PRINCIPAL INVESTIGATOR: Jonathan M. Hernandez, MD

STUDY TITLE: A Single-Arm Phase II Study of Hepatic Artery Infusion Pump Chemotherapy with Floxuridine and Dexamethasone in Combination with Systemic Chemotherapy for Patients with Colorectal Cancer Metastatic to the Liver

STUDY SITE: NIH Clinical Center

Cohort: Affected Patients

Consent Version: 07/21/2025

WHO DO YOU CONTACT ABOUT THIS STUDY?

Jonathan M. Hernandez, MD, by phone at 240-760-6072 or email at jonathan.hernandez@nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive. Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

There are approximately 150,000 new cases of colorectal cancer diagnosed annually in the United States. Approximately 60% of people with colorectal cancer develop liver metastases over the course of their disease. The standard treatment for patients with unresectable colorectal cancer metastatic to the liver is a combination of chemotherapy drugs.

As many people have liver-only disease at the time of progression, liver-directed chemotherapy presents a viable option. Hepatic Artery Infusion Pumps (HAIPs) as devices to deliver liver-directed chemotherapy have been used most frequently and have been shown to be very effective in several clinical trials.

In this study we are going to use a new combination of the Medtronic pump and Codman catheter for hepatic artery infusion (HAI).

The Medtronic pump has been approved by U.S. Food and Drug Administration (FDA) to deliver drugs via intravenous infusion or injection to spinal canal, so that it reaches the cerebrospinal fluid.

The Codman catheter has been approved by FDA as a component of another Codman hepatic pump, developed to connect pump and hepatic artery.

As the Medtronic pump and Medtronic pump in combination with the Codman catheter are not approved by FDA to deliver drugs directly to the liver, the use of these devices on this study is considered to be experimental.

The Medtronic pump in combination with the Codman catheter is an investigational device which has not been fully evaluated to be implanted to your abdomen and deliver drugs directly to the liver. That is why significant risks may exist for this device which will deliver drugs continuously over two weeks at constant flow pump rate into the hepatic artery.

Additionally, in this protocol we intend to study tumor and liver characteristics of participants. We believe, this scientific research will help to offer better treatment options to people with colorectal and other cancers.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You are being asked to take part in this study because you have been diagnosed with colorectal cancer with metastases to the liver, and your cancer progressed or did not completely go away with first line of chemotherapy. Standard chemotherapy usually does not cause tumors to disappear completely, but we think that delivering chemotherapy through the pump directly to your liver may increase the likelihood of a significant response.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 39 people will receive the study drug at the NIH.

DESCRIPTION OF RESEARCH STUDY

Before you begin the study

Before you begin this study, you will need to have exams and tests to make sure it is safe for you to have the operation/chemotherapy and you are eligible for this study. These tests may be done under a separate protocol:

- Medical history and physical exam
- Routine blood tests (about 2-4 tablespoons, as some tests may not need to be repeated if done recently):

  - Tests for Hepatitis B and C
  - HIV testing: As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV an infectious disease specialist will decide if you can still participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.
  - Serum or urine pregnancy test if you are a woman who can have children
- Electrocardiogram (ECG)
- CT scans
- If there is no available tumor sample from a previous surgery, a biopsy will be performed to confirm the diagnosis.
- Co-enrollment on the Surgical Oncology Program's tissue collection protocol 13C0176 ("Tumor, Normal Tissue and Specimens from Patients Undergoing Evaluation or Surgical Resection of Solid Tumors").

We may access data in your medical record that was collected under other protocols and use it for research in this study, so you do not have to repeat procedures/tests. These could be data about your medical history as well as from other clinical tests and procedures that are like ones being done on this study. If you are co-enrolled in another NIH protocol (such as 13C0176), then research data and/or specimens, collected in either study, may be shared with and used for research in either study, with IRB approval. The sharing of these data and/or specimens could allow us to not need to repeat the same research tests, and could also mean that we do not need to collect specimens from you more than once for the same research test.

You will not be allowed to participate if we find that you are not eligible.

During the study

HAIP installation laparotomy

Once you have completed all the testing and your physician has reviewed the results to determine that this procedure is safe for you, you will be admitted to the hospital. Most patients are admitted the evening before their operation. Your physician will explain the surgical procedure and will answer any questions you may have.

You will be given general anesthesia (so that you sleep through the surgery) and will undergo an abdominal operation requiring an incision. General anesthesia may be given through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm), a face mask, or through a tube in your nose or throat. The general anesthesia may make it difficult to think once you wake up after your surgery, but this is temporary. However, because a side effect of general anesthesia is that it may take longer to fully recover then it will feel like at the time, you should plan ahead of time not to make any important decisions for 24 hours after the operation has been completed.

You will undergo an abdominal operation requiring an incision. During this operation, a catheter will be placed into one of the arteries feeding blood into the liver (and the tumors). This catheter will then be attached to the pump, which will lay underneath your skin between your ribs and hip on the left side of your abdomen. We will check the pump during the procedure to make sure that drug from the pump is flowing correctly to your liver. This check will be done by injecting a small amount of radioactive material (called a tracer) through the pump and then using imaging machines to take pictures showing the inside of your body.

The pump is about the size of a hockey puck. It looks a lot like a big subcutaneous access port. You will be able to feel it, and so will we, because we will infuse the chemotherapy into it every 2 weeks.

Following the procedure, you will likely remain in the hospital for 3 or 4 days. Adequate pump placement and perfusion of the liver will be verified prior to discharge from the hospital. The verification of proper pump performance may be repeated before start of chemotherapy treatment.

HAIP chemotherapy treatment

The HAIP will be infused every two weeks with heparinized saline or the drug.

Treatment will be administered to you on a 4-week (28 days) cycle basis. You will need to come to the Clinical Center every 2 weeks.

Drug pump therapy with Floxuridine (FUDR) and Dexamethasone in a Heparin/Saline solution will be started on Day 1 of each cycle. The pump will be filled with the mixture of FUDR, Dexamethasone and Heparin/Saline which will continuously perfuse the liver for 14 days. On Day 15 of each cycle, the pump will be emptied and filled with Heparin/Saline solution (to keep the pump from going dry).

It is very important that you keep all your refill appointments. Your pump can run dry if it is not refilled regularly. If that happens, it could become clotted and damaged. Please call us if you cannot keep a refill appointment. Tell your team if you will be out of town at any point while you have your pump.

Depending on your blood test results during treatment, the study doctor may decide to have your pump filled with additional Dexamethasone in Heparin/Saline solution if it is necessary for your care. This may be done at any time during your treatment and will not change your treatment schedule.

Standard of care systemic chemotherapy

On Cycle 1 Day 15 you will receive standard of care chemotherapy administered to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) or through a mediport.

Beginning from Cycle 2 you will receive standard of care chemotherapy on Day 1 and Day 15 of every following cycle delivered intravenously.

Depending on your medical history and previous treatments, the study doctor will decide what standard of care regimen is best for you. If you experience unbearable toxicity with one of the drugs, study doctor will change systemic therapy and put you on another regimen.

Standard of care chemotherapy will be based on the combination of drugs:

- Oxaliplatin
- 5-Fluorouracil/Leucovorin
- Irinotecan
- Cetuximab
- Panitumumab

If you are unable to come to Clinical Center for your standard of care chemotherapy, and we believe that it would be appropriate for your care, we may arrange for your home oncologist to administer your standard of care chemotherapy on Day 1 (+3 days) and Day 15 (+3 days) of each cycle, starting with Cycle 1 Day 15.

Standard of care subsequent operation

If your tumor(s) during the treatment shrink so that it can be removed completely, surgery will be performed to remove all of your tumors.

Re-treatment

If your disease comes back after this surgery and you still have the pump installed, we will repeat HAIP chemotherapy treatment and continue standard of care systemic chemotherapy. Before re-treatment we will do same tests as described in following section "Ongoing Procedures during each treatment cycle" and an imaging assessment - a CT scan of chest, abdomen and pelvis.

Ongoing Procedures during each treatment cycle

While you are on the treatment, on the first day of every cycle you will have:

- Physical exam, including vital signs
- Review of your symptoms and your ability to perform your normal activities.
- Routine blood tests (about 1 tablespoon) to find out if you are anemic, have low blood counts, your blood is clotting normally, the status of your immune system and if your liver, thyroid, kidneys, and other organs are working well.
- Blood (about 1 teaspoon) or urine pregnancy test if you are a woman who can have children.

Research tests

You will have a CT scan of your chest, abdomen and pelvis every 12 weeks while you are on treatment, so that we can see how you are responding to therapy.

In addition, we will also collect tissue samples from you for purposes of research only. Some of the analyses will be done outside of the NIH, but your samples will not contain any information that can identify you. These studies include:

- During pump installation, if considered safe by your surgeon, we will collect tissue samples of your tumor and normal liver. Please see Section **Tissue collection risk** for risk of this procedure. We will use these samples to study the difference in proteins, metabolism and microenvironment in your tumor in comparison to normal tissue.
- Additional tumor biopsy may be performed at the time of disease progression, if considered safe by your PI and if you agree, but this is not required. Please see Section **Risks from general** anesthesia

Risks of general anesthesia include temporary confusion and memory loss, although this is more common in the elderly, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, sore throat due to the breathing tube.

- Risks from biopsy for risk of this procedure. These samples will allow us to study effect of treatment on proteins, metabolism and microenvironment in your tumor and normal liver tissue and understand how tumors that were initially responsive to treatment became unresponsive.

  You may receive conscious sedation before undergoing a biopsy, if needed, and you will be informed of the additional risks prior to undergoing the procedure. Conscious sedation is usually given to help someone relax and minimize discomfort. It can be given as a pill, a shot, an IV or even inhaled. You may have to wait up to an hour to start feel the effects depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. You will be monitored throughout the procedure.
- If you have surgery post-treatment to remove the tumor(s), your liver tissue will be used in the development of a “liver model” – and your samples will be “live” in a special device in order to study the long-term effect of treatment on proteins, metabolism and microenvironment in your tumor and normal liver tissue.
- For research into the molecular mechanisms of tumor development, growth, and response to treatment, we will also keep some of your tumor and tissue samples “live” for a short period of time (up to 4 days) in our “SMART System” - which can test multiple treatments and allow us to study the effect of each treatment and how the treatment models compare to each other.

Genetic testing and return of results

Your tissue samples contain genes, which are made up of DNA (**d**eoxyribo**n**ucleic **a**cid) which serves as the "instruction book" for the cells that make up our bodies. We will use the tissue samples you provided to learn about how the genes in your tumor compare to genes in normal tissue. Your tissue will help us study how genes might play a role in colon cancer and other diseases. We will not share the results of these research tests with you.

When we are conducting the above genetic tests, it is possible that we could identify changes in other parts of your DNA that are not related to this research. These are known as “incidental medical findings”.

These include:

- Changes in genes that are related to diseases other than cancer.
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time that we first analyze your results, we will contact you. This could be many years in the future. If you want this to be done, we will draw an additional sample and send it for confirmatory testing. Once the results are available, if you would like to receive your results we will offer to have you come to NIH (at our expense) to have genetic education and counseling to explain this result.

If you do not want to come to NIH, we will help you find a local genetic healthcare provider who can explain it to you (at your expense).

If you are not contacted, you should not assume that that you do not have any gene variants that might be related to a disease.

When you are finished taking the drugs (treatment)

After completion of the pump chemotherapy, your doctor will offer to remove the pump, although the catheter will remain inside your abdominal cavity. If you decide to have the pump removed, this will require a trip to the operating room under sedation. You may choose to forgo removal of the pump and keep it in place, but in this case you will continue to have possible risks of this implanted device, described in Section **Risks or Discomforts of Participation**.

You will be invited for follow up safety visit approximately 1 month after the last day you take the study drug. At this safety visit, you will have the following tests:

- Physical exam and vital signs
- Review of your symptoms and your ability to perform your normal activities.
- Routine blood tests (about 1 tablespoon) to find out if you are anemic, have low blood counts, your blood is clotting normally and if your liver, kidneys, and other organs are working well.

After that, we will contact you by telephone, email, secure videocall or other NIH approved remote platform every six months to determine your health status and to find out about any new cancer treatments that you have begun.

BIRTH CONTROL

If you are a woman who is breast feeding or pregnant, you may not take part in the study because some of the medications used in this study may harm your unborn child. If you are lactating (but not breastfeeding) you will need to wait for 7 days or more after you finish study treatment before any breastfeeding may occur. If you are capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You will need to practice two effective forms of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment (the restricted period). If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control methods fail while you are in the study during the restricted period. If you think or know that you or your partner has become pregnant during the restricted period, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

If you are a sexually active person with a partner capable of becoming pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to a fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you are a male, you will need to use condoms during study treatment and for 3 months after you finish study treatment (the restricted period), in addition to the effective form of birth control used by your partner. If you think your partner has become pregnant during the restricted period, please contact the research team member identified at the top of this document as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

RISKS OR DISCOMFORTS OF PARTICIPATION

We want to make sure that you know about a few key risks right now. We will also give you more information in the **Possible side effects of the pump** section of this consent form.

If you choose to take part in this study, there is a risk that the pump may not be as good as the usual approach at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the pump. These side effects may be worse and they may be different than you would have with the usual approach to treat your cancer.

As with any metal implant, imaging (MRI) can be obscured by the pump.

Some of the most common side effects that the study doctors know about are:

- Infection
- Blood clots in an artery (with possible organ damage such as stroke and/or heart attack), which can be very serious and may result in death.
- Weakening of an artery that causes the vessel to bulge (aneurysm) or an injury that causes blood to collect between the layers of the vessel (pseudoaneurysm).
- Bile duct injury
- Pump error
- A blockage in the catheter, which will not cause any signs or symptoms but could keep the drugs from getting into your liver.
- Bleeding within the abdomen, which may cause pain, weakness, or shortness of breath.
- If pump is not emptied within 14 days or less (while you are receiving the study drugs) there is a risk of you receiving too much study drug, which can be toxic.

It is possible that you may experience other serious side effects if you take part in this study, including:

- An ulcer or sore that develops in the lining of the first part of the small intestine (duodenal ulceration)
- A hole that develops through the wall of one or more body organs (perforation), which may be due to the pump, the infusion of the study drugs through the pump directly to your liver, or both.

There may be some risks that the study doctors do not yet know about.

The pump used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood throughout the study, and he or she will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs/study approach.

Important information about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it difficult for you to have children.
- Some side effects may be mild. Others may be very serious and may even result in death.

Important information about how you and the study doctor can make side effects less of a problem for you:

- If you notice or feel anything different, tell the study doctor. He or she can check to see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The study doctor may adjust the study drugs to try to reduce your side effects

Laparotomy

- The contents of your stomach may be breathed into your lungs
- Allergic reaction to the drugs given during the procedure
- Hernia
- Infection at the incision site
- Bleeding

Possible side effects of the pump

The tables below show the most common and the most serious side effects of the study intervention that researchers know about. There may be other side effects that the doctors do not yet know about. If important new side effects are found during this study, the study doctor will discuss them with you.

RARE, AND SERIOUS In 100 people with the pump, 3 or fewer may have:
• Infection which could result in the need for IV antibiotics and/or repeat surgery to remove the pump. If this happens, it may be possible to reinsert the pump to an uninfected portion of the liver. • Blood clots in an artery (with possible organ damage such as stroke and/or heart attack) • A pump error, which will cause a beeping noise. If this happens, call the study doctor immediately so that you can see the doctor and the pump can be read. After your surgery to have the pump placed, you will get a manual about the pump that has more information about how to deal with the pump in daily and emergency conditions. • A blockage in the catheter, which will not cause any signs or symptoms but could keep the drugs from getting into your liver • Bleeding within the abdomen, which may cause pain, weakness, or shortness of breath If this happens, it can be treated by a procedure to block the blood vessel (embolization). • If pump is not emptied within 14 days or less (while you are receiving the study drugs) there is a risk of you receiving too much study drug, which can be toxic.

Additional possible risks of the pump include the following:

- An accumulation of fluid in a pocket like area of tissue at the implant site (pocket seroma)
- The pump "flipping" upside down (pump inversion)
- The pump changing position ("movement" or "migration") within the body
- An allergic reaction or immune system response to the implanted pump and catheter materials
- A part of the pump stops working (component failure) which may result in a possible loss of and/or change in your in therapy, drug overdose, or loss of ability to program the pump
- Catheter damage, dislodgement (no longer being connected to the pump), or changing position ("migration"), any of which may result in a possible loss of and/or change in your in therapy, as well as the potential of tissue damage, serious injury, or death due to perforation of vital organs and/or major blood vessels.

Risks from changes in the way the pump works

Several factors can affect the way the pump works, which could create additional risks. Any change in altitude, for example, can change the pressure inside the pump. Do not travel by air or go scuba diving until you have talked to the study doctor, so that the pump settings can be adjusted. The pump is also set to work in the body at normal body temperature. Minor changes in temperature do not affect the pump, but a persistent high fever could change the way the pump works. In rare cases, the effects of these changes could lead to serious injury or death.

Although we are not yet aware of this problem, there is the possibility of leakage from the catheter connection. This connection will sit in the pump pocket on top of your abdominal wall and below your subcutaneous abdominal fat. If a leak were to happen, chemotherapy could potentially come in contact with unintended parts of your body or keep it (all or some) from going into your liver. This could cause pain, swelling, or other problems.

Medication Risks

Floxuridine (FUDR)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Floxuridine, more than 30 may have:
• Low blood counts. Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding. • Mouth sores • Diarrhea (may be severe)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Floxuridine, from 10 to 29 may have:
• Poor appetite • Nausea and vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Floxuridine, from 10 to 29 may have:
• Hair loss • Elevated liver enzymes (temporary increase in alkaline phosphatase, lactate dehydrogenase, transaminase, and bilirubin). • Hand -foot syndrome (Palmar-plantar erythrodysesthesia or PPE) -skin rash, swelling, redness, pain and/or peeling of the skin on the palms of hands and soles of feet. • Stomach ulcers

RARE, AND SERIOUS In 100 people receiving Floxuridine, 10 or fewer may have:
• Inflammation of the gallbladder and/or liver bile ducts • Reduced blood flow to your heart (myocardial ischemia) • Fever • Weakness • Lethargy

Oxaliplatin

COMMON, SOME MAY BE SERIOUS In 100 people receiving Oxaliplatin, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting, constipation, loss of appetite • Tiredness • Bruising, bleeding • Infection, especially when white blood cell count is low • Numbness and tingling of the arms and legs • Feeling of "pins and needles" in arms and legs • Pain • Fever, cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Oxaliplatin, from 4 to 20 may have:
• Blood clot which may cause swelling, pain, or shortness of breath • Abnormal heartbeat which may cause fainting

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Oxaliplatin, from 4 to 20 may have:

- Hearing loss
- Dry eye, mouth, skin
- Swelling and redness of the eye
- Blurred vision with chance of blindness
- Visual loss
- Problem with eyelid
- Fluid in the belly
- Heartburn, passing gas
- Difficulty walking, opening mouth, talking, with balance and hearing, smelling, eating, sleeping, emptying the bladder
- Swelling of the body which may cause shortness of breath
- Blockage of the airway which may cause shortness of breath, cough, wheezing
- Bleeding from multiple sites including vaginal bleeding, bleeding of the testis, or bleeding of the brain
- Internal bleeding which may cause black tarry stool, blood in vomit or urine, or coughing up blood
- Damage to organs which may cause shortness of breath
- Sores in throat or mouth which may cause difficulty swallowing
- Chills
- Swelling and redness at the site of the medication injection
- Liver damage which may cause yellowing of eyes and skin
- Kidney damage which may require dialysis
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Weight gain, weight loss, dehydration
- Dizziness, headache
- Changes in taste, voice
- Abnormal body movement including the eye and eyelid
- Stroke which may cause paralysis, weakness
- Inability to move shoulder or turn head
- Muscle weakness
- Seizure
- Worry, confusion, depression
- Increased urination
- Stuffy nose, shortness of breath, hiccups, sinus problems
- Scarring of the lungs
- Hair loss, itching, rash, hives

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Oxaliplatin, from 4 to 20 may have:
• Increased sweating, flushing, hot flashes • High blood pressure • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Oxaliplatin, 3 or fewer may have:
• Redness, pain or peeling of palms and soles • Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

5-Fluorouracil/Leucovorin

COMMON, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil/Leucovorin, more than 20 may have:
• Elevated liver enzymes • Constipation • Hair loss • Diarrhea • Fatigue • Nausea • Vomiting

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving 5-Fluorouracil/Leucovorin, from 3 to 20 may have:
• Rhinitis and bleeding from the nose • Weight gain or weight loss • Swelling and redness of the eye • Headache • Pain • Dyspepsia • Taste change • Difficulty breathing

