FOR IRB USE ONLY
APPROVED BY: IRB-01
IRB ID #: 202303162
APPROVAL DATE: 10/10/24

INFORMED CONSENT DOCUMENT
Main

Project Title: Assessing the Immunomodulatory Effects of Pharmacologic Ascorbate with Durvalumab (MEDI 4736) in Non-Small Cell Lung Cancer: A window of opportunity trial

Principal Investigator: **Muhammad Furqan MD 319-353-8155; (or after hours at 319-356-1616)**
University of Iowa Hospitals and Clinics
200 Hawkins Drive
Iowa City, IA 52242 USA

Research Team Contact: **Mimi McKay 319-353-8155; (or after hours at 319-356-1616)**

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 stage I Non-Small Cell Lung Cancer (NSCLC) that was found to be suitable for surgery as a first line treatment.

The usual treatment for your disease is to remove the tumor with surgery, and then evaluate after surgery if other additional treatments such as chemotherapy or targeted therapy are needed.

The purpose of this research study is to compare three different ways of treating stage 1 NSCLC, to see if adding treatment before surgery can reduce the chance of the tumor recurring after surgical removal.

In this study, patients will be randomly assigned to one of three treatments:

- Durvalumab followed by surgical resection of the tumor.
- Durvalumab plus ascorbate (also known as vitamin C), followed by surgical resection of the tumor.
- Surgical resection alone. No therapy prior to surgery. This is the same as standard care for your disease.

Durvalumab is a type of immunotherapy, which means it is intended to help the immune system to attack the tumor. Durvalumab has been FDA approved for the treatment of other cancers, including

stage III NSCLC after chemo-radiation, extensive stage small cell lung cancer, and locally advanced biliary tract cancer, however, durvalumab has not been FDA approved for Stage I NSCLC, which means the way it is used on this study is investigational.

Ascorbate (vitamin C) is used as an immunomodulator, which means it is intended to boost the effects on the immune system. Ascorbate (vitamin C) is considered investigational as it is being used in this study, because it is not FDA approved for the treatment of any cancer.

HOW MANY PEOPLE WILL PARTICIPATE?

Up to 100 people will be screened to be in this study, and of those, we plan to enroll 36 patients to the treatment arms.

HOW LONG WILL I BE IN THIS STUDY?

Your participation in this study will last approximately 3 years. The exact number of study center visits will depend on which study arm you are assigned.

This research study is split into 3 periods:

- Screening Period: may last for up to 42 days
- Treatment period:
    - If you are assigned to a study group receiving treatment before surgery you will have study treatment for 4 weeks, then you will be scheduled for surgery.
    - If you are in the group receiving the standard care, then you will have surgery without receiving treatment prior.
- Follow-up: You will be followed for 3 years after your surgery. The visits will be more frequent for the first year of follow up, for years 2 and 3 they will be every 6 months.

WHAT WILL HAPPEN DURING THIS STUDY?

Most of these tests and procedures are standard of care for your disease and will be done even if you are not in this study; they will not be repeated for study purposes. The results of these will be used in our research.

The study visits are outlined in further detail below.

Screening

The following procedures will be performed during the Screening Visit, if not already done for your regular care:

- Medical history and demographics
- Physical exam with vital signs, weight, and height
- ECOG Performance Status (an assessment of how well you are functioning)
- 12-lead ECG
- We will collect your tumor biopsy results including PD-L1 result (if this was performed)
- Review of prior/current medications
- Urine sample for urinalysis

- Pulmonary function tests
- CT or PET/CT to assess disease status
- Brain MRI or CT
- Blood will be for the following clinical laboratory tests:
    - CBC (complete blood counts with differential)
    - Clinical chemistry including liver function test
    - Thyroid function tests
    - Pregnancy test (for women of childbearing potential only)

If the results of our screening tests show that you are eligible to continue to study treatment, you will be randomly assigned to receive one of the three study treatments, either:

- **Arm A:** will receive durvalumab 1500 mg two times, 3 weeks apart.
- **Arm B:** will receive ascorbate 75 g intravenously three times a week for 4 weeks, as well as durvalumab 1500 mg two times, 3 weeks apart.
- **Arm C:** will receive surgery on the usual schedule, will not receive any therapy before surgery.

