

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

STUDY NUMBER: 12-C-0151      PRINCIPAL INVESTIGATOR: David S. Schrupp, M.D.

STUDY TITLE: Phase II Evaluation of Mithramycin, an Inhibitor of Cancer Stem Cell Signaling, in Patients with Malignancies Involving Lungs, Esophagus, Pleura, or Mediastinum

Continuing Review Approved by the IRB on 08/06/18

Amendment Approved by the IRB on 10/15/18 (L)

Date posted to web: 10/26/18

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?**

The purpose of this study is to test if giving an experimental agent, called mithramycin, can cause tumors in lungs, esophagus, pleura, or mediastinum to shrink, and to test the safety of the agent.

Mithramycin is an experimental drug which was tested as an anti-cancer therapy in the 1960's and was found to have activity (shrink some tumors) against some forms of cancer but was never broadly accepted as a treatment due to serious side effects. Mithramycin is considered experimental because it has not been approved by the US Food and Drug Administration (FDA) for treatment of your type of cancer. Because of its prior activity, researchers have continued laboratory research on the ability of mithramycin to fight specific cancers. In the laboratory mithramycin is active against cancers of the chest, including lung and esophageal cancer and mesothelioma as well as sarcomas.

PATIENT IDENTIFICATION	<b>CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY</b> <ul style="list-style-type: none"> <li>• Adult Patient or</li> <li>• Parent, for Minor Patient</li> </ul> NIH-2514-1 (07-09) P.A.: 09-25-0099 File in Section 4: Protocol Consent (1)
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None of the first twelve patients evaluated on this study responded to therapy; we believe that this was due to the fact that we were unable to use higher doses of mithramycin because of reversible liver damage in about two-thirds of the patients. However, we were able to determine that the liver damage is only associated with certain changes in the genes, ABCB4, ABCB11, RALBP and CYP8B1 which code for proteins that are involved in bile flow and drug metabolism in the liver. As a result of this, all additional patients enrolled on the study will be those whose genes, ABCB4, ABCB11, RALBP and CYP8B1 are of the type that are not associated with liver damage from mithramycin. By doing this, we hope to be able to administer higher doses of mithramycin more safely.

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

You are being invited to participate in this study because you have cancer and have certain genetic characteristics associated with resistance to liver damage caused by mithramycin that is not shrinking with known effective therapies.

**How many people will take part in this study?**

As many as 57 patients may participate in this study. If you decide to participate, you will undergo a series of tests to make sure you are eligible, including blood tests and scans as described below.

**Description of Research Study****What will happen if you take part in this research study?***Before you begin the study (work up)*

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. These tests will be performed on a separate protocol.

- A medical history
- Physical exam
- Vital signs (blood pressure, pulse, temperature)
- Blood tests
- Urine tests
- Pregnancy test (if you are a woman who could have children)
- Echocardiogram, MUGA, or cardiac MR - tests that check the function of your heart
- We will also do whatever X-rays, CT scans, or other tests are needed to check your tumor

- Review of your tumor tissue to confirm your diagnosis
- A blood test to determine your ABCB4, ABCB11, RALBP and CYP8B1 gene status

*During the Study*

If the exams, tests and procedures show that you can be in the study, and you choose to take part, you will be admitted to the hospital at NIH and given mithramycin through an IV (intravenous – small plastic tube put in a vein in your arm or neck) over about 6 hours. You will receive mithramycin every day for 7 days. If you do not have unacceptable side effects or worsening of your cancer, this treatment can be repeated every 21 days. This is called a cycle. Your dose may be increased after cycle 1 if there are no unacceptable side effects. You will receive the first cycle of mithramycin as an inpatient in the hospital so that we can monitor you carefully for side effects and treat them. You may receive subsequent cycles as an outpatient if your doctor believes this is safe for you.

