# Research Study Informed Consent Document

**Study Title for Participants:** Testing the addition of a radiation sensitizing drug, IPdR, to the usual chemotherapy treatment (capecitabine) during radiation therapy for rectal cancer

**Official Study Title for Internet Search on http://www.ClinicalTrials.gov:** Protocol 10410, "Phase I study of IPdR in Combination with Capecitabine and Radiotherapy for Rectal Cancer" (NCT# 04406857)

## Overview and Key Information

## What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have rectal cancer that is considered locally advanced (has grown outside the rectum but has not yet spread to distant parts of the body) and you have not yet been treated with surgery.

## Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

## Why is this study being done?

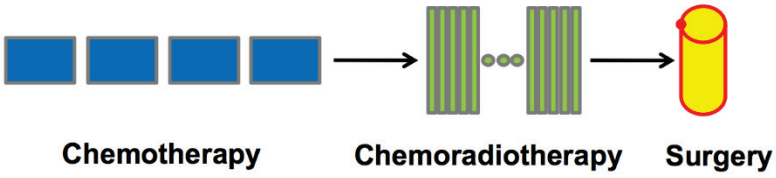
This study is being done to answer the following question:

What is the highest dose of IPdR that can be given safely and tolerably (with manageable side effects) with the usual drug capecitabine, and radiation therapy (RT) for patients with locally advanced rectal cancer?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your rectal cancer. The usual approach is defined as care most people get for rectal cancer.

## What is the usual approach to my rectal cancer?

The usual approach for patients who are not in a study is treatment with chemotherapy, chemotherapy in combination with RT, and then surgery.




You have already received the usual chemotherapy phase of treatment. There are several chemotherapy drugs like capecitabine approved by the Food and Drug Administration (FDA) that are commonly used with RT (chemoRT). Patients then usually have surgery 2-3 months after finishing the chemoRT phase to remove any remaining rectal cancer. For patients who get the usual approach for this cancer, about 70 out of 100 are free of cancer after 5 years.

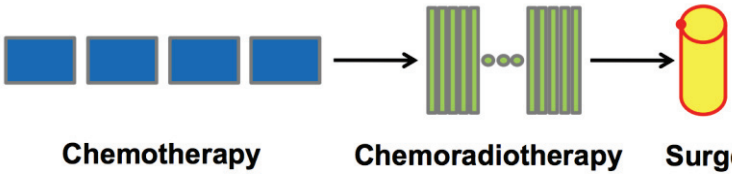
## What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

## What will happen if I decide to take part in this study?

If you decide to take part in this study, you will get capecitabine with the study drug IPdR, and you will get RT. IPdR capsules are taken by mouth once a day. IPdR capsules are taken on an empty stomach, either 1 hour before or 2 hours after meals, 7 days per week, until your radiation therapy is complete. On days when you will also get radiation treatment, your IPdR dose should be taken between 30 minutes and 2 hours before radiation begins. These doses can be taken at home. Capecitabine tablets are taken by mouth with a glass of water twice a day, about 12 hours apart and within 30 minutes of a meal, on days when you get RT. You will take capecitabine tablets on Monday morning through Friday evening only, each week until your radiation therapy is complete. This combination is called chemoRT and will take about 6 weeks. After you finish chemoRT, your doctor will watch you for side effects for 4 weeks. You will have an appointment at that time for your doctor to talk with you, examine you, and obtain some follow-up blood tests.

About 8 to 12 weeks after you finish the study treatment, you will have surgery. As is usual, the specimen removed by the surgeon during this surgery will be examined by a pathologist, and the pathologist will check if there are any rectal cancer cells still left in the specimen or if all of the rectal cancer cells have been killed by the chemotherapy and chemoRT.




| | | |
|---|---|---|
| Usual ChemoRT | Radiation therapy (RT) | 28 doses – (Monday through Friday, Weeks 1- 6) |
| | Capecitabine | Tablet by mouth twice a day (Mon AM-Fri PM) during RT |
| Study treatment adds | IPdR | Capsule by mouth once a day (7 days/week) during RT |

## What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

**Risks**

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

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

There is also a risk that you could have side effects from the study drug, IPdR. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

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

- Diarrhea
- Dehydration

There may be some risks that the study doctors do not yet know about. Other side effects may be very serious and even result in death.

**Benefits**

There is some evidence in animals implanted with human colorectal cancer tumors that adding IPdR to the usual approach can shrink and/or stabilize the cancer for longer than the usual approach alone. However, we do not know if this will happen in people with rectal cancer. It is unlikely that adding IPdR to the usual approach will help you live longer than the usual approach alone. This study may help the study doctors learn things that may help other people in the future.

## If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

## Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the, Institutional Review Board (IRB), FDA, or study sponsor (NCI). The study sponsor is the organization who oversees the study.

**It is important that you understand the information in the informed consent before making your decision.** Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

## What is the purpose of this study?

The purpose of this study is to test the safety and tolerability of the study drug called IPdR when added to a usual treatment for rectal cancer, capecitabine along with radiation therapy. We are also trying to determine the highest dose that has manageable side effects. This drug has been tested in animals and in people with radiation therapy, but has not been tested in combination with capecitabine plus radiation therapy or in subjects with rectal cancer. This study tests

different doses of the drug to see which dose is safe to give along with capecitabine and radiation therapy for people. There will be about 20-30 people taking part in this study.

## What are the study groups?

Different people taking part in this study will get different doses of the study drug, IPdR.

Treatment schedule: You will take IPdR capsules by mouth once a day. You will take IPdR capsules on an empty stomach, either 1 hour before or 2 hours after meals, for about 6 weeks. On days when you will also get radiation treatment, your IPdR dose should be taken between 30 minutes and 2 hours before radiation begins. These doses can be taken at home. You will start taking IPdR capsules on the first morning of radiation treatment every day (7 days a week), and will stop after the last radiation treatment. You will also take capecitabine tablets twice daily (morning and evening) on days that you receive RT. Radiation treatment consists of 28 doses of radiation, which will be given to you over a period of about 6 weeks. Because radiation treatments are usually given Monday through Friday, you will take capecitabine Monday morning through Friday evening each week of RT. Capecitabine should be taken within 30 minutes after a meal (breakfast and dinner). See the study calendar at the end of this document for more information.

The first person taking part in this study will get the lowest dose. If the drug does not cause serious side effects, which will be observed for a period of 4 weeks following chemoRT, the second person in the study will get double the dose that the first person received. The study doctor will watch each participant carefully as they increase the dose. The doses will continue to double for every new participant until someone has serious side effects. When this happens, if the side effect is severe, the dose doubling stops. If the side effect is serious but not severe, two new participants will get the same dose as this person. If neither of these two people also has serious side effects, the dose will continue to double for each new participant.

When one participant has a severe side effect or at least two participants have serious but not severe side effects at a given dose, dose doubling stops. Three new participants will get this dose and be watched for side effects. If none of these people have serious side effects, the next group of three participants will receive a slightly higher dose. If only one participant has serious side effects at a given dose, three more participants will get this dose. If none of these new participants has serious side effects, the dose will increase slightly for a group of three new participants. When at least two participants getting the same dose experience serious side effects, dose increases stop. Once the highest dose with manageable side effects is found, the study is stopped.

You will not be able to get additional doses of the study drug IPdR. This drug is not approved by the FDA for treatment of your disease.

## What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you

join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

You will need to have blood samples taken for the study. Blood samples will be collected on Days 8, 21, and 35 during study treatment at multiple time points before and after taking the IPdR capsules to check the level of IPdR in your blood and also to check the effect of IPdR on your blood cells. On these days (Days 8, 21, and 35), you will be instructed about the specific time to take your IPdR dose.

- On Day 8- Three teaspoons of blood will be drawn prior to taking IPdR morning dose, and then another two teaspoons at 30 min, 1 hour, 2 hours, and 4 hours after taking IPdR
- On Days 21 and 35- Three teaspoons of blood will be drawn at 1-2 hours following IPdR morning dose

The timing (about 8-12 weeks following completion of chemoRT) and procedure for your surgery to remove any remaining tumor is the same as if you were not on this study.

If you are on this study, some of the tissue from your surgery will be tested to see if there are any remaining tumor cells, and if so, if there is any IPdR in them. This testing uses some of the tissue from your surgery, but no extra tissue will be removed at the time of surgery for this test. This testing is a required part of the study. You and your study doctor will not get the results of this testing.

A patient study calendar is attached at the end of this document. It shows how often these procedures will be done.

## What risks can I expect from taking part in this study?

### General Risks

If you choose to take part in this study, there is a risk that the addition of the study drug, IPdR, to the usual approach may not be as good as the usual approach alone for your rectal cancer at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The study drug, IPdR used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check

with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 4 months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

**Blood Draw Risks**

Some of the risks from drawing blood from your arm may include pain, bruising, light-headedness, and rarely, infection. For most people, needle punctures to get blood samples do not cause any serious harm. The multiple, and frequent blood draws for research testing may be burdensome and inconvenient given the time you need to stay in the clinic. In addition, the frequent needle sticks in your arm may be uncomfortable if you do not have an infusion line or it cannot be used. Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

**Side Effect Risks**

The study drug 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 test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drug.

Here are important things to know about side effects:

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

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

You should notify your doctor immediately at the first sign of poorly formed or loose stools or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.

