INFORMED CONSENT DOCUMENT

Project Title: **Phase 1b/2 Neoadjuvant High Dose Ascorbate with Concurrent Preoperative Radiation in Patients with Locally advanced Soft Tissue Sarcomas of Extremity, Trunk and Retroperitoneum**

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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 one of your extremities, your trunk or in the retroperitoneum that can't be removed by surgery and you are a candidate for preoperative radiation therapy.

The purpose of this research study is to see if high dose ascorbate (Vitamin C) in combination with radiation therapy will reduce the size of your tumor. We hope that high doses of ascorbate together with radiation therapy will work better in killing the cancer cells, than either treatment alone.

High dose ascorbate is not approved by the U.S. Food and Drug Administration for any cancer. It is considered investigational for patients with locally advanced soft tissue sarcoma of the extremity, trunk and retroperitoneum, which means that it has not been approved by the U.S. Food and Drug Administration. The combination of high-dose ascorbate and radiation therapy has been shown to be safe and well tolerated in patients with glioblastoma multiforme, but has not been studied in patients with sarcoma.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 35 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 5 years. You will receive treatment with ascorbate three times a week for 5 weeks. You'll also receive radiation therapy during the same 5 weeks. Each visit will last from 2 - 4 hours. After your treatment has finished, you will have follow up visits according to recommended standard of care, for about 5 years.

WHAT WILL HAPPEN DURING THIS STUDY?

COVID-19 Pandemic Adjustments

Due to the coronavirus pandemic (COVID-19), your doctors or study nurses ***may*** choose to skip some research-only tests. These tests are not for safety and do not impact your well-being. These are:

- Ascorbate levels
- Research blood sampling for biomarkers (how the ascorbate affects your body)
- Research-MR imaging (T2*)

You can also decline to have these tests done if you would prefer to reduce your time at UIHC.

Normally, you would have your MRIs and blood tests performed at UIHC for this study. However, due to the pandemic, your doctor may want to you to have these tests done elsewhere. If so, the tests results will be sent to UIHC and reviewed by your cancer doctors. They will also be added to your UIHC medical record.

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.

- Medical history
- Physical examination including vital signs.
- Electrocardiogram (ECG) 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.
- 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. The CT scans done during this study are considered standard of care.
- 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.
- An optional MRI may be done if your tumor is in your extremities and if you agree. This is a research-only procedure done to see if a new type of MRI will be useful in planning for radiation therapy treatment. There will be a place at the end of this consent form to let us know if you agree to this MRI.

- 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.
- If you agree, we would like to take an optional tumor biopsy from you at this time, in order to compare the immune markers on your tumor from before treatment is started to samples we take after you receive treatment. To perform the biopsies, ultrasound will be used to guide a needle into the tumor which will be used to remove a core sample of the tumor. These biopsies will be used for only for research, they will not contribute to decisions about your care. You do not have to agree to this optional biopsy to participate in this study, Please initial your choice below:

_____ Yes, I agree to allow a biopsy of my tumor to be collected prior to receiving any study drug, to be used on this study as well stored for future research.

_____ No, I do not want to participate in the pre treatment biopsy

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.

<u>During your study treatment</u>

If the tests show you can proceed, you will begin receiving treatment.

- You will have blood drawn weekly during the 5 weeks of treatment to check your blood counts, kidney function, liver function and electrolyte levels. You will also have blood drawn for research labs during weeks 1, 3 and 5 as well as when you've finished treatment.
- Physical examinations (including vital signs such as blood pressure and pulse) will be done during visits at weeks 1, 3 and 5.
- You will receive ascorbate infusions three times a week for 5 weeks. You'll also receive radiation therapy daily, Monday – Friday, during the same 5 weeks.
- At various points throughout the study visit you will be asked about changes in your health and/or use of medications.
- Three optional MRIs may be done if your tumor is in your extremities and if you agree. These would be done at the following times:
    - During screening as part of your planning in radiation oncology or as part of a diagnostic MRI if that is being done (listed above in the list of tests done before you begin study treatment).
    - During week 3 of treatment.
    - At the end of the study.

<u>After your study treatment</u>

- You will have a follow-up appointment in the Holden Comprehensive Cancer Center 4 to 6 weeks after your final ascorbate treatment.
- Follow up appointments will be scheduled to see how you are doing, according to the standard of care, for about 5 years or until progression of your cancer is seen.

Tissue/Blood/Data Storage for Future Use

As part of this study, we are obtaining blood samples from you. We would like to study your blood samples in the future, after this study is over. Your sample, information, and/or data may be placed in a central repository or other national repositories sponsored by the National Institutes of Health or other Federal agencies. If this happens, it may be stripped of identifiers (such as name, date of birth, address, etc). Other qualified researchers who obtain proper permission may gain access to your sample and/or data for use in approved research studies that may or may not be related to in the purpose of this study.

The tests we might want to use to study your blood samples may not even exist at this time. Therefore, we are asking for your permission to store your blood samples so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding sarcoma, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your blood samples might be used to develop products tests, or discoveries that could be patented and licensed. In some instances, these may have potential commercial value and may be developed by the Investigators, University of Iowa, commercial companies, and organizations funding this research, or others that may not be working directly with this research team. However, donors of blood samples do not retain any property rights to the materials. Therefore, there are no plans to provide financial compensation to you should this occur.

Your blood samples will not be used for research involving whole genome sequencing.

Your blood samples will be stored *with a code which may be linked to your name and medical record number*. If you agree now to future use of your blood samples but decide in the future that you would like to have it removed from future research, you should contact **Dr. Varun Monga at 319-384-9497**. However, if some research with your blood samples has already been completed, the information from that research may still be used.

A part of the fresh sarcoma tissue removed at the time of surgery will be used to conduct research tests. The tests may include looking for immune cells, amount of iron in sarcoma tissue and genetic tests to understand which cancers responded to the treatment and which did not. The cancer tissue will be stored in wax blocks and may be used for testing in the future. The findings of this research testing will be shared with the scientific community.

Please place your initials in the blank next to Yes or No for each of the questions below:

My blood samples may be stored/shared for future research in sarcoma.

_____ Yes _____ No

My blood samples may be stored/shared for future research for any other purpose.

_____ Yes _____ No

My sarcoma tissue may be used for research tests and stored/shared for future research in sarcoma

_____ Yes _____ No

If you agreed to provide us a tumor sample prior to treatment earlier in this form, it will be kept and stored for future research in the same manner as the samples describe above.

WILL I BE NOTIFIED IF MY DATA\BIOSPECIMENS\IMAGES RESULT(S) IN AN UNEXPECTED FINDING?

The results from the data, samples and images we collect in this research study are not the same quality as what you would receive as part of your routine health care. The data, sample and image results will not be reviewed by a physician who normally reads such results. Due to this, you will not be informed of any unexpected findings. The results of your data, samples and images will not be placed in your medical record with your primary care physician or otherwise. If you believe you are having symptoms that may require care, you should contact your primary care physician.

WHAT ARE THE RISKS OF THIS STUDY?

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%)
- Blood pressure elevation that may result in the need to be treated with medication <10%
- 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%

Radiation Therapy

You will receive radiation treatments in the course of this study. The radiation treatments are considered standard care for your condition. You will receive experimental drug therapy in addition to radiation, because it is thought that the combination may increase the effectiveness of the treatment. This experimental addition of ascorbate may also intensify radiation effects on some normal tissues, and increase the risk of radiation-related side effects. Short-term risks include skin changes such as redness, hair loss, or delayed wound healing; and long-term risks include causing a new tumor. The extent to which the risks of radiation therapy will be boosted by the addition of ascorbate is not known.

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.

Tumor Biopsy

The risks of the tumor biopsy include pain, infection, and bleeding. These risks are similar to the risks of the tumor biopsy you had at diagnosis.

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.

Testing for Reportable Diseases

If you decide to participate in this study, we may test you for Hepatitis B, Hepatitis C or HIV. The results of the test could indicate that you have Hepatitis B, Hepatitis C or HIV. If that happens, we will refer you to a doctor who specializes in treating Hepatitis B, Hepatitis C or HIV. We will make every effort to keep your personal information confidential. However, we are required by law to report positive tests to the Iowa Department of Public Health. Becoming aware of a diagnosis of Hepatitis B, Hepatitis C or HIV could have serious personal and/or social consequences, including difficulty obtaining health insurance or employment. For more information about the risks of Hepatitis B, Hepatitis C or HIV testing, please talk to your study doctor.

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.
- The optional MRIs.
- The optional biopsies.

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.
- Radiation therapy
- Any imaging, including standard 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 expense.

WILL I BE PAID FOR PARTICIPATING?

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

WHO IS FUNDING THIS STUDY?

The Holden Comprehensive Cancer Center is funding this research study. The University and the research team are receiving no payments from other agencies, organizations, or companies to conduct this research 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 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. . Under certain circumstances, the University of Iowa or the Governor of Iowa may determine that all human subjects research must be halted due to COVID-19. If this happens, we will tell you as soon as we are notified. We will work with you and your doctors to ensure your standard cancer care continues.

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 + Radiation 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.

Optional MRIs

The optional MRIs were described earlier in the consent document. Please indicate your preference by initialing in the appropriate place below:

I agree to have the three optional MRIs at screening, during week 3 of treatment and at the end of the study:

_____ Yes _____ No

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: 02/24/23.

_____ _____
(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)