This means that whichever study treatment you receive will be determined purely by chance, like flipping a coin. You will have a **1 out of 3** chance of being assigned to either Arm A, Arm B, or Arm C.

You will begin study treatment within 7 days of being randomized to a study arm.

Treatment
Some of these procedures are the same as were done for screening. If they were done in the last 7 days for screening, they may not need to be repeated for the first day of treatment.

For Patients in Arm A or Arm B:

Durvalumab: for patients randomized to Arm A & B – You will have durvalumab 1500 mg by IV infusions (through a needle in your vein) over 60 minutes on the first day of Week 1 and Week 4 of the study.

On the days you receive durvalumab infusions, during your clinic visit you will also have the following procedures:

- Physical exam with vitals and weight
- ECOG Performance Status (an assessment of how well you are functioning)
- Blood tests to monitor your health
- Blood will be drawn for research tests
- We will ask you questions about any side effects
- We will ask you about any other medications you are taking.

For patients in Arm A and Arm B, surgery to remove the tumor will be scheduled to occur weeks 5

to 9.

For Patients in Arm B:

Ascorbate infusions: for patients in Arm B only- In addition to the durvalumab infusions, you will also have ascorbate infusions 3 times a week for 4 weeks. These infusions are expected to take 120 minutes however, this may be longer if the infusion is interrupted or your doctor decides you need to receive the drug more slowly. These infusions will start on the same day as you start durvalumab, or after if needed. These can be consecutive days if the study treatment starts in the middle of the week or later part of the week.

You will also have blood drawn to monitor your health on days you have ascorbate infusions.

For Patients in Arm C:
Your surgery will be scheduled without delay, as it would be with usual care. The usual wait time at the University of Iowa is 6 weeks from the time of diagnosis to surgery, due to operating room scheduling.

You will have one study visit prior to surgery, to collect blood for research tests.

Follow up after surgery:

All patients will have a study visit 30 days and 90 days and 6 months after surgery At each of these visits, the following will occur:

- Physical exam, vitals and weight
- ECOG Performance Status
- Blood tests to monitor your health
- Blood will be drawn for research tests
- CT or PET/CT to assess disease status (only at 90 days post-surgery)
- We will ask you questions about any side effects
- We will ask you about any other medications you are taking.

Long Term Follow up:

You will be followed for survival or disease progression for 3 years. This will not be a study visit, rather we will check your medical chart, or we may call or email you to see how you are doing.

Lost to Follow Up
If for some reason your study doctor loses contact with you, we will make the following effort to regain contact with you by attempting to contact you or your emergency contact via phone on three occasions over a 6-week period. If unsuccessful, a certified letter will be sent to your last known mailing address. If there is no response to the certified letter, you will be considered lost to follow-up and withdrawn from the study.

If you withdraw your permission to any type of follow-up noted above, you must do so by contacting the Research Team Contact listed on page #1 of the consent document.

WILL I BE NOTIFIED IF MY DATA, TUMOR SAMPLES, BLOOD TESTS, OR IMAGING TESTS RESULT IN AN INCIDENTAL FINDING?

We may learn things about you from the study activities and tests that have nothing to do with the research or your tumor but that could be important to your health. If this happens, we will tell you about any findings of possible clinical significance. However, these tests are being done for research purposes, not for evaluating your health or detecting disease. If you are having any symptoms that you think require medical attention, you should see your doctor.

There may be benefits to learning about these incidental findings, such as early detection and treatment of a medical condition. But there are also risks, such as discovering an apparent abnormality, which on further testing turns out to be nothing important. This is a risk because you or your insurance company will have to pay for this testing. The research study will not cover the costs of any tests or consultations related to the evaluation of incidental findings.

WHICH PROCEDURES ARE CONDUCTED PURELY FOR RESEARCH IN THIS STUDY?

Throughout the course of this study, we are asking you to undergo certain procedures which are for research purposes only and may pose additional risk to you. These research-only items are listed below and the related risks are outlined in the risk section that follows.

- The ascorbate and durvalumab is being used purely for research purposes during this trial
- Blood that is collected for research tests

Tissue/Blood/Data Storage for Future Use

As part of this study, we are obtaining blood and tumor tissue from you. We will study your blood and tumor tissue for other research questions, 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 will be sent without any 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 the purpose of this study.

