Official title: Phase 1b/2 trial of preoperative niraparib, dostarlimab, and hypofractionated radiotherapy for the treatment of locally-advanced rectal cancers.

NCT Number: NCT04926324

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INFORMED CONSENT DOCUMENT

Project Title: Phase 1b/2 trial of preoperative niraparib, dostarlimab, and hypo-fractionated radiotherapy for the treatment of locally advanced rectal cancers
Phase 1b: determining the dose of niraparib

Principal Investigator: Joseph Caster, MD, PhD

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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 locally advanced rectal cancer and your cancer doctors have recommended radiation and chemotherapy as part of your treatment.

This research study combines niraparib and dostarlimab with radiation therapy. Radiation therapy is standard for your cancer. Niraparib (NER-wrap-a-rib) (Zejula™) is FDA approved for use in ovarian, fallopian, and peritoneal cancer but not rectal cancer. Dostarlimab (DOE-star-la-mab) (Jemperli) is FDA approved to treat endometrial cancer. Neither niraparib nor dostarlimab are approved for use in rectal cancer, but we think they may work as a treatment for rectal cancer. This is why we are doing the study.

The purpose of this study is to determine the best tolerated dose of niraparib when administered with both radiation and dostarlimab. We also want to identify the side effects of this combined therapy.

How Many People Will Participate?

Up to 55 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 involvement will last up to 15 weeks and involve up to 12 weeks of treatment. During your treatment, you will return every 3 weeks for a dostarlimab infusion and once daily for 5 days for radiation therapy. Each of these visits will be about 2 hours, depending on the clinic. You will need to return to UIHC for your follow-up for 2 years after radiation.

You will have life-long follow-up for this study. That means when you are no longer receiving the study treatment, we will still want to find out how you are doing. This is because the combined use of the drugs is investigational. We may visit you during your scheduled cancer treatment appointments or speak with your cancer doctors about how you are doing. We will review your UIHC medical chart about 4 times a year. If you no longer come to UIHC for your cancer care, we may contact you, 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 contact you by mail or phone, based on the results of that search.

It is very important that we stay in contact with you.

What Will Happen During This Study?

Testing for Reportable Disease

If you decide to participate in this study, we will test you for Hepatitis B and Hepatitis C. The results of the test could indicate that you have hepatitis, a viral disease of the liver. If that happens, we will refer you to a doctor who specializes in treating hepatitis. 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 could have serious personal and/or social consequences, including difficulty obtaining health insurance or employment. For more information about the risks of Hepatitis B and Hepatitis C testing, please talk to your study doctor.

Before you begin the study treatment

You will need to have some blood tests done to find out if you can continue to be in the study.
These tests are part of regular cancer care and would 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.

If obtained for the study, the results of these tests will be entered into your medical record:

- Blood will be taken to determine blood counts, liver, and kidney function.
- A PET/CT or CT scan of the chest, abdomen, and pelvis.
- A pelvic MRI.
- A urinalysis (test of your urine).
- Blood tests to check your bone marrow, liver, and kidney function.
- Blood test to check for hepatitis B and hepatitis C.
- If you inform us you are HIV positive, we will check your CD4 and CD8 lymphocyte count (we will *not* test for HIV).

- Physical exam with medical history and vital signs (blood pressure, heart rate, temperature, etc.)
- Pregnancy test (unless you are over 60 years old OR have gone through menopause and had your last menstrual over a year ago).

To participate in this study, you **must** agree to use an effective method of birth control. You must start using the birth control from the time you sign the consent document and until at least 180 days after your last dose of niraparib. Acceptable methods of birth control include birth control pills, intrauterine device, and abstinence. **Condoms and/or diaphragms are not considered effective birth control methods – even with spermicide.** Sperm must not be banked/donated for at least 90 days after the last dose of niraparib.

If you have questions about birth control methods, fertility, and/or sperm banking, please speak with your study nurse or your doctors. They will help guide you in these decisions.

