INFORMED CONSENT DOCUMENT

Project Title: **A Phase II Trial of Gemcitabine plus High-Dose Ascorbate in Locally Advanced Unresectable or Metastatic Soft Tissue and Bone Sarcomas in Adults**

Principal Investigator: **Varun Monga, MD**

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Research Team Contact: **Michelle Arnold, RN – 319-356-2778**

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have sarcoma in the soft tissue or bone that can't be removed by surgery or has returned after chemotherapy.

The purpose of this research study is to see if high dose ascorbate (Vitamin C) in combination with gemcitabine, a standard chemotherapy for sarcoma, will reduce the size of your tumor. We hope that high doses of ascorbate together with chemotherapy would work better in killing the cancer cells, while minimizing the side effects from chemotherapy.

High dose ascorbate is not approved by the U.S. Food and Drug Administration for any cancer. It is considered investigational for patients with soft tissue and bone sarcomas, which means that it has not been approved by the U.S. Food and Drug Administration.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 29 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement will last for approximately 2-1/2 years. For the first 6 months, you will receive treatment during weeks 1, 2 and 3 of each 4-week cycle. Ascorbate infusions will occur on Days 1, 2, 8, 9, 15 and 16. Gemcitabine infusions will occur on Days 1, 8 and 15. Each visit will last between 3 and 6 hours. After your treatment has finished, you will have followup visits every 3 months until progression of your cancer.

WHAT WILL HAPPEN DURING THIS STUDY?

Before you begin the study treatment

You will need to have some tests done to find out if you can continue to be in the study. Some of these tests are part of regular cancer care and may be done even if you do not join the study treatment. If you have had some of them recently, they may not need to be repeated. This is up to your doctor.

- Physical examination including vital signs.
- ECOG performance status will be assessed by asking you a few questions. This is a scale used to assess how your disease affects the activities of daily living.
- Electrocardiogram (ECG) and echocardiogram or nuclear medicine heart function test to check the function of your heart.
- Blood will be taken to determine blood counts, kidney function, liver function, electrolyte levels, and levels of an enzyme in your blood called G6PD. The result of the G6PD test will be added to your medical record.
- Urinalysis
- Pregnancy test (if you are a woman of child-bearing potential). The results of this test will also be added to your medical record.
- CT scan of the chest, abdomen and pelvis.
- MRI of your arms and/or legs if your tumor is located there.
- You will have blood drawn for research labs prior to the test dose of ascorbate to check the oxidative stress markers in your blood.
- A 15 gram test dose of ascorbate via IV infusion will be administered. If you do have a serious side effect or a significant medical event in the opinion of the study doctor, you will not continue in the study. Your study doctor will let you know if you are unable to continue in the study.

High dose ascorbate may interfere with finger-stick blood glucose readings. If you are using a finger-stick glucometer, you must discuss this with the study doctor. You may not be able to participate in this study.

During your study treatment

If the tests show you can proceed, you will begin receiving infusions of high-dose ascorbate and gemcitabine.

- You will visit your doctor for a physical examination, vital signs and standard-of care labs on Days 1, 8, and 15 of each 28-day cycle, prior to each high-dose ascorbate infusion. You will also return

on Days 2, 9 and 16 for a high-dose ascorbate infusion. Each ascorbate infusion will take approximately 2 hours to complete. You will have 6 cycles of treatment with high-dose ascorbate. You may be able to receive additional cycles of high-dose ascorbate, if you are responding well to the drug, and if your doctor thinks it's in your best interest.

- You will have an infusion of gemcitabine on Days 1, 8 and 15 of each 28-day cycle, after the infusion of high dose ascorbate. Each infusion will last approximately 90 minutes. You will have 6 cycles of treatment with gemcitabine. You may be able to receive additional cycles of gemcitabine, if you are responding well to the drug, and if your doctor thinks it's in your best interest.
- You will have blood drawn for research labs on several occasions, sometimes before your infusion, and sometimes after your infusion. This is to check the ascorbate levels and oxidative stress markers in your blood.
- At the end of Cycles 2, 4 and 6 you will have a CT of the chest, abdomen and pelvis and an MRI of your arms and/or legs if your tumor is located there.
- During your study treatment, you will have 6 visits to the clinic each month, and one extra visit every other month for scans.

<u>After your study treatment</u>

- You will have a follow-up appointment in the Holden Comprehensive Cancer Center about 28 days after your final ascorbate treatment. It is very important you keep this appointment. You will have a physical exam, blood drawn for standard-of-care labs and a CT scan and/or MRI of your tumor.
- Your next follow up appointments will be scheduled every 3 months until progression of your cancer is seen. At these visits you will have a physical exam, blood drawn for standard-of-care labs (first followup visit only) and for research purposes (first followup visit only). You will have a CT scan and/or MRI only if your doctor thinks it's needed. These tests are normal for your cancer care. It is important that you keep these appointments so we know how you are doing. We will also speak with you to see if there are any side effects from the ascorbate.

<u>WHAT ARE THE RISKS OF THIS STUDY?</u>

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Research related risks

Intravenous Ascorbate (Vitamin C)

Serious

- Diarrhea <10%
- Nausea or vomiting <5%
- Kidney stones <5%
- Precipitation of cystine, oxalate or urate crystals in the kidney resulting in kidney damage or failure <1%

Mild

- Dry mouth/thirst (>35%)
- Headache <5%
- Abdominal pain <5%
- Fatigue <5%
- Facial flushing <5%
- Sweating <5%
- Weakness <5%
- Injection site irritation may occur <2%
- Faintness or dizziness may occur with rapid IV administration <5%
- Ascorbic acid infusion may leak outside the vein, resulting in pain and irritation at the site <2%

Medical Imaging

There is a risk that ascorbate could interact with contrast used for medical imaging (CT, PET/CT, or MRI, for example), causing an increase in liver function tests. For this reason, you should let us know if you have any medical imaging scheduled during your chemotherapy / ascorbate treatments. We will not schedule ascorbate treatments on days you are scheduled to have medical imaging.

Blood Glucose Readings

High-dose ascorbate has been shown to interfere with finger-stick blood glucose tests (the finger-stick blood sugar tests diabetics use). We do not know how long after an infusion the ascorbate interferes with these tests.

High-dose ascorbate does not interfere with serum or plasma glucose tests done by medical laboratories (when blood is taken from your vein).

If you need to have your blood sugar checked by a finger-stick test, or a doctor has told you to start checking your blood sugar with a finger-stick test, **you must tell us immediately**. Call 319-356-1616 and ask for the hematology-oncology fellow on call. When the operator connects you, tell the doctor you are participating in Dr. Monga's Ascorbate for Sarcoma study.

Risks from drawing blood

Drawing blood may cause pain, bruising, bleeding or infection at the site of the needle stick. Care will be taken to avoid these complications.

Risks associated with standard chemotherapy

Gemcitabine

Risks and side effects related to gemcitabine include:

Likely Side Effects:

- Nausea and vomiting (69%)
- Anemia or lowered red blood cells (68%)
- Lowered white blood cells, which may make you more likely to get an infection (63%)
- Lowered number of a specific type of white blood cells called neutrophils (63%)
- Abnormal liver function laboratory results which may indicate irritation of the liver (68%)
- Protein in your urine (45%)
- Fever. Fever was frequently associated with other flu-like symptoms and was usually mild. (41%)
- Blood in your urine (35%)
- Rash (30%)
- Lowered platelets (24%)
- Diarrhea (19%)
- Hemorrhage or loss of blood (17%)
- Increased concentration of nitrogen in the blood (elevated BUN lab) (16%)
- Infection (16%)
- Loss of Hair (15%)
- Increased bilirubin or jaundice, which is yellowing of the skin, mucous membranes or eyes which can come from bilirubin, a byproduct of old red blood cells (13%)
- Stomatitis (mouth inflammation) (11%)
- Somnolence (drowsiness) (11%)
- Paresthesia (a sensation of burning, prickling, tingling, or creeping on the skin) (10%)
- Fatigue (8%)

