Protocol Title: A Pilot Phase 2 Study of Eribulin in Angiosarcoma and Epithelioid hemangioendothelioma (EHE)

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Main ICF

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have Angiosarcoma or Epithelioid hemangioendothelioma (EHE). This research study is studying a drug as a possible treatment for this diagnosis.

The name of the study drug involved in this study is Eribulin.

For purposes of this research, you will be referred to as a "participant".

It is expected that about 16 people will take part in this research study.

Eisai, a pharmaceutical company, is supporting this research study by providing the study drug and funding for the research study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational drug to learn whether the drug works in treating a specific disease. "Investigational" means that the drug is being studied.

This research study is a Pilot Study, which is the first time investigators are examining this study drug in participants with Angiosarcoma or EHE.

The FDA (the U.S. Food and Drug Administration) has not approved Eribulin for your specific disease but it has been approved for other uses.

In this research study, we are studying how safe and effective Eribulin is in participants with Angiosarcoma or EHE.

Eribulin was created to mimic the structure of a chemical that is released from a sea sponge. We believe that this drug has anti-cancer effects on tumors by blocking proteins called microtubules, among other functions. It may work by preventing the cancer cells from dividing and eventually cause the tumor cells to die similar to other drugs that target microtubules.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment including chemotherapy.
- Take part in another research study.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Sometimes it is hard to keep track of all of the details and procedures that are part of a research study. We will describe them in this consent form and you can refer to this at any time during the research study.

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, demographics, and any allergies.
- **Physical Exam,** which includes your vital sign, height, and weight measurements.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Blood Tests,** no more than 2 teaspoons of blood will be taken for research purposes.
- **Urinalysis,** for routine clinical purposes
- **Electrocardiogram (ECG),** which measures your heart's electrical activity
- **An assessment of your tumor** by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) or PET (Positron Emission Tomography) scans
- **Biopsy,** this will be used to see how the study drug is affecting your tumor.

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Study Treatment Overview:

- **A medical history.**
- **Physical Exam.**
- **Performance status**.
- **Blood Tests**
- **ECG**
- **An assessment of your tumor**.
- **Biopsy.**
- **Infused Study Drug:** You will be given Eribulin every Day 1 and Day 8 of each 21 day cycle into your vein (by intravenous infusion) over 2-5 minutes. This will continue until your disease gets worse or you are taken off of the study.

Research Study Plan:

	Pre- Study	Cycle 1			Cycle 2+			Off Study
		Week 1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	Week 1 (Day 1)	Week 2 (Day 8)	Week 3 (Day 15)	
Medical History	X	X	X		X	X		
Physical Exam	X	X	X		X	X		X
Performance Status	X	X			X			X
Blood Tests	X	X	X		X	X		X
Urinalysis	X							
ECG	X	X			X[I]			
Tumor Assessment	X	Every 6 weeks for the first 7 cycles (before Cycle 3, Cycle 5, Cycle 7) and then every 9 weeks onward (before Cycle 10, Cycle 13, etc.)						
Biopsy	X				X*			
Eribulin Administration		X	X		X	X		

*: The second biopsy will occur before the first tumor assessment at the end of cycle 2

Planned Follow-up:
We would like to keep track of your medical condition. We would like to do this by having you come into the clinic within 28 days of your last dose. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be on the study treatment so long as you don't have disease progression or until you are taken off of the study treatment.

You may be taken off the research study drug for many reasons including if:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- You are a female and become pregnant or plan to become pregnant
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Eribulin:

Frequent (10% or more chance that this will happen)

- A temporary decrease in the numbers of white blood cells, infection fighting cells (leucopoenia and neutropenia) which may increase the risk of infections. You may require hospital admission and treatment with antibiotics. In some cases infections can be life threatening. Your doctor may prescribe a medication to increase the number of white blood cells if necessary.
- A decrease in the number of red blood cells (cells that carry oxygen). A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- Fever (raised body temperature).
- Damage to the nerves in the arms and legs, which leads to numbness, the feeling of “pins and needles” and/or muscle weakness in the hands and feet. While many subjects experienced improvement of their symptoms following discontinuation of Eribulin treatment, a small number continued to have these problems.
- Nausea and/or vomiting
- Diarrhea
- Constipation