Active Treatment

If you continue on study, you will have four parts to your treatment: priming, radiation, infusion, and surgery. You will return about one to two weeks before you start radiation for your radiation therapy planning. During that time, you will receive a prescription for your study drug, a copy of your pill diary, and instructions for taking the drug. You will also have these additional tests completed if you have not had them recently. The results will be added to your medical record. This may be done any time before your first dose of study drug:

- Electrocardiogram (ECG) to check your heart
- If you are capable of getting pregnant: a pregnancy test
- A blood test to check your thyroid function
- A blood test to measure your CD4 and CD8 lymphocytes – a type of white blood cell
- A review of the medications you are currently taking and why you are taking them
- A questionnaire about your current symptoms and how you are feeling (this will be done on a tablet). The questionnaire has six questions. You can skip any question you would like to.

Priming (Study Week 1)

The week before you begin radiation therapy, you will begin taking the niraparib. Niraparib is a capsule you take by mouth once a day at bedtime. You will need to mark on the pill diary what time you take the niraparib.

Your niraparib dose: ☐ 100 mg once a day ☐ 200 mg once a day

Your study doctor or nurse will meet with you on the day you are to start your niraparib. They will review how to take the study medication and complete the pill diary. They will also ask if you have had any changes in your symptoms and have you complete the tablet questionnaire. This is added to your medical record.

While you are taking niraparib, you must check your blood pressure at least once a week. If you cannot have it done at UIHC, your study nurse will speak with you about checking it at home.

Radiation (Study Week 2)

The week after you start the niraparib, you will have your radiation therapy. The radiation is once a day Monday through Friday. You will receive the same radiation therapy you would if you were not in this study. During your radiation week you will:

- Continue to take your niraparib at bedtime.
- Bring your niraparib pill diary for your study nurse to review.
- Receive your first infusion of dostarlimab on the same day as your first dose of radiation. The infusion will be after your radiation and take about 30 minutes. Your visit to the infusion center will be longer – about 1 ½ hours.
- Complete the tablet questionnaire about your current symptoms and how you are feeling. You can skip any question you would like to.
- Have blood tests to check your bone marrow, kidney, and liver function.
- See your study doctor and/or study nurse on the first day and your last day of your radiation treatment to see how you are doing. It is important to share how you are feeling and if you are experiencing any side effects.

Infusions (Study Weeks 3-12)

After you complete your radiation therapy, you will continue to take the niraparib and receive dostarlimab infusions. We will schedule your appointments for you. During this time, you will:

- Continue taking niraparib at bedtime and completing the pill diary.
- Receive dostarlimab infusions once every 3 weeks for a total of 4 doses (one during radiation plus three during this phase).
- See your cancer doctor before each infusion.
- Have blood tests to check your bone marrow, liver function, kidney function, and thyroid function.
- Have blood tests to measure your CD4 and CD8 lymphocytes
- Have your urine checked (urinalysis) to check your kidney function.
- Have a review of the medications you are currently taking and why you are taking them when you meet with your cancer doctor and study nurse.
- Complete the tablet questionnaire about your current symptoms and how you are feeling. This is done on the day you meet with your cancer doctor and study nurse. You can skip any question you would like to.
- If you are capable of getting pregnant, a pregnancy test will be done before each infusion

You will stop niraparib one week prior to your surgery. Your study nurse and cancer doctors will tell you when to take your last dose**. It is important that you return any unused drug to your study nurse and also the pill diary**.

Flexible Sigmoidoscopy

An important part of this research study is learning if the study medications increase the effect of radiation therapy. One evaluation that is very important to investigate this is a flexible sigmoidoscopy with biopsies.

This will be done during study week 8 – about 6 weeks after you complete your radiation therapy. This will be like the other flexible sigmoidoscopies you have had done for your cancer diagnosis and evaluation.

Your study nurse will schedule this for you and review preparation instructions. You will need to have a driver for this procedure.

You will be informed of the findings from the flexible sigmoidoscopy and the biopsies by your cancer doctors. The results will also be added to your medical record.

Follow-Up

After you complete your study treatment, you will receive chemotherapy as prescribed by your cancer doctor. You will also be evaluated for how your cancer responded to treatment and if you need surgery. The chemotherapy, evaluation, and surgery (if you need it) are not a part of the study.

