Title: A phase II trial of pharmacological ascorbate with concurrent chemotherapy and radiation therapy

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INFORMED CONSENT DOCUMENT

Project Title: A phase II trial of pharmacological ascorbate with concurrent chemotherapy and radiation therapy

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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 been diagnosed with lung cancer and your doctors recommended radiation therapy with chemotherapy.

The purpose of this research study is to determine if adding high doses of intravenous ascorbate (vitamin C) changes chemoradiation treatment effectiveness and/or changes tolerability. We will also study your blood to see if vitamin C affects blood components.

Ascorbate (vitamin C) is considered investigational as it is being used in this study. This means it has not been approved by the U.S. Food and Drug Administration for this purpose.

How many people will participate?

Approximately 60 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 active treatment will be about 7 to 9 weeks (the length of your radiation treatment). You will have active follow-up visits at UIHC for 2 years but you will have lifelong follow-up for this study.

During your radiation therapy, you will have three extra appointments a week for the ascorbate infusions. This is for the study. The infusion appointments will last about 2 hours. Your radiation treatment will last approximately 7 weeks.

Everyone will have life-long follow-up for this study. That means when you are no longer receiving the ascorbate (the study drug), we will still want to find out how you are doing. We may visit you during

your scheduled cancer treatment appointments or speak with your cancer doctors about how you are doing. If you no longer come to UIHC for your cancer care, we may contact you or any alternative contacts you provide us for this study, the emergency/alternate contact listed in your medical records, or your local physicians to find out how you are doing. If we do not have your current address, we may do an internet-based search to find where you are currently living and may contact you by mail or phone, based on the results of that search.

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)

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

Normally, you would have your CT cans, PET scans, 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 study treatment

You will have blood tests done to find out if you can 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 study doctor.

- Blood tests to determine blood counts, kidney function, liver function, electrolyte levels, iron 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.

Samples to be used later: We will ask you to complete some study related tasks before you begin treatment. If you do not continue with the study, these test results will be shredded and not used.

- Research blood sample. This provides a baseline sample for blood components that we think will change due to treatment. This is optional.

You will have an IV to give you a test dose of ascorbate. This dose is 15 grams, about one-sixth of what you will get for the research treatment. This is to see if you can tolerate the high-dose ascorbate. The results will be added to your medical record.

You will need an infusion port (Infusaport) for this study. This device allows for the safe delivery of ascorbate during the infusions; one of these devices is required because repeated high-doses of ascorbate can irritate veins. An Infusaport is a surgically implanted dome that connects to a large vein.

IMPORTANT: 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**, as you may not be able to participate in this study.

We will provide you a pocket card you can carry with you. You should, or a caregiver, should provide this to a healthcare professional during any treatment you receive away from UIHC.

Study Treatment

If the tests show you can proceed, you will begin chemotherapy, radiation therapy, and the ascorbate infusions. Information about your ascorbate therapy, including the dose and your response to it, will be added to your medical record. This means other doctors can see that you are being treated with ascorbate.

You will receive the same radiation therapy and chemotherapy you would if you were not in this study:

1. You will receive chemotherapy (paclitaxel, carboplatin) once a week, every week, during your radiation therapy.
2. You will receive radiation therapy once a day, Monday through Friday. You will have breaks for weekends and holidays.
3. You will receive ascorbate infusions three times a week
   - Each dose is 75 grams and takes about 2 ½ hours total
   - We will schedule the appointments for you. They will be in radiation oncology or the Cancer Center's infusion center
   - You will have your blood pressure taken before and after each ascorbate infusion. If your blood pressure is too high, you may need to see a doctor before you can leave.
   - If you do not feel well, or have a reaction to the ascorbate, you may need to stay longer. If this happens, you will stay until the doctor decides you are able to leave.
   - We will draw blood to check ascorbate levels after your first infusion, after your first week of infusions, about midway through your therapy, and the last ascorbate infusion you receive. These results will not be added to your medical record.
4. You will meet with your radiation doctor once a week find out how you are doing. This is standard for your cancer. The research nurses will also meet with you to discuss how you are feeling and if you are experiencing any problems or have any concerns or questions.
5. You will have blood tests standard for your cancer care. They check how your kidneys, liver, and bone marrow are functioning.

