INSTITUTE: National Cancer Institute

STUDY NUMBER: 12-C-0135 PRINCIPAL INVESTIGATOR: Brigitte Widemann, M.D.

STUDY TITLE: Phase I/II Trial of Mithramycin in Children and Adults with Refractory Extracranial Solid Tumors (Phase I) or Ewing Sarcoma and EWS-FLI1 Fusion Transcript (Phase II)

Continuing Review Approved by the IRB on 01/12/15

Amendment Approved by the IRB on 12/24/14 (E) Date posted to web: 01/22/15

Phase I Portion

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.

If you are signing for a minor child, "you" refers to "your child" throughout the consent document.

Why is this study being done?

The purpose of this study is to test the safety and tolerability of a drug called mithramycin in children and adolescents with solid tumors. Once a safe dose of mithramycin is determined, we will test whether mithramycin can shrink tumors in children and young adults with Ewing sarcoma who have a specific molecular change in their tumor.

Mithramycin is an experimental drug that was tested as a cancer therapy in the 1960's and was found to have activity against some forms of cancer, but was never broadly accepted as a treatment. 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 a variety of childhood solid tumors, and in particular Ewing sarcoma. Prior research studies did not provide doctors with the highest safe dose of mithramycin in children, so in the first phase (Phase I) of this study, we will determine the highest safe dose.

Once the highest safe dose is established, this dose will be used to test if mithramycin is effective in shrinking tumors in individuals with Ewing sarcoma in the second phase of the study. This informed consent is for patients participating in the first phase of the study.

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

You are being invited to participate in this study because you have advanced cancer that is not responding to known effective therapies.

How many people will take part in this Study?

Up to 18 children and adolescents will take part in phase I of the study.

Description of Research Study

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

Before you begin the study

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.

- 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 or MUGA and an EKG, tests that checks 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

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 28 days. This is called a cycle. 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 will also be given dexamethasone every day in order to prevent mithramycin liver toxicity. You may receive subsequent cycles as an outpatient if your doctor believes this is safe for you.

The dose for the first children enrolled on the study will be based on the side effects seen in adults. Between 3 and 6 children will receive mithramycin at each dose. There will be two doses tested in this study. If the side effects are not too severe, the next group of children will receive a higher dose. This is called 'dose escalation'. Whatever dose you start at, your dose will not be increased. If you have bad side effects, the drug will be stopped or delayed. You will be given medicines to help treat any side effects that you might have.

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

- Physical exam every week
- Blood tests daily during mithramycin treatment and then twice a week for the rest of the cycle

Between doses we will ask you to fill out forms to help keep track of any symptoms you may experience and any medications you may take.

Scans and x-rays to evaluate your tumor will be done after every 2 cycles (about 2 months, 4 months, etc).

RESEARCH STUDY TESTS AND PROCEDURES

We would also like to do some extra research tests. These tests will help us learn more about mithramycin and may help children who receive this drug in the future. The information learned from these tests will not change the way you are treated, and the results of these tests will not be returned to you. You can still be a part of the main study even if you say 'no' to taking part in any of the optional biology studies. The maximum amount of blood taken from you is based on your age and will not be more than the blood volume limit set for research by the NIH. We will not draw more than 1 teaspoon of blood for every kilogram (2.2 pounds) of your body weight in a single day and not more than 2 teaspoons of blood for every kilogram (2.2 pounds) of your body weight in an 8 week period. For example, if you weigh 85 pounds (weight of some 12 year olds), your weight in kilograms is about 38 kg; therefore we would not draw more 38 teaspoons (12.5 tablespoons) in one day and not more than 76 teaspoons (or 25 tablespoons) of blood in an 8 week period.

A check box for your decision about taking part in each optional test is provided at the end of this consent form. The following is a description of each of the optional tests.

Pharmacokinetic Studies (PKs)

We want to find out how mithramycin is processed and then cleared from the body. These tests are called pharmacokinetic (PK) tests. They will measure the amount of mithramycin in the blood at different time points during treatment.