While you are receiving cycles of mithramycin, you will be watched closely for any adverse effects. You will need to have the following procedures and tests:

- Physical exam every cycle
- Blood tests daily during mithramycin treatment and twice weekly for the rest of the first and second cycles (less often for subsequent cycles)
- Ultrasound evaluation of the liver prior to the beginning of treatment and each time scans and x-rays for tumor evaluation are done (after every 4 cycles)

Scans and x-rays to evaluate your tumor will be done after every 4 cycles

Pharmacokinetic Studies (PKs)

Blood samples will be obtained from you to see how much of the mithramycin is in your blood (pharmacokinetics). These samples are about 3 mL (about ½ teaspoon) of blood each and will be taken before the drug begins, and periodically, up to 10 additional times during and after the first mithramycin infusion (on day 1), and then just before and at the completion of the mithramycin infusion on days 2, 4 and day 7 of your first 2 cycles. A sample may also be obtained 24 and 48 hours after the day 7 dose. Approximately 60 mL (4-tablespoons) of blood will be drawn for PK studies at each of the two cycles.

Biopsy of Tumor Tissue

If a small sample of tumor tissue can be safely obtained, you will be required to have a biopsy of tumor tissue in order to participate in the study. The biopsy may be done by needle (in which a needle is inserted through your skin to collect tumor tissue) or by endoscopy (in which a flexible tube with a camera on the end is used to help view the tumor and collect samples from it). Biopsies will be done under imaging guidance (CT, MRI, or ultrasound as deemed appropriate by the interventional radiologist performing the biopsy). Imaging helps the specialized radiologist know that the needle has been placed into the tumor mass. Typical risks of such procedures

STUDY NUMBER: 12-C-0151

CONTINUATION: page 4 of 12 pages

include, but are not limited to, bleeding, infection, pain, and scarring. You will be counseled in more detail about the procedure, and you will be asked to sign a separate consent form that will describe the procedure and its risks at that time. Your safety is the most important thing at all times. Sometimes tissue can be obtained safely and comfortably with local anesthesia alone. If you require sedation or anesthesia before undergoing a biopsy, you will be informed of the risks and you will be asked to sign an additional consent.

This biopsy will be performed prior to starting treatment and then 8 days (+/- 1) after you have started the second cycle of mithramycin to evaluate the effects of this drug on your tumor tissue.

Biopsies are a very important part of this trial and are done for research purposes, but are not required for your medical care. Willingness to undergo tumor biopsies is required for taking part in this study. No more than two mandatory biopsy procedures will be performed during the study. However, if your tumor exhibits dramatic response to mithramycin, additional biopsies may be requested, but not required. Such biological information is critical for helping determine how the drug is killing cancer cells, and if not, why not.

Trained personnel will perform these biopsies. If any complication occurs, we will offer medical care. If upon attempting the first biopsy procedure, no tissue can be obtained or it has caused you harm, the second biopsy procedure will not be done. After you are enrolled in this study, if for any reason the biopsies cannot be done safely, you can still receive the study drugs but the biopsies will not be performed.

This research study involves exposure to radiation from up to 2 CT scans. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 1.6 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

*Follow up and Evaluation of Experimental Regimen*

Once the mithramycin is stopped, you will need to come back to NIH for evaluation (physical exam and blood work) until you recover from any side effects. Afterwards, you will visit with your local doctor for weekly physical exams and blood work.

**Birth Control**

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. If you become pregnant on the study, you should tell your study doctor or nurse at once and you will be taken off of mithramycin immediately. Further, if the pregnancy is taken to term, the outcome will also be recorded in study records. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study and for at least two months after finishing treatment with mithramycin.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

**Risks or Discomforts of Participation****What side effects or risks can I expect from being in this study?**

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the mithramycin. In some cases, side effects can be serious, long lasting, or may never go away. Rarely there is a risk of death. We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study.