After your study treatment

We will schedule a follow-up appointments in UIHC-Radiation Oncology at 4 weeks, 6 months, 12 months, and 2 years after you complete radiation therapy. **It is important you see your radiation doctor at these visits to evaluate side effects from radiation.** Side effects from radiation can take months or even years to develop.

At each of these visits, you will be seen by your radiation doctor. This is standard for your cancer. The research nurses will also meet with you to discuss how you are feeling and if you are experiencing any problems or have any concerns or questions.

You will have a PET/CT scan to find out how your cancer responded to treatment about 3 weeks after completing radiation. This is standard and will be entered in your medical record.

You will have pulmonary function tests at about 6 and 12 months after you complete your radiation therapy. This is also standard for your cancer and will be entered into your medical record.

If you receive care locally, we will ask you to sign a release of information so we can obtain copies of those medical records if we think they are relevant to your study treatment.

You will have life-long follow-up for this study.

Optional: Research Blood Samples

We want to know how the cancer treatments affect your body in addition to the standard clinical tests your doctors order. We are interested in learning if there is a molecule or marker (biomarker) that can predict how the treatment works for patients. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

We are asking you provide about 1 to 2 teaspoons of blood at the following times:

- Before starting treatment
- Midway through your radiation treatment (week 3 or 4 of radiation)
- During the last week of radiation treatmentIf you end treatment early
- About 3-4 weeks after you complete radiation therapy (about the time of your PET/CT scan)

These samples are different than the blood samples we take to check your ascorbate levels.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please initial your answer.

_____ Yes, I choose to provide a blood sample at each appointment

_____ No, I choose not to provide a blood sample. This will not affect my treatment under the study or treatment I would otherwise receive.

Tissue/Blood/Data Storage for Future Use

As part of this study, we are obtaining blood from you. We are also obtaining your medical images (X-rays, CT, MRIs, and PET scans, for example). If you have further surgery, we would also like to get a sample of any tumor tissue. We would like to study your blood, tumor tissue, and medical images in the future, after this study is over.

The tests we might want to use to study your blood and tumor tissue may not even exist at this time, and may not be related to lung cancer. The methods we might want to use to study your images may not be known at this time. We are asking for your permission to store your blood, your tumor tissue, images,

treatment records and link them to the outcomes of your treatment so that we can evaluate them in the future.

These future studies may provide additional information that will be helpful in understanding lung cancer or other human diseases, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your blood and tumor tissue might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

If you agree now to future use of your blood and tumor tissue, but decide in the future that you would like to have it removed from future research, you should contact Dr. Bryan Allen at (319) 356-3693. However, if some research with your blood and tumor tissue has already been completed, the information from that research may still be used.

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

My blood may be used for future research.

_____ Yes_____ No

My tumor tissue (if available) may be stored/shared for future research.

_____ Yes _____ No

My medical images may be stored/shared for future research.

____ Yes ____ No

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)

Mild

- Dry mouth/thirst (>35%)
- Transient blood pressure elevation (≥ 35%)
- Chills (thought to be related to the cool temperature of the IV solution) (>35%)
- Headache <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%

- Abdominal pain <5%
- Increase in iron levels which could potentially cause liver damage
- Risk of gout, gout-like symptoms, or exacerbation of existing gout (<2%)

Serious

- Diarrhea <10%
- Hypertensive urgency (<5%)
- Seizure associated with infusion (<5% - this has occurred only in patients with brain cancers)
- Nausea or vomiting <5%
- Kidney stones <5%
- Deposits of crystals in the kidney resulting in kidney damage or failure <1%

Infusion of ascorbate may increase the risks of your standard chemotherapy.

Infusa-Port

For this study, you will need to get a Port (Infusa-Port). This is routine in patients undergoing a lot of chemotherapy. This will reduce the need to routinely use needles to infuse drugs or draw blood.