Blood cells removed from the blood samples may be used to conduct whole genome sequencing. Cell lines are produced by growing blood cells in a laboratory and allow us to have a source of the DNA without having to redraw your blood. These blood cells can be stored for decades or more. The DNA, and\or genome sequencing results and data will be made available to researchers trying to learn more about the cause of diseases.

Each of the cells in your body contains DNA. DNA is the instruction manual that determines your appearance in things like eye color or how tall you can be. Your DNA may also lead to higher or lower risk of certain diseases. Your environment will also determine some of your disease risk.

Your DNA is a string of four building blocks, called "bases." These bases are represented by the letters G, A, T, and C. There are billions of these letters strung together in every human's DNA and they are arranged in packages like words. Each of these "words" have specific jobs in the body. Most of the time the letters are the same in everyone. But about 1% of the population might have an "A" where someone else has a "G." This difference can explain why some people have blue eyes and others brown eyes, or why some have a high risk for a certain cancer and others a low risk. All these letters come together to create your "genome sequence", a kind of book of your genetics. It's now possible to read off each of these letters and read your complete genome sequence. Your DNA sequence is unique to you. You inherit your DNA in almost equal parts from each of your parents. In very rare cases, your genome can also change through "mutations." A mutation is like if you tried to copy a page from a book, but misspelled some words. Mutations usually result from copying errors that occur in certain letters when being passed from parent to child.

When we take a sample of your blood/tissue for this study, it will go to a lab to read off those letters and give us a report on your genome. This information will then be compared with other genomes to see how they may be the same or different. It is our hope this will help us to better understand how the human body works and/or what causes it to not work well, as when someone has a disease.

The tests we might want to use to study your blood and tumor tissue may not even exist at this time. Therefore, we are asking for your permission to store your blood and tumor tissue so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding NSCLC, 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, 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, organizations funding this research, or others that may not be working directly with this research team. However, donors of blood and tumor tissue 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 and tumor tissue will be stored labeled only with a code which will be linked to your identity. 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 Muhammad Furqan MD 319-353-8155. However, if some research with your blood and tumor tissue has already been completed, the information from that research may still be used.

Genetic Research

One purpose of this study is to look at genes (DNA) and how they affect health and disease. Genes are the instruction manual for the body. The genes you get from your parents decide what you look like and how your body behaves. They can also tell us a person's risk for certain diseases and how they will respond to treatment.

Genetic Information Nondiscrimination Act (GINA)

A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Based on this new law, health insurance companies and

group health plans are prohibited from requesting your genetic information that we get from this research. This means that they may not use your genetic information when making decisions regarding your eligibility for insurance coverage or the amount of your insurance premiums. Be aware that this new federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. The law also does not prohibit discrimination if you are already known to have a genetic disease or disorder.

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.

Risks of Ascorbate:

Serious: (These risks were grade 3 which means they were considered serious in these instances)

Common (10% or more patient experience)

- High blood pressure that requires treatment

Rare (less than 3% of patients experienced)

- Nausea
- Diarrhea
- Kidney stones
- Atrial fibrillation (irregular heartbeat)
- Fatigue
- Edema limbs (swelling of the limbs due to excess fluid)

Mild:

Common (10% or more of patients experience)

- High blood pressure
- Dry mouth
- Nausea
- Low sodium levels in the blood (Hyponatremia)

Uncommon (3% to 9.9% or more of patients experience)

- Abdominal pain
- Joint or muscle pain
- Dizziness
- Chills
- Edema limbs (swelling of the limbs due to excess fluid)

- Faintness or dizziness may occur with rapid IV administration
- Low level of calcium in the blood
- Low level of potassium in the blood
- Low level of magnesium in the blood
- Low blood pressure
- Reaction at the injection site
- Sensory neuropathy (feeling of numbness, prickling or tingling in the body)
- Sweating
- Weakness

Rare (less than 3%)

- Anemia (low levels of healthy red blood cells)
- Blurred vision
- Bronchopulmonary hemorrhage
- Cognitive disturbance
- Dehydration
- Dyspnea- Shortness of breath
- Flushing
- Hiccups
- High level of sodium in the blood
- Increase in liver enzymes AST/ALT
- Infusion-related reaction
- Injection site irritation
- Kidney injury
- Oral dysesthesia (A burning feeling in the mouth)
- Rash
- Sinus tachycardia (heartbeat faster than normal)
- Sore throat
- Tinnitus (ringing in the ears)
- The ascorbic acid infusion may leak outside the vein, resulting in pain and irritation at the site

Blood Glucose Readings with Ascorbate

High-dose vitamin C (Ascorbate) has been shown to interfere with finger-stick blood glucose tests (the finger-stick blood sugar tests diabetics use). 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. 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 are assigned to Arm B it is important that you tell your doctor right away if another doctor has requested you monitor your blood sugar. Also, if you see another doctor, it is important to let them know that a finger stick might have false values.