The study will have the following assessments. We will schedule them for you:

1 week after completing treatment

- Have blood tests to check your bone marrow functions

During cycle 4 of your chemotherapy

- A blood test to measure your CD4 and CD8 lymphocytes – a type of white blood cell

If you have surgery

- We will obtain a sample of the tumor tissue to test for tumor infiltrating lymphocytes and analyze for treatment effects

After your study treatment

We will schedule a follow-up appointments in UIHC-Radiation Oncology at 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.

These follow-up visits will be routine except we will ask you to complete the tablet questionnaire. Like before, you do not have to answer any questions you do not want to.

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

After you complete the 2-year follow-up visit, you will still be followed for this study. We may visit you during your scheduled cancer treatment appointments or speak with your cancer doctors about how you are doing. We will review your medical chart about 4 to 6 times per year. 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.

Tumor Tissue and Data Storage for Future Use

As part of this study, we are obtaining images (CT scans, MRIs), data from your medical record, and tumor tissue from you. We would like to study your imaging, data, and tumor tissue in the future, after this study is over. Your imaging, 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 stripped of identifiers (such as name, date of birth, address). Other qualified researchers who obtain proper permission may gain access to your imaging 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 imaging, data, and/or tumor tissue may not even exist at this time. Therefore, we are asking for your permission to store your imaging, data, and/or tumor tissue so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding cancer, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your imaging, data, and/or 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 imaging and/or 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 imaging, data, and/or tumor tissue will be stored *with a code which may be linked to* your name, date of birth, and medical record number. If you agree now to future use of your imaging, data, and/or tumor tissue but decide in the future that you would like to have it removed from future research, you should contact Joseph Caster, MD, at 319-353-8836. However, if some research with your imaging and/or tumor tissue has already been completed, the information from that research may still be used.

This study does not test the DNA of your tumor sample (DNA is the instruction manual that determines your appearance in things like eye color or how tall you can be). **This study also does not conduct whole genome sequencing**, a method of creating a DNA "blue print" of you –either your healthy cells or your tumor cells.

Please initial your choices below

My tumor tissue may be stored for future cancer research by Dr. Caster:

yes _____ no: _____

My imaging may be stored and shared for future cancer research:

yes _____ no: _____

My data may be stored and shared for future cancer research:

yes _____ no: _____

Will I Be Notified If My Imaging or Sigmoidoscopy Results In An Unexpected Finding?

We may learn things about you from the study activities which could be important to your health or to your treatment. If this happens, you will be informed of any unexpected findings of possible clinical significance that may be discovered during review of results from the imaging (CT, MRI), the sigmoidoscopy, and the tumor biopsy performed for this study. The results from the imaging, sigmoidoscopy, and biopsy we collect in this research study are the same quality as what you would receive as part of your health care. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as feeling worried about a finding for which no treatment is available).

These procedures are performed clinically and will be entered into your medical record. Your cancer doctors will be made aware of the findings and discuss them with you. If there are other findings that need to be communicated to another doctor, your cancer doctor will discuss that with you as well.

The biopsy and the imaging will be reviewed by a physician who normally reads such results and they will inform us if there are any unexpected findings. We will provide you with this information so that you may discuss it with your primary care physician. However, if you believe you are having symptoms that may require care prior to receiving any information from this study, you should contact your primary care physician. The study team/study will not cover the costs of any follow-up consultations or actions.

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 we did not anticipate, associated with being in this study.

Your study doctor will explain the risks, side effects, and discomforts that may be experienced related to non-study drugs which are part of usual care.

Research Related Risks

Side Effects Requiring Immediate Medical Attention:

The side effects listed below require IMMEDIATE MEDICAL ATTENTION OR ADVICE.

Call the study doctor right away if you have any of these side effects:

- Allergic reactions can be life-threatening. Symptoms may include difficulty breathing, shortness of breath, low blood pressure (feeling lightheaded, dizziness), tingling around the mouth, rash.
- Rash, itching, blisters, or pale or yellow skin.
- Yellowing of the whites of your eyes or blurry vision.
- Abnormal thinking, confusion, personality changes, headache and/or neck stiffness.
- Diarrhea, stools that are black or bloody, stomach area pain, nausea or vomiting
- Bleeding or bruising more easily than normal. Bleeding may require urgent medical attention, including a transfusion (receiving blood or blood products by vein). Low platelet counts may increase your risk of bleeding and bruising.
- You feel tired, weak, or short of breath. These symptoms may be caused by low red blood cell counts and require a blood transfusion.
- Hair loss or feeling cold.

- Low neutrophil counts may be associated with infection, sometimes severe and life-threatening (neutropenic infection, neutropenic sepsis):
  - Symptoms of severe life-threatening infection may include fever, chills, feeling of low blood pressure (light-headedness, dizziness, fainting), decreased urination, rapid pulse, rapid breathing or shortness of breath
- Decrease in the number of all types of blood cells (pancytopenia)
- Low blood cell counts due to a problem in the bone marrow or blood cancer starting from the bone marrow (Myelodysplastic Syndrome [MDS] or Acute Myeloid Leukemia [AML]). MDS/AML, including fatal cases, have been reported with use of niraparib. If you experience prolonged haematological toxicities, contact your study doctor for haematologist evaluation.
- High blood pressure (hypertension) including severe increase in blood pressure (hypertensive crisis) has been reported with the use of niraparib. If you have pre-existing hypertension, your doctor will determine if your blood pressure is adequately controlled before starting niraparib.
  - Symptoms of a severe increase in blood pressure may include blurry vision, headache, nausea, vomiting, confusion, passing out, seizures, weakness or numbness on one side of body or in one arm or leg and/or difficulty talking (symptoms of a stroke), trouble breathing, chest pain, pain in the upper or lower back, urine that is brown or bloody
- Posterior Reversible Encephalopathy Syndrome (PRES), a rare neurological side effect has been reported with niraparib treatment.

If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

<u>Niraparib</u>

Safe Handling of Drug
Caregivers should wear gloves if they need to touch the niraparib capsules. You should notify any caregivers of this information, to ensure the appropriate precautions are taken.

Niraparib has moderate influence on the ability to drive or use machines. Patients who take niraparib may experience weakness, fatigue, difficulty concentrating and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

PARP Inhibitor Class Effects. Class effects are potential risks that are associated with a particular group of drugs. Niraparib belongs to the group known as poly (ADP-ribose) polymerase inhibitors (PARP) inhibitors. These class effects are potential risks for the group of drugs but have not yet been identified as side effects for niraparib.

Secondary Primary Malignancy. PARP inhibitors may cause a new primary cancer (that is, a cancer other than the one for which you have been treated). In 2 studies comparing niraparib to placebo (sugar pill), new primary cancers were observed in a small number of patients who took niraparib or placebo.

Very Common, some may be serious (10% or more of patients may have this happen)

- Decrease in the number of blood platelets that help blood to clot
- Anemia which may require blood transfusion
- Decrease in the number of white blood cells (leukopenia) that fight infection

- Decrease in the number of neutrophils (neutropenia), a type of white blood cells (leukocytes) that fight infection
- High blood pressure (hypertension)
- Abnormal heartbeat, including feeling like your heart is skipping beats or beating harder than usual (palpitations)
- Infection, especially when white blood cell count is low, which may cause painful and frequent urination, upper airway infection, nose and throat infection
- Shortness of breath
- Cough
- Headache
- Dizziness
- Tiredness, weakness
- Difficulty sleeping
- Pain including in the belly, muscles, joints, and back
- Heartburn, indigestion
- Nausea, vomiting, diarrhea
- Constipation
- Decreased appetite

Common, some may be serious (1% to 10% of patients may have this happen)

- Infection due to low white blood cell counts (neutropenic infection)
- Low blood cell counts due to a problem in the bone marrow or blood cancer starting from the bone marrow (Myelodysplastic Syndrome [MDS]/Acute Myeloid Leukemia [AML])
- An irritation or infection in the tubes that carry air in and out of the lungs, that causes a cough (bronchitis)
- Fast heart beat (tachycardia)
- Swelling of arms and legs
- Muscle pain
- Rash
- Weight loss
- Worry, depression
- Impaired concentration, understanding, memory and thinking (cognitive impairment)
- Swelling and redness of the eye (conjunctivitis)
- Nose bleeds
- Sore, red mouth (stomatitis)
- Swelling or irritation of the lining of the mouth, throat, esophagus, stomach or intestines (mucosal inflammation/mucositis)
- Abnormal taste in mouth (dysgeusia)
- Dry mouth
- Increased skin sensitivity to sunlight and increased risk of sunburn
- Low blood potassium

- Increased level of creatinine in your blood (blood creatinine increase), which may be a sign of kidney damage
- Increased levels of substances in the blood produced by the liver, which may be a sign of liver injury (aspartate aminotransferase [AST] increased, alanine aminotransferase [ALT] increased, gamma-glutamyl transferase [GGT] increased)
- Other abnormal labs (alkaline phosphatase [ALP] increased)
- Allergic reaction (hypersensitivity, including anaphylaxis).

Uncommon (happens in about 1% of patients and may require emergency treatment)

- Fever with low white blood cell count (febrile neutropenia)
- Severe life-threatening infection due to low white cell counts [associated with low blood pressure and possible organ failure (for example, heart, kidney and/or liver), (neutropenic sepsis)]
- Low counts of all three types of blood cells: red blood cells, white blood cells, and platelets)
- Confusion (confusional state/disorientation)
- Seeing or hearing things that are not really there (hallucination)
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing (non-infectious pneumonitis)

Rare but Serious (happens in < 1% of patients but requires emergency treatment)

- Posterior reversible encephalopathy syndrome (PRES) - changes in the brain that can cause symptoms including headache, confusion, seizures and visual loss associated with magnetic resonance imaging (MRI) finding. The symptoms tend to resolve after a period of time, although visual changes sometimes remain.
- Extremely high blood pressure—a top number (systolic pressure) of 180 millimeters of mercury (mmHg) or higher or a bottom number (diastolic pressure) of 120 mmHg or higher—that can damage blood vessels, cause a stroke, or other problems.

Dostarlimab

As of January 2022, dostarlimab has been studied in about 1800 patients with advanced or recurrent solid tumors in clinical trials, with about 1160 of these patients receiving dostarlimab in combination with other medicines. Some of the side effects mentioned below can be life-threatening or fatal.

Very Common (happens more than 10% of time)

- Decrease in the number of red blood cells that carry oxygen. Low red blood cells count may make you feel tired or short of breath and symptoms may require a blood transfusion (anemia)
- Feeling sick to the stomach (Nausea)
- Vomiting
- Frequent watery stools (Diarrhea)
- Itchy skin (Pruritus)
- Rash
- Fever (Pyrexia)

- Increased levels of substances in the blood produced by the liver which may be a sign of liver injury (transaminases increased)
- Underactive thyroid gland (hypothyroidism)

Common (happens 1% to 10% of time)

- Decreased production of adrenal hormones resulting in possible weakness and/or low blood pressure (adrenal insufficiency)
- Overactive thyroid gland (hyperthyroidism)
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing (pneumonitis)
- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and cause nausea and vomiting, fever, and rapid heart rate (pancreatitis)
- Inflammation of the colon that can cause stomach pain or diarrhea (colitis)
- Muscle pain (myalgia)
- Chills

Less Common (happens up to 1% of time)

- Destruction of red blood cells which can cause tiredness, dizziness, yellow skin or fast heart rate (autoimmune hemolytic anemia)
- Inflammation of the thyroid gland (thyroiditis)
- Pituitary gland inflammation (hypophysitis)
- Severe high blood sugar due to uncontrolled diabetes (diabetic ketoacidosis)
- Diabetes requiring insulin (type 1 diabetes mellitus)
- Inflammation of the eye which can cause redness, blurred vision or vision loss (uveitis)
- Muscle pain involving several muscles (polymyalgia rheumatica)
- Kidney inflammation (nephritis)
- Myasthenia gravis
- Immune-mediated arthritis
- Inflammation in the brain (encephalitis)
- Inflammation of the heart muscle (myocarditis)
- Inflammation of the liver (Hepatitis)
- Inflammation of the lining of the stomach (Gastritis)
- Inflammation of the food pipe (Esophagitis)
- Inflammation of the small intestine (Enteritis)
- Inflammation of blood vessels in the gastrointestinal tract (Vasculitis gastrointestinal)
- Inflammation of the muscle which can cause weakness, swelling and pain (Myositis)
- Inflammation throughout the whole body leading to high or low temperatures, low blood pressure, increased heart rate, increased rate of breathing and low or high white blood cell count (Systemic Inflammatory Response Syndrome)
- Infusion-related reactions which can occur within 24 hours after receiving an intravenous infusion, or which can be delayed for up to about 2 weeks. Infusion-related reactions may include dizziness or fainting, flushing, rash, fever, chills, shortness of breath, increased or decreased blood pressure,

increased heart rate, swelling of the lips, tongue or face, feeling sick to your stomach, back pain or pain at the site of infusion. Although infusion-related reactions are usually reversible, they can be severe or life threatening. (Infusion related reactions)

There are rare but serious immune-related adverse events which have been seen when dostarlimab was used alone or in combination with other medicines:

- Overactive immune-system cells which damage body tissues and organs leading to signs of uncontrolled fever, enlarged spleen, low blood count and liver test abnormalities. This disease (hemophagocytic lymphohistiocytosis, HLH) can be fatal.
- A neurological disorder where the immune system attacks part of the peripheral nervous system that can cause tingling in the feet and hands, pain, muscle weakness, and problems with coordination (Guillain-Barre syndrome).

There may be other risks called class effects that have been seen in patients receiving other drugs that work like dostarlimab. These effects could also occur with dostarlimab. They are potential risks but not known as side effects for dostarlimab so far. The most significant class related side effects are "immune-related," meaning side effects caused by increased activity of the immune system, which can affect multiple organs of the body including gastrointestinal tract, endocrine system, cardiovascular system, lungs, liver, skin, musculoskeletal system and nervous system. These other immune-related side effects may be life-threatening or fatal.

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 dostarlimab and niraparib 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 dostarlimab and/or niraparib is not known.

Potentially life-threatening short-term complications such as developing a hole in the wall of your rectum or bladder, or a severe bleeding event are extremely rare with radiation alone but can occur. We don't know if the risk of these are increased when niraparib and dostarlimab are added to radiation, but since they may make the radiation more effective, they may make these events more common.

We will closely monitor you for any unforeseen side effects that result from the interaction between the radiation therapy, the dostarlimab, and the niraparib.

Flexible Sigmoidoscopy with Biopsies

You will undergo a flexible sigmoidoscopy after you complete your radiation therapy. It will be like your prior sigmoidoscopies.

- Bleeding and perforation are the most common complications from flexible sigmoidoscopy.
- Most cases of bleeding occur in patients who have tissue removed (biopsy).
- The doctor can treat bleeding that occurs during the flexible sigmoidoscopy right away.

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 dostarlimab or niraparib.

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.

Breastfeeding

You cannot join this study if you are breastfeeding. You cannot store breast milk for future use. If you are breastfeeding, and wish to join the study, you must stop until at least 8 weeks after the final study drug dose. You must discuss this with your study doctor.

Individuals Capable of Becoming Pregnant

If you are 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 highly 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 Joseph Caster, MD at 319-353-8836 as soon as possible.** You may stop receiving study drug until pregnancy is confirmed. If pregnancy is confirmed, you will be withdrawn from the study. If this should happen, the study doctor will ask to follow the progress of your pregnancy. You will be asked to review another consent document if this should occur. You have the right to decline.

Information for Individuals Who Can Father a Child

Animal studies have shown niraparib can cause a reversible decrease in sperm count. Participants in this study must also understand that there is a risk in taking a study drug when the effect on a fetus is unknown. If your partner becomes pregnant during this study, you must contact the study doctor immediately. Your pregnant partner should also contact their doctor.

What Are The Benefits Of This Study?

It is possible that the combination of niraparib and dostarlimab with radiation may be more effective than receiving radiation alone. It is still not fully known how treatment with niraparib, dostarlimab, and radiation will affect locally advanced rectal cancer and your condition could become better, stay the same, or become worse as a result.

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 rectal cancer.

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. For example, instead of being in this study, you could receive radiation therapy alone. You could also opt to be in a different clinical trial. There may be other clinical trials open at the University of Iowa or in other medical hospitals. You can ask your doctor about them or look them up on www.ClinicalTrials.gov

Will It Cost Me Anything To Be In This Study?

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

- If a pregnancy test is needed for study, you will not be charged for the pregnancy test.
- You will not be billed for the hepatitis blood tests.
- You will not be billed for the study drugs (niraparib, dostarlimab).
- You will not be billed for the flexible sigmoidoscopy, biopsies, or interpretation at study week 8.

You may need to take time off from work to participate in this study if you experience a side effect. Additionally, you and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses:

- Travel expenses to get to your appointments.
- Co-payments and co-insurance related to your healthcare, including any hospitalizations.
- Any medical imaging, including CT scans, MRI scans, or any PET imaging.
- Your radiation therapy and visits with a radiation oncologist.
- The infusion charges for the dostarlimab.
- Visits with your medical oncologist and your surgical oncologist
- Blood tests to check your liver, kidney, bone marrow, and thyroid cancer.
- Additional blood tests ordered for a side effect from your cancer therapy.
- You will be billed for standard follow-up visits after your cancer therapy, including radiation therapy or medical oncology follow-up visits.

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?

GlaxoSmithKline (GSK) is funding this research study. This means that the University of Iowa is receiving payments from GlaxoSmithKline 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 GlaxoSmithKline 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,
- The National Cancer Institute (NCI),
- GlaxoSmithKline (GSK), the company providing the study drugs
- GlaxoSmithKline (GSK) or their designee may also inspect any part of your medical record for the purposes of auditing the conduct of the study
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

In the future, may continue to use your health information that is collected as part of this study. For example, GlaxoSmithKline may combine information from this study with the results of other studies to re-analyze the safety and effectiveness of the study drugs, to evaluate other products or therapies, to develop a better understanding of a disease, or to improve the design of future research studies. GlaxoSmithKline may also share information from the study with regulatory agencies in foreign countries.

To help protect your confidentiality, we will use a research ID in place of any information that may identify you. We will use your initials with that identifier as well. Any printed materials are stored in Radiation Oncology in closed offices that are locked after routine business hours. All electronic information is kept on password protected servers. 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. A copy of the informed consent document will be available on this website. 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, GlaxoSmithKline (GSK), the Holden Comprehensive Cancer Center, the U.S. Food and Drug Administration, and the National Cancer Institute. GlaxoSmithKline (GSK), the National Cancer Institute, the U.S. Food and Drug Administration, and 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 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:

Joseph Caster, MD, Ph.D.
Department of Radiation Oncology – UIHC
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 or GlaxoSmithKline (GSK) might decide to end your participation in this research study earlier than planned. This might happen because:

- You do not follow the study instructions.
- You no longer meet the criteria for the remainder of the study.
- You need medicine that is not allowed during the study.
- You develop a medical condition that makes you unqualified for the study.
- The Study Doctor thinks it is best for you to discontinue your participation in the study.
- You have an injury or side effect that is "serious or severe".
- The study is cancelled or stopped.

What If I Have Questions?

We encourage you to ask questions. If you have questions about the research study itself, please contact:

Joseph Caster, MD, PhD
Phone number: 319-356-3693

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

Joseph Caster, 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. Caster's rectal cancer study.

In the event of a serious medical emergency, call 911.

If you believe you are experiencing a research-related injury, please contact:

Joseph Caster, MD, PhD
(319) 356-7601 *telephone* (Monday through Friday, 8 a.m. – 5 p.m.)
or

(319) 356-1616 (24 hour telephone number)
Ask the operator for the Radiation Oncology resident on call. They will connect you. When you are connected with the fellow, tell them you are a participant Dr. Caster's rectal cancer study.

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.

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