If you agree, we would like to obtain blood samples from you. These samples are about 3 mL (about ½ teaspoon) of blood each and will be taken before the drug begins, and at the middle and end of 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 cycle. A sample will also be obtained 24 and 48 hours after the day 7 dose. A total of 24 mL of blood will be drawn (approximately 4-5 teaspoons) will be drawn for PK studies.

Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you.

I agree to have the pharmacokinetic studies performed in this study.

Yes No Initials_____

Pharmacodynamic studies

We would also like to take a small amount of blood for research tests called pharmacodynamic studies (PD). These tests will help us learn more about mithramycin and may help children who receive this drug in the future. The information learned would not change the way you are treated, and the results of these tests will not be given to you. A total of 1 mL of blood will be drawn (approximately 1/5 teaspoon) at the following time points: before the first dose of mithramycin, before the dose at the start of every other cycle. Prior to this blood sample you will need to not eat or drink anything for 10-12 hours. You should also avoid antacids or any medication that helps you have a bowel movement like Reglan, Metamucil, Miralax, for 48 hours prior to the blood test.

The amount of blood we are drawing for research studies is safe to draw even from small children.

Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you.

I agree to have research blood drawn for pharmacodynamic studies performed in this study.

Yes No Initials_____

Archival Tumor Tissue

One of the tests we would like to perform is done on tissue previously obtained from your tumor. It is called immunohistochemistry or IHC and is used to evaluate for NR0B1 expression. NR0B1 is a gene which gives directions (or encodes) for a protein normally found in the body. Mutations or changes in the NR0B1 gene may result in mishappen or nonfunctional proteins, which may lead to certain disorders. We plan to test tumor tissue that was previously obtained during surgery or a biopsy. We will not ask you to have a biopsy to do this test. This is a research test and the information learned will not change the way you are treated, and the results of these tests will not be given to you.

I agree to allow previously obtained tumor tissue to be used for research tests in this study.

Yes No Initials_____

Review of Scans

Copies of the scans used to diagnose your tumors and scans taken to see if your tumor is responding to treatment will be sent to a central review center as part of our quality control program.

We will also have a radiologist review the scans of your tumor to study a new method of measuring the volume of tumors in patients with Ewing Sarcoma. Currently we measure tumor size by two common methods: one method measures the longest length of the tumor, and the second method measures the length and the width, or two dimensions of the tumor. In the proposed scan review, we will compare these two methods with a new method that measures the volume, or 3 dimensions, of the tumor to see which method gives us the best information for determining tumor size.

How long will I be in the study?

You may be in the study until one of the following occur:

- Your tumor gets worse
- The side effects of mithramycin are too harmful for you
- You need a treatment that is not allowed on this study
- You are not able to follow study-related treatment instructions
- New information becomes available that suggests this is not the best treatment for you
- The study is not in your best interest
- The study is stopped

Your doctor may decide to take you off the study drug if any of these occur; you will be told the reason you are being taken off the mithramycin.

When you are finished taking the drugs (treatment)

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, and at least 30 days after the last dose of mithramycin. Afterwards, the study doctor will refer you back to your local health care provider.

Study Chart

Cycle 1		**Subsequent Cycles**	
DAY	**WHAT YOU DO**	**DAY**	**WHAT YOU DO**
Before starting study	Come into the clinic and do the following: • Routine blood tests • Urine tests • Pregnancy test if you are able to have children • Physical exam by your doctor • MRI, PET or CT scan • EKG • Get a disease evaluation that will be done by your doctor. Depending on the results of this evaluation, your doctor will tell you whether or not you may begin this study.		
Day 1	Receive oral/IV dexamethasone (12 hours before study drug) Come to NIH hospital and do the following: • Routine blood tests • Physical exam • EKG • Prior to first dose of study drug receive oral/IV dexamethasone • Get the study drug mithramycin • Twice daily for 24 hours after the last dose of study drug receive oral/IV dexamethasone • Blood drawn before and after mithramycin infusion for PKs • Blood drawn for PD studies if you have Ewing sarcoma (Phase I and II)	Day 1	Come to NIH hospital and do the following: • Routine blood tests • Physical exam • EKG • Get the study drug mithramycin • Twice daily for 24 hours after the last dose of study drug receive oral/IV dexamethasone • Blood drawn for PD studies (Phase I and II) on Cycles 3, 5, 7, 9, 11, and 13.