- Coughing
- Low blood counts

RARE, AND SERIOUS
In 100 people receiving 5-Fluorouracil/Leucovorin, 2 or fewer may have:

- Numbness and tingling of the arms and legs
- Secondary malignancies
- Problems with the heart

Irinotecan

COMMON, SOME MAY BE SERIOUS

- Diarrhea that can occur during the infusion of irinotecan or immediately after and may be associated with abdominal cramping, a runny nose, tearing, salivation, sweating, flushing (feeling of warmth and red cheeks), and difficulty adjusting your eyes to light.
- Nausea
- Vomiting
- Loss of appetite
- Fewer white blood cells in the blood.
- A low number of white blood cells can make it easier to get infections
- Fever
- A feeling of weakness and tiredness
- Hair loss
- Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
- An increase in the blood of a type of white blood cell called an eosinophil. These are sometimes associated with allergic reactions.
- Inflammation and/or sores in the mouth, throat and/or esophagus
- Infections

OCCASIONAL, SOME MAY BE SERIOUS

- Fewer red blood cells and platelets in the blood.
- A low number of red blood cells can make you feel tired and weak
- A low number of platelets causes you to bruise and bleed more easily
- Diarrhea that may occur later from 1 day to 2 weeks after irinotecan which could cause excessive loss of water and salts from the body

- Constipation
- Pain at the injection site
- A slow heart beat
- Low blood pressure
- Shortness of breath with cough
- Headache
- Acid or an upset stomach (heartburn)
- Confusion or sleepiness

RARE, AND SERIOUS
• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate • Severe loss of water from the body (dehydration) which if untreated may cause low blood pressure and severe loss of salts such and sodium and potassium from the body and could lead to the kidneys failing which could be life-threatening • Inflammation of the lungs which could lead to chest pain and shortness of breath and which may be life-threatening • Inflammation of the part of the intestine known as the colon which can lead to infection, blood in the stools and abdominal pain • Blood clots which may be in rare cases life-threatening • A stoppage (or blockage) of the intestine which may require treatment

Cetuximab

COMMON, SOME MAY BE SERIOUS
• Skin problems, such as rash, itching and nail changes, which may be severe • Feeling tired • Weight loss and poor appetite • Diarrhea • Nausea • Vomiting • Abdominal pain • Constipation • Inflammation of the mouth • Low level of magnesium in blood • Low blood counts • Difficulty breathing

COMMON, SOME MAY BE SERIOUS
• Cough • Numbness and tingling of the extremities • Elevated liver enzymes • Headache • Infection

OCCASIONAL, SOME MAY BE SERIOUS
• Insomnia • Fever • Confusion • Chills • Anxiety • Depression • Dehydration • Low level of calcium and/or potassium in blood • Pain in bone and joint • Eye irritation • Infusion reaction

RARE, AND SERIOUS
• Infusion reactions may be serious in some patients. This reaction can be severe with difficulty breathing, itching, and low blood pressure • Problem with your heart

Panitumumab

COMMON, SOME MAY BE SERIOUS
• Skin problems such as dermatitis acneiform (acne like bumps on skin), pruritus (itching), erythema (redness of the skin), rash, skin exfoliation (flaking of skin), paronychia (fingernail infection), dry skin, skin fissures and others

OCCASIONAL, SOME MAY BE SERIOUS
• Low level of magnesium in blood • Infusion reactions: fever, chills, difficulty breathing, and low blood pressure, which may be fatal • Diarrhea • Photosensitivity • Skin problems that may be life-threatening and fatal, such as serious infection involving any layer of the skin, abscesses, sepsis, fatal disease with blisters, erosions, and skin sloughing (shedding of skin that may result in open wounds) have also been observed.