When you have the Port placed, you will most likely experience some discomfort and soreness afterwards. That will go away. There is also a small risk of infection, bleeding, or collapsed lung from the Port placement. The doctors and nurses will review with you how to take care of the Port so that risk is reduced.

Glucose Readings

High dose ascorbate (like you are receiving for this study) has been shown to interfere with finger – stick blood glucose readings. It creates a false (fake) high value. This means after you receive the ascorbate infusion, a finger-stick glucometer would show very high levels of blood sugar, even though your blood sugar is normal. This is also true for a urine analysis. Your urine would show high levels of sugar in it because of the ascorbate. We do not know how long these false readings last.

It is important that you tell your doctor right away if another doctor has requested you monitor your blood sugar or test your urine. Also, if you see another doctor, it is important to let him or her know that a finger stick or urinalysis might have false values.

If you or your doctors have questions, please call (319) 356-1616 and ask for the radiation oncology resident on-call. When they connect you, please tell them you are participating in Dr. Allen's Vitamin C XACT Lung study and you have questions about blood sugar levels.

Radiation Sensitization

You will receive radiation treatments in the course of this study. The radiation treatments are considered standard of care for your condition. This experimental addition of ascorbate may also intensify radiation effects on some normal tissues, and increase 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 ascorbate is not known.

We will closely monitor you for any unforeseen side effects that result from the interaction between the radiation therapy, the chemotherapy, and ascorbate (vitamin C).

Financial Risk

Not all insurance companies allow participation in clinical trials. Your insurance company may change your co-payments or deny payment if you participate in a clinical trial. To help reduce this risk, we will contact your insurance company to determine if they cover clinical trials – but this is not a guarantee of payment. You may also have additional healthcare costs if you have a side effect from the ascorbate.

Confidentiality and Clinical Trials

By participating in a clinical trial, there is a risk of loss of confidentiality of your medical information. We will protect your confidentiality as described in the "What About Confidentiality" section of this document.

Risks associated with standard therapy

You would have these risks even if you were not participating in the study. They are related to the therapies and treatments that are standard for your cancer.

Carboplatin

Likely

- A decrease in white blood cells, which could lead to infection
- A decrease in platelets, which could lead to bleeding
- Nausea and/or vomiting
- Diarrhea
- Fatigue
- Loss of hair
- Temporary changes in blood tests which measure kidney or liver function
- Low sodium in the blood, which could result in bloating and puffiness in the face and fingers, nausea, vomiting, muscle weakness, headache, and disorientation
- Low magnesium in the blood, which could result in increased irritability of the nervous system with spasms of the hands and feet, muscular twitching, and cramps
- Low calcium in the blood, which could result in numbness or tingling around the mouth or in the feet and hands, as well as in muscle spasms in the face, feet, and hands
- Low potassium in the blood, which could result in muscle weakness, cramping, muscle limpness, and/or irregular heartbeat

Less Likely

- Weakness, loss of strength
- Pain
- Mouth sores
- Tingling, numbness, burning pain in hands and feet, which may be persistent or permanent
- Inflammation of the lung, which could lead to cough and shortness of breath

Rare but serious

- Blurred vision
- Hearing loss
- Allergic reactions
- Irregular heartbeats
- Shortness of breath
- Hemolytic-uremic syndrome (HUS), a disorder that results in the destruction of red blood cells and platelets with decreased kidney function

- A risk of developing a second cancer unrelated to the treated lung cancer, which may occur months or years after initial treatment
- Death

Paclitaxel

Likely

- Low pulse
- Low blood pressure
- Loss of hair
- Tingling, numbness, burning pain in hands and feet
- A decrease in white blood cells, which could lead to infection
- A decrease in platelets, which could lead to bleeding
- Skin redness or rash
- Fatigue
- Nausea and/or vomiting
- Mouth sores
- Diarrhea
- Anemia, a lower than normal number of red blood cells
- Swelling of the legs, arms, or feet
- Cardiovascular changes on EKG (test that measures electrical signal of heart)