**You should talk to your study doctor about any side effects that you have while taking part in the study.**

*Likely*

- Decreased blood level of calcium
- Nausea or vomiting
- Diarrhea
- Loss of appetite

- Mouth sores
- Decreased platelets (the blood cell that helps blood clot)
- Decreased red blood cells (the blood cells that carry oxygen)
- Abnormal levels of white blood cells (the cells that prevent infection)
- Temporary increase in some liver function studies which should return to normal as soon as the drug is stopped

*Less Likely*

- Bleeding including nose bleed
- Fever
- Drowsiness
- Weakness
- Tiredness
- Pain, redness, soreness or swelling of the area where the IV goes in the skin
- Skin changes, blushing of the face
- Headache
- Mental depression, restlessness, irritability
- Muscle or stomach cramps, possibly due to a low blood level of calcium
- Abnormal levels of blood elements including phosphorus or potassium.
- Increase blood levels of liver enzymes, which may indicate damage to the liver
- Increased blood levels of kidney function tests, such as creatinine, urea or protein

*Rare but Serious*

- Bleeding that may require a transfusion of blood or blood products. Bleeding may result in bloody or black stools, or vomiting blood, or blood nose, or small broken blood vessels under the skin.
- A significant rash called toxic epidermal necrolysis characterized by widespread and severe skin irritation has been reported with mithramycin.

While receiving mithramycin, you should avoid any drugs that contain salicylates, a component of aspirin, such as Aspirin, Bufferin, Ascriptin, Aspergum, Anacin, and some Alka-Seltzer products and some cold preparations, as they may increase the risk of bleeding.

When the WBC is low (neutropenia), fever may be a sign of significant infection. When fever and neutropenia is present, hospitalization for administration of intravenous antibiotics may be necessary.

Because mithramycin may decrease the production of red cells (the part of the blood that carries oxygen and gives energy) and platelets (the part of the blood that helps prevent bleeding), it is possible that you will require transfusions with red cells or platelets. When these transfusions are required will vary from participant to participant and can be discussed with your doctor. Most transfusions have no side effects. However, you may have an allergic reaction (a rash, hives or very rarely, difficulty breathing that can be so severe as to result in death). A separate informed consent will be obtained should you need a blood transfusion.

### **Potential Benefits of Participation**

#### **Are there benefits to taking part in this study?**

The potential benefit of the treatment with mithramycin is that it may cause your cancer to stop growing or to shrink for a period of time. It may lessen the symptoms, such as pain, that are caused by the cancer. It is unlikely that this treatment will cure your cancer. Because there is not much information about the effect of mithramycin on the type of cancer that you have, we do not know if you will benefit from taking part in this study. Information learned from this study may help future patients with cancer.

### **Alternative Approaches or Treatments**

#### **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 (such as hormone therapy and/or systemic chemotherapy).
- 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.

### **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. 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 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.

### **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.
- 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.

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.

### **Certificate of Confidentiality**

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

STUDY NUMBER: 12-C-0151

CONTINUATION: page 9 of 12 pages

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

### **Conflict of Interest**

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. 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.

### **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 the 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.

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MEDICAL RECORD

**CONTINUATION SHEET for either:**  
NIH 2514-1, Consent to Participate in A Clinical Research Study  
NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

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STUDY NUMBER: 12-C-0151

CONTINUATION: page 10 of 12 pages

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.

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PATIENT IDENTIFICATION

**CONTINUATION SHEET for either:**  
NIH-2514-1 (07-09)  
NIH-2514-2 (10-84)  
P.A.: 09-25-0099  
File in Section 4: Protocol Consent

### 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, David S. Schrump, M.D., Building 10, Room 4-3940, Telephone: 240-760-6239. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your tissue for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

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

STUDY NUMBER: 12-C-0151

CONTINUATION: page 12 of 12 pages

<b>COMPLETE APPROPRIATE ITEM(S) BELOW:</b>			
<b>A. Adult Patient's Consent</b> 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	<b>B. Parent's Permission for Minor Patient.</b> 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		_____ Print Name	
<b>C. Child's Verbal Assent (If Applicable)</b> 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			
<b>THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE            FROM AUGUST 06, 2018 THROUGH AUGUST 05, 2019.</b>			
_____ Signature of Investigator	_____ Date	_____ Signature of Witness	_____ Date
_____ Print Name		_____ Print Name	