RARE, AND SERIOUS
• Lung scarring • Inflammation in the eye • Hole (puncture) in the protective layer on the outside of the eye (cornea), which may lead to vision loss/blurred vision, excessive tearing, eye pain, serious infection, and if not treated may lead to blindness (corneal perforation) • Severe dehydration that can lead to kidney failure

Dexamethasone

COMMON, SOME MAY BE SERIOUS
• High blood pressure • High blood glucose • Stomach upset • Burning in stomach from excess stomach acid • Increased risk of infection • Increased appetite • Weight gain • Thinning of bones • Increase pressure in eyes • Personality changes, e.g., irritability, euphoria, mania • Feelings of depression • Pulmonary tuberculosis • Vision problems • Acne, allergic dermatitis, dry scaly skin

Research Procedure Risks

Tissue collection risk

During surgery to install liver pump, if considered safe by your surgeon, we may collect samples of your tumor and normal liver for research purposes. There is a slight risk this may cause additional bleeding, infection or damage to your liver.

Risks from general anesthesia

Risks of general anesthesia include temporary confusion and memory loss, although this is more common in the elderly, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, sore throat due to the breathing tube.

Risks from biopsy

This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site. If received, the most common risks of conscious sedation last up to a few hours after being given can include drowsiness, feeling slow or sluggish, low blood pressure, headache, and nausea. Tumor biopsy will be done by a specialist using the CT scanner or ultrasound to guide the biopsy needle into the tumor to ensure accuracy. We will give you more information about the risks of radiation during the CT guided biopsy on this study in this consent form below.

Blood collection

Side effects of blood draws include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop. The amount of blood collected on this study will be a maximum of about 2.5 tablespoons at once, or about 10 tablespoons over 8 weeks.

Echocardiogram

An echocardiogram is used to evaluate the structure and function of your heart. It uses harmless sound waves which bounce off the heart structures as a series of echoes. The echoes are recorded on moving graph paper or a videotape. This procedure is associated with minimal discomfort.

CT scans

CT scans are a type of common standard imaging test used in the diagnosis of cancer. The most common discomfort is the length of time a patient must lay still during a scan. Occasionally, a patient may become uncomfortable with the closed space of the machines. If this occurs, your doctor can order a medicine to help you relax during this scan. If a contrast agent (the special dye) is given with the scan there is a small risk of having a reaction to the contrast. In that small group of patients who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was given, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely do these symptoms require any treatment. In very rare cases, people have had severe reactions that affect their breathing and heart rhythm. If you have had a reaction in the past, be sure to tell you doctor or nurse about it.

An IV catheter may need to be inserted for administration of the contrast agent or anesthetic. This can cause pain at the site where the IV is placed and carries a small risk of bruising, infection, or inflammation of the skin and vein with pain and swelling.

For IV contrast: You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach.

For oral contrast: You may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

See also risks from radiation below.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from nine CT scans, and the radiation from the one-time check of your pump during the pump installation. The amount of radiation you will receive in this procedure is about 9.46 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans and one time check of your pump function that you get in this study will expose you to the roughly the same amount of radiation as 31.5 years of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 0.9 out of 100 (0.9%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives.

Psychological or Social Risks Associated with Return of Incidental Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your research results could mean something about your family members and might cause you or your

family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Protections Against Misuse of Genetic Information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will make persons with your disease live longer. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the treatment's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease gets worse during treatment

- if you develop unacceptable toxicity to the FUDR
- if there will be technical difficulties with pump
- if you become pregnant
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

After therapy is stopped, we would like to see you for a safety visit 30 days after your last dose.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

CONFLICT OF INTEREST (COI)

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines or the guidelines of their home institution, but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand cancer or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial

compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my identifiable specimens and data to be stored and used by the study team for future studies as described above.

_____ Yes _____ No

Initial Initial

Will your specimens or data be shared with other researchers for use in other studies?

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code (not with your name or other information that could be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will be widely available to anyone who wants it.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

I give permission for my **de-identified** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In some cases, it may help other researchers to know that the specimens or data were collected from you (i.e., they will have your identifiers). If we share your identity with other researchers, their study will be reviewed and approved by an Institutional Review Board who will make sure that the study team is protecting your confidentiality.

I give permission for my **identifiable** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

Information about all the people (including you) in this study may be combined to create what is called summary information. The summary information may be placed in a database and shared in scientific publications. This information will help the researchers understand if some patterns are more common than others among everyone who was a part of this study. The summary information will be available to anyone without the need for any permission. The risk of anyone identifying you based on this information is very low.

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others who should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or that no one will gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dr. Jonathan Hernandez, MD, jonathan.hernandez@nih.gov, 240-760-6072. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Witness:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.