Less Likely

- Injection site reaction
- Blurred vision
- Skin or nail darkening
- Aches and pains in muscles and joints
- Fever

Rare but serious

- Temporary changes in blood tests measuring liver function
- Abnormal heart rhythms, which could be life threatening
- Severe allergic reactions
- Temporary “bright spots” in vision
- Severe rash called “Stevens- Johnson Syndrome” that can cause fever and severe eruptions of blisters which can occur on the skin of the trunk of the body, mouth, eyes, and genitals
- Death

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 cannot participate in this study if you are pregnant. 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 Bryan Allen, MD at 319-353-8836 as soon as possible.

What are the benefits of this study?

You may or may not benefit from 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 lung cancer tumors.

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 tumor (chemotherapy and radiation) 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 ascorbate drug (the study drug). This is provided to you by the study.
- You will not be charged for the glucose-6 phosphatase dehydrogenase (G6PD) test. The study will pay for this.
- You will not be charged for the blood tests to determine the ascorbate levels in your blood. These are not clinical tests and are provided by the study.

However:

- You (and your insurance company) will be charged for the infusion of the study drug (ascorbate).
- You (and your insurance company) will be charged for the placement of the central catheter (PICC) or an infusion port (Infusaport) being used to infuse the vitamin C.
- You (and your insurance company) will be charged for the Carboplatin and Paclitaxel. This is standard for your cancer.
- You (and your insurance company) will be charged for your radiation therapy. This is standard for your cancer.
- You (and your insurance company) will be charged for your doctors' visits and any other blood tests. You would have those normally for your cancer care.
- You (and your insurance company) will be charged for the imaging required to plan radiation therapy. This is done once before treatment and during week 4 of your radiation therapy. This is standard for your cancer.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses. **You must check with your insurance carrier** about these costs before agreeing to participate. **Some health insurance companies do not allow clinical trial participation.** If your insurance company denies participation in clinical trials, **you are held liable for any charges they will not pay.**

Will I be paid for participating?

You will receive one $15 gift card to use at the UIHC cafeterias each week you receive ascorbate infusions during your radiation and chemotherapy treatment. The study will also provide parking for you.

Who is funding this study?

The National Institutes of Health (NIH) and McGuff Pharmaceuticals, Inc. are funding this research study. This means that the University of Iowa is receiving payments from NIH or McGuff Pharmaceuticals 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 NIH or McGuff Pharmaceuticals 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 National Institutes of Health (NIH),
- The National Cancer Institute (NCI)
- McGuff Pharmaceuticals, Inc.,
- 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. The research ID does use your initials. All printed documents are stored in a locked office at the hospital. Any blood and tissue 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 health care 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 health care 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, the National Institutes of Health, McGuff Pharmaceuticals, Inc., 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 health care 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:

Bryan G. Allen, M.D., PhD
Department of Radiation Oncology, University of Iowa Hospitals and Clinics
200 Hawkins Drive, 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 may also obtain blood tests to make sure you are doing okay. We may ask if there is a specific reason why you no longer want to participate. If you don't want to discuss it, that's okay.

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 might decide to end your participation in this research study earlier than planned. This might happen because your disease has gotten worse or because you had a reaction to the ascorbate treatment. 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, contact:

Bryan Allen, MD, PhD at 319-356-3693

If you believe you are developing any side effects, or are having symptoms that you are concerned about, please contact:

Bryan Allen, MD, PhD
(319) 356-7601 *telephone* (Monday through Friday, 8 a.m. – 5 p.m.)
tell the nurse that you are a participant in Dr. Allen's Vitamin C study for lung cancer.

If you experience a research-related injury, please contact:

Bryan G. Allen, MD, PhD
(319) 356-7601 telephone (Monday through Friday, 8 a.m. – 5 p.m.)

or

(319) 356-1616 (24 hour telephone number)
Tell the operator you are a research subject. Ask for the Radiation Oncology resident on call and tell them you are a participant in Dr. Allen's Vitamin C study for lung cancer.

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: 07/28/26.

_____ _____
(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)