your skin. This enables us to form a picture of the temperature of your KS lesions and thus assess the blood flow in the Kaposi's sarcoma lesions. We do not believe that the camera and lights will harm you. These experimental imaging studies will be performed twice during the first cycle then repeated after the sixth cycle and after the last cycle of therapy.

When you are finished taking the drugs, we will continue to follow you in clinic every 3 months for up to 2 years to make sure that your KS does not return or get worse. If the KS should get worse during the observation, a second course of therapy may be possible within the study, and we would discuss further treatment options with you.

The following Study Chart outlines what will happen if you choose to participate.

Screening for Eligibility

- Medical History and Physical Exam
- Review of Biopsy
- Blood and Urine Studies
- Cardiac MUGA and EKG
- Chest X-Ray



Treatment

Induction Phase: IV Bevacizumab once, followed 7 days later by Liposomal Doxorubicin and Bevacizumab every 3 weeks for 6 cycles

Maintenance Phase: IV Bevacizumab every 3 weeks for 11 cycles

Monitoring: Review of side effects
 Physical Exam, including blood pressure
 Blood and Urine Samples
 Cardiac MUGA and EKG after completing induction phase

Research: Blood and saliva samples
 Additional biopsy (optional)
 Non-invasive imaging

Stop treatment: Completion of one year of therapy
 Progressive KS
 Patient preference
 Unacceptable toxicity



After treatment

- Clinic visit every three months or as needed for up to 2 years
- Research blood and saliva samples

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Standard of Care Treatment:

Treatments required for those participating in the study may include standard medications. For example, patient-volunteers who are HIV positive must agree to take combination antiretroviral therapy. Those who develop hypertension while participating in this study will be prescribed blood pressure medications based on national guidelines for the management of hypertension. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. Furthermore, participation in the study may include additional procedures to document the extent of KS in your case. In such a case, you may be asked to sign a separate consent form for any additional treatment procedures not outlined in this consent.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- Intrauterine device (IUD)
- Hormonal [birth control pills, injections, or implants]
- Tubal ligation
- Vasectomy
- Barrier Methods [condoms]

Alternative Approaches or Treatments

People with advanced KS have several FDA approved therapy options for the management of advanced KS. These include liposomal daunorubicin, liposomal doxorubicin, or paclitaxel. Those who are HIV positive should be taking combination antiretroviral therapy. For patients with AIDS-associated KS who are not taking combination antiretroviral therapy at the time of diagnosis, additional therapy may be deferred to see if the KS improves with the treatment of HIV. However, this approach generally takes longer than approaches that incorporate chemotherapy, and may not be appropriate for people with advanced AIDS-associated KS. Patients with limited or mild KS may be treated with radiation therapy, interferon- α , injection of chemotherapy into the KS tumor, or topical treatments.

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

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- 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. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation**What side effects or risks can I expect from being in this study?****Likely (10% or greater incidence)**

- Weakness
- Fever
- Hypertension
- Protein or blood in urine
- Mouth sores
- Nausea
- Nose bleed
- Low platelet counts (increased risk for bleeding)
- Low white blood cells (increased risk for infection)
- Anemia (low red blood cell counts, increased fatigue and mild shortness of breath)
- Infections
- Pain
- Discomfort from blood draws, catheter placement or biopsies

Less Likely (less than 10% incidence)

- Diarrhea
- Vomiting
- Dehydration
- Constipation
- Difficulty swallowing
- Weight loss

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- Asymptomatic abnormalities in liver tests
- Gastrointestinal ulcers (esophagus, stomach, intestine, rectum or anus)
- Gum bleeding
- Bleeding hemorrhoids
- Blood clots (thrombosis) in veins or arteries
- Abdominal swelling
- Leg swelling
- Pleural effusion (fluid collection between ribs and lungs)
- Dizziness

Less Likely (less than 10% Incidence), continued

- Anxiety, depression or panic attack
- Cough
- Herpes outbreak
- Hoarseness
- Kidney dysfunction
- Hair loss
- Rash
- Wound healing complications
- Hand and foot redness (hand-foot syndrome)
- Abnormalities in blood levels of sodium, calcium, potassium, and magnesium or glucose
- Muscle or joints aches
- Cataracts
- Increased tearing
- Elevation in the level of bilirubin (a waste product of the liver), may lead to jaundice or discolored urine

Rare but Serious

- Gastrointestinal perforation
- Fistula formation (abnormal hole or connection between organs)
- Peritonitis (inflammation or infection of the abdominal cavity)
- Hernias at sites of surgery
- Bleeding from lungs, gastrointestinal tract, bladder or vagina
- Bleeding after surgical procedures
- Pancreatitis
- Liver Failure
- Bone marrow failure – Severely decreased red blood cells, white blood cells and platelets
- Severe hypertension with headaches, confusion or other neurological symptoms

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- Stroke
- Chest Pain / Heart Attack / Myocardial Infarction
- Pulmonary Embolism
- Abnormalities in heart rhythm
- Acute pulmonary edema (shortness of breath due to fluid in the lungs)
- Heart failure
- Seizures, confusion, blindness (Reversible posterior leukoencephalopathy syndrome)
- Severe kidney dysfunction
- Acute infusion reaction (pain, low blood pressure, difficulty breathing)
- Death

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental combination of liposomal doxorubicin with bevacizumab followed by bevacizumab alone will cause your KS to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. Because this study includes an effective FDA drug approved for KS, we expect that most participants will have some degree of tumor shrinkage while participating in this study. However, we do not know if the combination of liposomal doxorubicin with bevacizumab will be as good as or better than liposomal doxorubicin alone. We cannot predict whether you will benefit directly from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer. Potential benefits could include shrinking of your KS or lessening of your symptoms, such as pain and swelling, which are caused by the cancer. Additionally, you may require less liposomal doxorubicin than usually needed through participation in this study.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.

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- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board
- Qualified representatives from Genentech, the pharmaceutical company who produces Bevacizumab.

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.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Genentech or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any

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samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases **cannot** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process

<http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf>. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to \$15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using bevacizumab, a drug developed by Genentech, through a joint study with your researchers and the company. This means it is possible that the results of this study could lead to payments to NIH scientists and to the NIH. By law, government scientists are required to receive such payments for their inventions. You will not receive any money from the development of bevacizumab.

Optional Biopsy

A punch skin biopsy will be performed. Prior to the biopsy, you will receive local anesthesia through a small injection into the area of skin surrounding the biopsy site. One or two half-centimeter samples of KS will be removed with a needle during the skin biopsy. You may require a stitch after the biopsy. Risks of the biopsy include local oozing of blood or discomfort. Infection is a rare complication of skin biopsies. The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor biopsy for the research tests in this study.

Yes No Initials _____

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Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials _____

2. My specimens and data may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No Initials _____

3. My specimens and data may be used to evaluate genetic changes in genes called VEGF and VEGF-R. These genes may be involved in one's risk for KS, as well as the way the drug bevacizumab works. NIH researchers are interested in studying these genes, in a preliminary way, in patient-volunteers with KS who are receiving bevacizumab.

Yes No Initials _____

4. Someone may contact me in the future to ask permission to use my specimens and/or data in new research not included in this consent.

Yes No Initials _____

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Robert Yarchoan, M.D., Building 10, Room 6N106, Telephone: 301-496-0328. You may also want to contact the lead research nurse, Ms. Kathleen Wyvill at 301-496-8959. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/
Legal Representative

Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian

Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian

Date

Print Name

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE
FROM MARCH 13, 2017 THROUGH MARCH 12, 2018.**

Signature of Investigator

Date

Signature of Witness

Date

Print Name

Print Name