High Iron markers with Ascorbate:
High dose vitamin C (Ascorbate) mobilizes and interacts with iron markers in the body which temporarily increase blood iron markers including "Ferritin" and "transferrin Iron saturation" on blood tests. These makers usually normalize after few weeks or months of completing high dose vitamin C infusions. These temporary changes in the blood do not result in any organ damage from this process.

Possible Side Effects of Durvalumab
Durvalumab works by boosting the immune system. This may cause side effects, which can occur while the drug is given or after the drug is given (within hours, days, weeks, or months after).

Most of the possible side effects listed below are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. Some patients may need to delay doses of durvalumab to allow the side effects to get better. The most important possible side effects, which are listed below, may occur because of the way durvalumab works on the immune system and they have been seen in patients treated with durvalumab in clinical studies. Side effects like these have also been seen in clinical studies with other drugs that are very similar to durvalumab. Management of these side effects may require the use of drugs such as steroids or other agents which can affect your immune system and reduce inflammation.

Very common side effects (seen in 10% or more of people)
- Diarrhea
- Rash/dry itchy skin
- Imbalance of thyroid hormones so the thyroid is underactive (hypothyroidism): Symptoms may include but are not limited to fatigue, increased sensitivity to cold, constipation, dry skin, unexplained weight gain, puffy face, muscle weakness, slow heart rate, thinning hair, and impaired memory. The condition can be treated with replacement thyroid hormone.
- In addition to these side effects, frequently reported adverse effects include feeling tired, nausea, vomiting, abdominal pain, constipation, body aches, joint pains, upper respiratory tract infections, decreased appetite, shortness of breath, cough, and fever.

Common side effects (seen 1-9% of people)
- Inflammation in the lungs (pneumonitis): Symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. **Tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.**
- Imbalance of thyroid hormones so the thyroid is overactive (hyperthyroidism): Symptoms include anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly having heart palpitations. Depending on the severity of the symptoms, treatment may include just monitoring the symptoms, treating the symptoms themselves, and/or giving medicine to block the thyroid hormone.
- Liver problems: Increases in the blood level of substances called enzymes found within your liver cells may occur. The enzyme changes are unlikely to make you feel unwell. However, if these blood enzyme levels become very high, your study doctor may need to stop the study medication.

- Kidney problems: You may have an increase of creatinine levels in your blood. Creatinine is a protein marker that measures kidney function. The increased creatinine is unlikely to have any symptoms or make you feel unwell.
- Infusion Related Reactions: Reactions may occur during or after the infusion of study medication. The reaction may cause fever or chills and a change in blood pressure or difficulty in breathing which might be serious. **Tell your study doctor right away** if you experience any of these symptoms even if it has been several days after the infusion has been completed.
- In addition to these side effects, commonly reported adverse effects: a hoarse voice, painful urination, night sweats, pneumonia, oral thrush (fungal infection in the mouth), dental and oral soft tissue infection, pain in muscles and joints (myalgia), buildup of fluid causing swelling in the legs, and influenza.

Uncommon side effects (seen in 0.1-1% of people)

- Problems with your adrenal glands (adrenal insufficiency): May cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement
- Interstitial lung disease, a term for a group of disorders that cause scarring of the lungs and permanent breathing problems.
- Inflammation of the liver called hepatitis. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal.
- Nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- Inflammation of the skin (dermatitis)
- Inflammation of the muscles or associated tissues, such as blood vessels that supply the muscles (myositis/polymyositis). Symptoms can include muscle weakness and aches, tired feeling when standing or walking, muscle pain and soreness that does not resolve after a few weeks.
- Inflammation of the intestine (colitis). It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening. Tell your study doctor right away if you have any of these symptoms.
- Inflammation of the thyroid gland (Thyroiditis)