Less likely side effects

- Itching (<1%)
- Constipation (<1%)
- Loss of muscle or nerve function which may cause weakness or numbness (similar to having your hand or leg "fall asleep," and which may be associated with some clumsiness of movement) (10%)
- Allergic reaction (<1%)
- Fluid collection (including swelling of the legs and/or arms), and narrowing of the air passages of the lung(20%)
- Radiation recall (changes to the skin in previously irradiated areas) (<1%)
- Inflammation of the lung tissue (pneumonitis) (<1%)
- Hyperglycemia (<1%)

Rare side effects

- Cardiac dysfunction (<1%)
- Encephalopathy (a disease that can damage your brain) (<1%)
- Renal toxicity (<1%)

Women Capable of Becoming Pregnant

If you are a woman who is capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to your fetus, or risks to your fetus that we did not anticipate, associated with being in the study. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. If you believe or know you have become pregnant while participating in this research study, please contact **Dr. Varun Monga at 319-384-9497** as soon as possible.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because of knowledge gained toward finding a better way to treat sarcoma.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could receive the standard treatment for your disease or opt to be in a different clinical trial.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will have additional costs for being in this research study.

You will not be charged for:

- The study drug (ascorbate). This is provided to you by the study.
- The blood tests done for research purposes only. These are not clinical tests and are provided by the study.

You (and your insurance company) will be charged for:

- Infusion of the study drug (ascorbate). You should check with your insurance carrier about these costs before agreeing to participate
- Gemcitabine and its infusion. This is standard for your cancer.
- Any imaging, including MRI or CT scans. This is standard for your cancer.

- Your doctors' visits and any ordered blood tests. You would have those normally for your cancer care.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The University of Iowa Adolescent Young Adult (AYA) Cancer Program and St. Baldrick's Foundation are providing funding for this research study. This means that the University of Iowa is receiving payments from the AYA Cancer Program and St. Baldrick's Foundation to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from the AYA Cancer Program or St. Baldrick's Foundation for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- the U.S. Food and Drug Administration (FDA)
- The Holden Comprehensive Cancer Center
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will we will keep study documents and binders in locked offices.

Electronic information will be stored on password protected computers. Where feasible, we will use a research ID to minimize using your name. All printed documents are stored in a locked office at the hospital. Any blood samples that we take for research testing are dated and named using your Research ID. They are also stored at the University in a locked room. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your medical record chart that you are participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires your healthcare provider to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study and for your treatment. Once your healthcare provider has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, the U.S. Food and Drug Administration, and the Data and Safety Monitoring Board of the Holden Comprehensive Cancer Center.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes your healthcare provider to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

Varun Monga, MBBS
University of Iowa Hospitals & Clinics
200 Hawkins Drive, C21 GH
Iowa City IA 52242

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

If you decide to leave the study early, we will ask you to discuss your cancer treatment plans with your doctors so that you continue to receive clinical treatment for your cancer. We will also:

- need to take blood samples to make sure your kidneys, liver, and bone marrow are functioning
- meet with you to discuss the side effects, if any, you had from ascorbate

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers or study sponsor might decide to end your participation in this research study earlier than planned. This might happen because you have a bad reaction to the study drug or because in our judgment it would not be safe for you to continue.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Varun Monga, MBBS at 319-384-9497. If you experience a research-related injury, please contact: Varun Monga, MBBS at 319-384-9497. If you are calling after hours or on a weekend, please call 319-356-1616 and ask the operator for the Hematology / Oncology fellow on call. Tell the operator that you are a participant in Dr. Monga's Ascorbate study for Sarcoma.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 05/10/19.

_____ _____
(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)