Days 2-7	• Routine blood tests • Get the study drug mithramycin • Twice daily for 24 hours after the last dose of study drug receive oral/IV dexamethasone • EKG on days 4 & 7	Days 2-7	• Routine blood tests (cycles 2, 3) • Routine blood tests twice weekly (cycles 4 to the end) • Get the study drug mithramycin • Twice daily for 24 hours after the last dose of study drug receive oral/IV dexamethasone • EKG on day 7
Days 1, 2, 4, 7, 8, 9	Blood drawn for mithramycin PKs		
Day 9 to 28	Come into the clinic and do the following: • Routine blood tests twice per week • Physical exam by your doctor every week	Day 9 to 28	Come into the clinic and do the following: • Routine blood tests twice per week (cycles 2 and 3) • Routine blood tests weekly for cycles 4 to the end • Physical exam by your doctor every week
		Every 2 cycles	Come into the clinic and do the following: • Routine blood tests • Physical exam by your doctor • MRI or CT scan • Disease evaluation that will be done by your doctor. Depending on the results of this evaluation, your doctor will tell you whether or not you may continue the next cycle

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 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. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Other medications

There are several medications, such as aspirin or ibuprofen, which are not allowed during participation in this study, as these medications may increase the risk for mithramycin side effects, such as bleeding. It is very important that you contact your doctor prior to starting a new medicine (including herbal or over the counter medications) to check if it is OK to take it. The study team will provide you and your home doctor with a list of medicines, which you should not take.

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
- 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?

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 from a serious side effect. 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.

Side Effects from Mithramycin

Likely

- Decreased blood level of calcium
- Nausea or vomiting
- Diarrhea
- Loss of appetite
- Mouth sores
- Increase blood levels of liver enzymes, which may indicate damage to the liver (which may be severe)
- Increase in LDH, which is an indicator of damage to your cells.

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
- 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)
- Muscle or stomach cramps, possibly due to a low blood level of calcium
- Abnormal levels of blood elements including phosphorus or potassium.
- 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). In addition, although the blood bank that services our patients is excellent, there is at least a theoretic possibility of infections such as AIDS or hepatitis being transmitted by blood. The blood bank is very good at screening for these diseases and the chance of these problems is very small. A separate informed consent would be obtained should you need a blood transfusion.

Side Effects from Dexamethasone

- High blood pressure
- High Blood glucose
- Stomach upset,
- Burning in stomach from excess stomach acid
- Increased risk of infection
- Increased appetite
- Weight gain
- Thinning of bones
- Increase pressure in eyes
- Personality changes, e.g., irritability, euphoria, mania

- Feelings of depression
- Pulmonary tuberculosis
- Vision problems
- Acne, allergic dermatitis, dry scaly skin
- Destruction of bone tissue

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 extremely unlikely that this treatment will cure your cancer. Because there is not much information about the mithramycin effect on cancers in humans, 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.

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 even 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.

Will my 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. 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, quality assurance, and data analysis include:

- Representatives of the National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in overseeing research
- The Institutional Review Board (IRB) of this hospital

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

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.

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.

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/or 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. 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, Dr. Brigitte Widemann at Telephone: 301-496-7387, or Ms. Donna Bernstein, Building 10, Room13C101, research nurse for the study, Telephone: 301-435-7804 . You may also call the Clinical Center Patient Representative at (301) 496-2626. If you have any questions about the use of your specimens and data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

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	**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 consent to take part in this study.	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 Adult Patient/ Legal Representative Date	Signature of Parent(s)/ Guardian Date
Print Name	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 JANUARY 12, 2015 THROUGH JANUARY 11, 2016.

Signature of Investigator	Date	Signature of Witness	Date
Print Name		Print Name	