- Hair loss
- Loss of appetite
- Feeling tired and weak (Fatigue)
- Headache
- Pain, in particular back pain, bone pain, muscle pain and pain in extremities

Occasional (Between a 1-10% chance that this will happen)

- Heartburn
- Abdominal pain
- Dry mouth
- Inflammation of the inside of the mouth including the tongue, lips, cheeks and gums
- Decrease in the number of platelets (cells that help the blood clot), known as thrombocytopenia, that may result in bruising or taking longer to stop bleeding
- Difficulty breathing and cough
- Increased risk of infection, such as a urinary tract infection (passing urine more often and/or painful urination) and upper respiratory infections (cough, sore throat, and runny nose). Infections may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.
- Depression (sense and feeling of sadness)
- Difficulty falling asleep and /or staying asleep
- Increase of some blood liver enzymes called AST and ALT, which may indicate damage to the liver
- Decreased levels of potassium in the blood. Low levels of potassium can cause an abnormal heart rate. This could cause an irregular heartbeat, which can be serious and life threatening.
- Decreased levels of magnesium in the blood. Low levels of magnesium could cause weakness and muscle cramping. Rarely, heart rhythm abnormalities may occur.
- Decreased levels of calcium in the blood. Low levels of calcium could cause weakness and/or cramping. When severe, it can cause muscle twitching and/or contractions, abnormal heart beats or seizures.
- Dehydration
- Swelling and build-up of fluid in the limbs
- Muscle cramps/muscle weakness

- Increased production of tears
- Dizziness (lightheadedness)
- Changed sense of taste
- Weight loss
- Mucosal inflammation – irritation of the lining of the intestines and other internal organs.
- Rash, this can involve the skin, eyes, mouth and genitals. The rashes can be serious and life threatening including blisters and skin peeling (Stevens Johnson syndrome, toxic epidermal necrolysis).
- Itching

Uncommon (Less than a 1% chance that this will happen)

- Pneumonia
- Severe life threatening infection with blood poisoning (sepsis). This may or may not be associated with a decrease in the number of white blood cells
- Increase of a liver enzyme in the blood called GGT and increased levels of bile pigment (bilirubin) in the blood, which may lead to loss of appetite, vomiting or nausea, fatigue, abdominal pain, a yellowing of the skin, dark-colored urine and itchy skin. This may indicate damage to the liver.
- Anxiety

Rare (Less than a 0.1% chance that this will happen)

- Allergic reaction that may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, it can be severe or life threatening.
- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.
- Inflammation of the liver, which may cause yellowing of the skin and eyes, nausea, abdominal pain, fatigue, and fever.
- Widespread inflammation of the lungs which may cause chest pain, shallow breathing, shortness of breath, headaches, and muscle aches. This may lead to scarring of the lungs.

Risks Associated with Biopsies:
Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Reproductive Risks:
The drugs used in this research study may affect a fetus. While participating in this research study and for 4 months after, you should not become pregnant or father a baby, and should not nurse a baby. We can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

Risks of Genetic Testing:
There is a risk that your test results could lead to genetic discrimination. A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, this law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. There may be other unknown privacy risks.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.
If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the drug. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You will not be charged for Eribulin.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Brigham and Women's Hospital: (617) 732-5524 or (617) 732-7485
- Dana-Farber Cancer Institute: (617) 632-3455
- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237)

K. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form. The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

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.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital

- Gregory Cote, MD, PhD: (617) 726-8748

Dana-Farber Cancer Institute (DFCI) and Brigham and Women's Hospital (BWH):

- Suzanne George, MD: (617) 632-5204
  24-hour contact: DFCI: Suzanne George, MD at (617) 632-3352 beeper 41224

24-hour contact: Please contact Massachusetts General Hospital at 617-724-4000 and ask that your doctor be paged.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt

under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug used in the study and for the purpose of this or other research relating the study drug and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor of the study, its subcontractors, representatives, business partners, and its agent: DF/HCC
- The funder of the study, its subcontractors, representatives, business partners, and its agent: Eisai
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

O. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant
or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate