PRINCIPAL INVESTIGATOR: Robert J. Kreitman, M.D.

STUDY TITLE: Randomized Phase II Trial of Rituximab with Either Pentostatin or Bendamustine for Multiply Relapsed or Refractory Hairy Cell Leukemia

STUDY SITE: NIH Clinical Center

Cohort: *Eligibility*

Consent Version: *09/21/2022*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

This consent form is to determine your eligibility for our study involving treatment with pentostatin plus rituximab versus bendamustine plus rituximab for multiply relapsed Hairy Cell Leukemia (HCL) and Hairy Cell Leukemia variant (HCLv).

Description of Research Study

The primary objective of the study is to determine if response in each regimen is higher than what you might expect from rituximab alone, and to determine which regimen might be better. Before the protocol begins to randomize the patients, it will be necessary to make sure the proposed dose of bendamustine plus rituximab, which has been shown to be safe in a similar form of leukemia, is also well tolerated in HCL. 12 patients will therefore receive bendamustine plus rituximab without being randomized. If toxicity is observed in HCL patients which is more than what we would expect from other leukemia patients, the protocol may need to be changed before patients get randomized. Otherwise, the bendamustine-rituximab dose will be considered appropriate and patients will then be randomized to receive either this dose of bendamustine + rituximab, or pentostatin plus rituximab. If you take one treatment, and either get worse or respond but then relapse, you may then 'cross over' to the other regimen, as long as you are still eligible. If you previously received one of the regimens and did not respond, you may receive the other regimen only and you would not be in the groups that would be compared. We first need to determine if you are eligible for this study.

You may not yet be eligible for our study with pentostatin and rituximab or bendamustine plus rituximab for several reasons, like having a disease which is not considered hairy cell leukemia/hairy cell leukemia variant, or having results of blood counts which are not in the correct range to be eligible. If so, you may still be eligible in the future. Your blood, bone marrow, tumor or other tissue may also be tested for other factors for research purposes. However, this consent does not permit any additional studies that would test for genes (i.e. tendency for diseases) that might be inherited from you by your children.

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

Blood samples will be drawn at your local medical doctor or previously obtained bone marrow samples will be sent to NIH. We may collect up to a half-cup of blood to test for your eligibility and collect research samples for this study. Some of these research studies will be performed under the companion protocol 10-C-0066. You will be asked to sign another consent prior to having any samples collected.

The following tests or procedures are needed to determine whether you are eligible for this trial:

- Medical history: A complete review of your medical history, including obtaining information about your diagnosis and previous treatments, and reviewing information about your other conditions.
- Physical examination including weight and height, and vital signs
- Performance status: an evaluation of your ability to perform everyday activities.
- Lab blood and urine tests, to check for blood counts, organ function, and for signs of infection.
- Pregnancy test in women who can have children. Pregnant women will not be allowed on study.
- Test for hepatitis B and C.

- HIV test. As part of this study, we will test you for infection with HIV, the virus that causes AIDS. If you are infected with HIV, you will not be able to take part in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infections, and the importance of informing your partners at possible risk because of your HIV infection
- Bone marrow biopsy samples, whether they are obtained at NIH or elsewhere, and whether the bone marrow test has already been done or not yet done. Your tumor tissue may be obtained from prior surgeries or from a biopsy that you might elect to have for purposes of determining if you are eligible for this study. Any biopsy or other procedure would be done only if needed and only after you sign an additional informed consent related to the specific procedure.

Specimens to be saved for additional tests

We would also like to draw blood for the following research studies:

- Neutralizing antibodies: Antibodies a patient might make to certain protein drugs which block their effect against cancer cells. You may or may not consider receiving these protein drugs in the future. Requires about 1 teaspoon.
- Cytotoxicity assays. Hairy cells from the blood or bone marrow may be tested outside the body with anti-cancer drugs to determine if they can be killed. Requires 1-3 tablespoons.
- Soluble CD25, CD22, and other tumor markers: Your hairy cells make these proteins and since they fall off the cells and go into the blood, the blood can be tested for them to estimate the amount of hairy cell leukemia cells in your body. Requires about 1 teaspoon.
- HLA (Human leukocyte antigen) typing to better understand the immune system in patients with hairy cell leukemia/variant. HLA is the human leukocyte antigens, a complex of proteins on your white blood cells which allow your body to determine whether the cell is yours or not. Requires about 1 teaspoon.
- Samples of blood to study certain toxicities of other treatments used for hairy cell leukemia/variant, including hemolytic uremic syndrome (HUS). Requires about 1/2 teaspoon.
- Flow cytometry assays, where your hairy cells are tested with antibodies outside your body to determine how much of each tumor marker is present on the hairy cells. In flow cytometry, your blood after being drawn goes into a tiny tube where lasers determine whether the tumor markers are present and, if so, how much. Requires about 1/2 tablespoon.

You will be given the opportunity to decide whether you want to participate at the time of collection.

Assays which could have an impact on both patients and their children, including studies of genetic cancer risk, will not be done. Your research specimens, when sent outside the NIH, will only be identified by the study code, subject number, and date and time of collection.

Risks or Discomforts of Participation

Blood draws

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting and infection.

Urine collection

There is no risk related to urine collection.

Bone marrow aspirate and/or biopsy

This involves inserting a needle into a large bone such as the pelvis and removing a small amount of bone marrow fluid (aspiration) and a sample of solid bone marrow tissue (biopsy). The aspiration is usually performed first with a smaller needle than is used in the biopsy.

A numbing agent that can cause a stinging or burning sensation may be injected at the site of your bone marrow aspiration/biopsy. The needle will go through the skin into the bone and may produce a brief, sharp pain. As the sample is taken from the bone, there may be a brief, sharp pain. This procedure may cause some discomfort, however not all participants experience discomfort. The entire procedure will take about 1 hour to complete. We will call you about 2 days after the procedure to see how you are doing.

The possible side effects associated with a bone marrow aspiration/biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent. Soreness near the site may last for a couple of days after the procedure. You may have more pain, risk of bleeding and bruising if you complete both aspiration and biopsy rather than just the aspiration. If your pain is severe or you develop a fever, please contact the study team immediately.

Local anesthesia

Biopsy may be done under local anesthesia. Potential side effects of local anesthesia include drowsiness, headaches, blurred vision, twitching muscles or shivering, continuing numbness, weakness or pins and needles sensation.

Potential Benefits of Participation

We do not know if you will receive personal medical benefit from allowing us to test your blood or other tissue. However, this testing may make you eligible for our trial of treatment of Hairy Cell Leukemia or Hairy Cell Leukemia variant with pentostatin and rituximab or bendamustine plus rituximab. If you become eligible for our treatment study, you would need to give additional informed consent regarding the risks of the treatment.

Alternative Approaches or Treatments

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

You may choose not to be tested for eligibility or to have any other studies done.

Conflict of Interest (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy

of the COI 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.

The National Institutes of Health and the research team for this study are using Rituximab (Rituxan®) developed by Genentech and Biogen IDEC through a collaboration between your study team and the companies. The companies also provide financial support for this study.

Teva Pharmaceutical Industries is providing Bendamustine (Treanda®) for this study to NIH without charge. No NIH employee involved in this study receives any payment or other benefits from Teva Pharmaceutical Industries.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used 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 do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

The NCI generally does not cover expenses during screening. If you are scheduled for and begin treatment, the NCI will cover the cost for some of your expenses. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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 NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from Genentech and Biogen IDEC, the pharmaceutical company who produces rituximab, and Teva Pharmaceutical Industries, the pharmaceutical company who produces bendamustine.

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.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

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 Kreitman, kreitmar@mail.nih.gov, 301-480-6187. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

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

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.