Rare side effects (Seen in less than 0.1% of people)

- Type 1 Diabetes mellitus which may cause increased blood glucose levels (called 'hyperglycemia'): Symptoms may include weight loss, increased urination, increased thirst, and increased hunger. Type 1 diabetes will require replacement of insulin through injection. **Tell your study doctor right away if you have any of these symptoms.**
- Inflammation of the heart muscle (myocarditis). Symptoms can include chest pain, rapid or abnormal heartbeat, shortness of breath and swelling of your legs. **Tell your study doctor right away if you experience any of these symptoms**.
- Diabetes insipidus, a condition that causes an imbalance of water in the body. Symptoms can include intense thirst and dramatically increased urination (up to 10 times normal amount).

- Guillain-Barre Syndrome (inflammation of the nerves which may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness). This may lead to temporary paralysis and inability to breathe without help.
- Myasthenia gravis, a condition of the muscles that may make you feel weak and tired, have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing.
- Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement.
- Low blood cell counts (such as low red blood cells, white blood cells, and/or platelets).
- Other rare or less frequent events:
  - inflammation of the membrane surrounding the heart (pericarditis)
  - growths of tiny collections of inflammatory cells in different parts of the body (sarcoidosis)
  - inflammation of the middle layer of the eye (uveitis) and other events involving the eye such as inflammation of the cornea and optic nerves
  - inflammation of the brain or the membranes that cover the brain and spinal cord,
  - hardening and tightening of the skin and connective tissues (scleroderma) and loss of skin color (vitiligo)
  - blood events such as abnormal breakdown of the red blood cells (hemolytic anemia) and low levels of platelets (immune thrombocytopenia)
  - joint events such as an inflammatory disorder causing muscle pain and stiffness and autoimmune arthritis
  - Inflammation of the blood vessels (vasculitis)
  - Inflammation of the membranes around your brain and spinal cord (meningitis) not caused by an infection
  - Inflammation of the brain with confusion and fever (encephalitis) not caused by an infection
  - Inflammation of the skin causing peeling, itching, blistering and/or skin redness (pemphigoid). More severe reactions may involve the inside of your mouth, the surface of your eye and/or genital area.
  - Inflammation of the skin causing red, itchy patches of skin covered with thick, grey or silver scales (psoriasis)
  - Inflammation in the lungs caused by radiation therapy to the chest (radiation pneumonitis). It can develop up to 6 months after radiation therapy is over.
  - Blood clot that blocks an artery in the lung (pulmonary embolism). Symptoms may include sudden shortness of breath, chest pain, and coughing.
  - A serious condition when your lungs can’t get enough oxygen into the blood (respiratory failure).
  - Coughing up blood (hemoptysis)
  - A hole in the wall of your digestive tract, which may include bleeding (intestinal perforation and /or hemorrhage)
  - A condition where your heart cannot pump enough blood and oxygen to support the organs in your body (heart failure).

Patients with different types of cancer who have been treated with drugs like durvalumab in clinical trials may experience the side effects described below:

- **Inflammation of the pancreas** (pancreatitis). Pancreatitis usually causes symptoms of persistent upper abdominal pain (sometimes made worse by eating and drinking), nausea, vomiting and general weakness. Pancreatitis usually settles with simple measures, but it can be a serious condition and can be fatal. You may get an increase of lipase and amylase levels in a blood test (related to the pancreas) but not have any symptoms or feel unwell. Lipase and amylase are enzymes or protein markers that measure the function of your pancreas.
- **Other nervous system problems**: Symptoms can include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet. In rare situations there is the potential for the inflammation of the nervous system to be severe and cause damage to the nerve cells or breakdown in the communication between nerves and muscles (such as Guillain-Barre syndrome): Tell your study doctor right away if you develop double vision, have problems swallowing, if you start to feel weak very quickly or are having trouble breathing.
- **Allergic reactions**: Symptoms include swelling of the face, lips, and throat or difficulty breathing which might be serious. Some reactions can cause swelling, shortness of breath, fever, fatigue, nausea, kidney failure and confusion (cytokine release syndrome).
- **You may experience other infections** like urinary tract infection, respiratory tract infection and sepsis (blood infection).

In addition to the possible risks identified in patients treated with durvalumab, other immune-mediated side effects are possible that have not been observed and can result in inflammatory side effects in any organ or tissue.

Risk of delaying surgery: If you are assigned to Arm A or Arm B, you will receive 4 weeks of treatment prior to your surgery, and then your surgery will be scheduled for week 5 to 9. This means it is possible your surgery could occur later than it would have if you were not in this study. Currently, the usual time to surgery after diagnosis for your condition at UIHC is 6 weeks.

Genetic Research

One risk of giving samples for this research may be the release of your name that could link you to the stored samples and/or the results of the tests run on your samples. To prevent this, these samples will be given a code. Only the study staff will know the code. The name that belongs to the code will be kept in a locked file or in a computer with a password. Only the study staff will have access to your name.

Risks to Pregnancy

If you or your partner are planning to become pregnant, you should not join the study. If you are a woman who is capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. Both men and women must use a highly effective birth control method (<1% failure rate) 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 or your partner have become pregnant while participating in this research study, please contact Muhammad Furqan MD 319-353-8155 as soon as possible.

Highly Effective Methods of Contraception

Non hormonal Methods	Hormonal Methods
• Total sexual abstinence • Vasectomized sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Implants: Etonogestrel-releasing implants (e.g. Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel releasing intravaginal devices (e.g. NuvaRing®) • Injection: Medroxyprogesterone injection (e.g. Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol releasing transdermal system (e.g. Ortho Evra®) • Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study. If you are assigned to Arms A or B, the treatment received before surgery may help reduce the chance of your tumor returning after surgery, however, we are not sure if that will happen, which is why we are doing this study.

Regardless of the outcome of the trial, we hope that, in the future, other people might benefit from this study because of what we may learn about giving durvalumab with or without ascorbate prior to surgery

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 have surgery without participating in a clinical trial.

FOR IRB USE ONLY
APPROVED BY: IRB-01
IRB ID #: 202303162
APPROVAL DATE: 10/10/24

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

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

All procedures and tests done solely for this research study and not considered part of your regular medical care will be paid by the study. The study will pay for the cost of the durvalumab or ascorbate, if you will be receiving those drugs. The study will also pay for the research blood tests.

Any medications, tests or procedures that are part of your regular medical care will be billed to you/your health insurance company. If your health insurance company or Medicare requires any co-payment, co-insurance or deductible, you will be responsible for making that payment.

Examples of regular medical care or procedures for this study include:

- Administration of the study drug,
- Routine blood tests,
- Pregnancy tests, if applicable,
- Office visits/ physical exams at each visit.
- CT or MRIs
- Physician's charges,
- Antibiotics, pre-medications or other medications to manage side effects of treatment.

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?

Astra Zeneca is providing the durvalumab being used on this research study. No one on the research team will receive a direct payment or increase in salary from Astra Zeneca 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
- 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 use a subject code number instead of your name or other identifying information when collecting your medical record information. The list linking your name to your subject code will be kept in a secure database with access restricted to authorized persons. Any paper records, such as this consent form, will be kept in a restricted location in the hospital that is locked when no one is present. 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 your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are participating in this study. The information included 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 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.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care 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 for your treatment. Once University of Iowa Health Care 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, and outside clinical laboratories. The Data and Safety Monitoring Committee of the Holden Comprehensive Cancer Center may also inspect any part of your medical record for the purposes of

auditing the conduct of the study.

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 University of Iowa Health Care 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**:**

Muhammad Furqan MD
University of Iowa Hospitals and Clinics
200 Hawkins Drive C21 GH
Iowa City, IA 52242 USA

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 let us know so we can discuss with you what further options exist for your care.

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 in our judgment it would not be safe for you to continue, because you are or became pregnant, or because the researchers have decided to stop the study.

FOR IRB USE ONLY
APPROVED BY: IRB-01
IRB ID #: 202303162
APPROVAL DATE: 10/10/24

FOR IRB USE ONLY
APPROVED BY: IRB-01
IRB ID #: 202303162
APPROVAL DATE: 10/10/24

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Muhammad Furqan at 319-353-8155. If you experience a research-related injury, please contact: Dr. Muhammad Furqan at 319-353-8155. If it is after 5:00 PM or on a weekend, call 319-356-1616 and ask for the Hematology/Oncology Fellow on-call, and tell the hospital operator you are a research participant.

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): _____

_____ _____
(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.

_____
Name (printed)

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