**Drug Risks**

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

**Possible Side Effects of IPdR** (Table Version Date: April 12, 2019)

| **POSSIBLE, SOME MAY BE SERIOUS** |
|---|
| **Please Note: A safety study of single dose IPdR in 10 study participants resulted in no treatment-related side effects. However, some side effect data is available for iododeoxyuridine (IUdR) administered by continuous intravenous infusion in combination with localized radiation. Since oral IPdR is converted in the body to IUdR, the side effects of oral IPdR may be similar to those side effects observed in clinical trials of intravenous IUdR. The side effects observed in IUdR clinical trials are presented in this condensed risk list:**<br>• Blockage of the bowel which may cause belly pain, vomiting<br>• Internal bleeding which may cause black tarry stool, belly pain<br>• Anemia which may cause tiredness, or may require blood transfusion<br>• Diarrhea, nausea<br>• Bruising, bleeding<br>• Weight loss |
| **Additional side effects observed only in animal studies using IPdR:**<br>• Loss of appetite<br>• Muscle weakness<br>• Shortness of breath<br>• Tiredness |

**Possible Side Effects of Capecitabine** (Table Version Date: October 17, 2019)

| **COMMON, SOME MAY BE SERIOUS** |
|---|
| In 100 people receiving Capecitabine, more than 20 and up to 100 may have: |

| COMMON, SOME MAY BE SERIOUS<br>In 100 people receiving Capecitabine, more than 20 and up to 100 may have: |
|---|
| • Infection, especially when white blood cell count is low<br>• Bruising, bleeding<br>• Anemia which may require blood transfusions<br>• Diarrhea, loss of appetite, nausea, vomiting<br>• Sores in mouth which may cause difficulty swallowing<br>• Swelling of the body<br>• Pain<br>• Feeling of "pins and needles" in arms and legs<br>• Tiredness<br>• Fever<br>• Blisters on the skin<br>• Redness, pain or peeling of palms and soles |

| OCCASIONAL, SOME MAY BE SERIOUS<br>In 100 people receiving Capecitabine, from 4 to 20 may have: |
|---|
| • Abnormal heartbeat<br>• Constipation<br>• Blurred vision, dry or itchy eyes<br>• Muscle spasms, body aches<br>• Restlessness, irritability<br>• Swelling of face, fingers and lower legs<br>• Difficulty with balancing |

| RARE, AND SERIOUS<br>In 100 people receiving Capecitabine, 3 or fewer may have: |
|---|
| • Damage to the heart<br>• Internal bleeding which may cause blood in vomit or black tarry stools<br>• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat<br>• Difficulty speaking, walking or seeing |

**Additional Drug Risks**

The study drug, IPdR, could interact with other drugs. There are no known interactions of IPdR with other drugs, but always tell your doctor about any drugs (prescription or over the counter) that you are taking. Your study doctor will give you a clinical trial wallet card that lists the drugs you are taking. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

**Possible Side Effects of Radiation Therapy**

| COMMON, SOME MAY BE SERIOUS<br>In 100 people receiving radiation therapy, 20 to 100 may have: |
|---|
| • Reddening, tanning, or peeling of the skin<br>• Mild pain<br>• Hair loss<br>• Tiredness<br>• Diarrhea, nausea<br>• Anemia, which may require transfusion<br>• Infection, especially when white blood cell count is low |

| OCCASIONAL, SOME MAY BE SERIOUS<br>In 100 people receiving radiation therapy, 4 to 20 may have: |
|---|
| • Thickening and numbness of the skin<br>• Sores or ulcers on the skin or near the cancer location<br>• Permanent hair loss<br>• Bleeding from the skin<br>• Sores in mouth which may cause difficulty swallowing |

| RARE, AND SERIOUS<br>In 100 people receiving radiation therapy, 3 or fewer may have: |
|---|
| • Damage to internal organs<br>• Abnormal opening in internal organs which may cause pain and bleeding |

## What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.
- Bring your medication diary and the IPdR and capecitabine containers (even if they are empty) with you to each visit with your study team.

**For women:** Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 4 months after your last dose of study drug.

## What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of capecitabine and radiation therapy.
- the costs of the digital rectal exam and either a proctoscopy or sigmoidoscopy done as part of your pre-operative examination. Proctoscopy is a procedure that uses a proctoscope to look inside the anus and rectum. Sigmoidoscopy is the examination of the lower colon using a sigmoidoscope, inserted into the rectum. A proctoscope and a sigmoidoscope are thin, tube-like instruments with a light and a lens for viewing. They may also have a tool to remove tissue to be checked under a microscope for signs of disease.
- the costs of the surgery at about 8 to 12 weeks after you finish the study treatment.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The blood tests on the Day 8 to check the level of IPdR in the blood
- The blood tests on the Days 21 and 31 to check the level of IPdR in the blood and examine the effect of IPdR on your blood cells

You or your insurance provider will not have to pay for the IPdR while you take part in this study. As mentioned above, you or your insurance provider will be responsible for the costs of the capecitabine and radiation therapy.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

## What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

## Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study in the future. This would include any organization helping the sponsor/company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.

- You will not get reports or other information about any research that is done using your information.

## Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

## My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study.

**Participant's signature**

Date of signature

**Signature of person(s) conducting the informed consent discussion**

Date of signature

## 10410 – Patient Study Calendar

| | Pre-Study | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | 4 weeks after the completion of study treatment (Week 10) | Surgery at 8-12 weeks following completion of study treatment (Week 14-18) |
|---|---|---|---|---|---|---|---|---|---|
| IPdR[A] | | X----------X | | | | | | | |
| Capecitabine[B] | | X----------X | | | | | | | |
| Radiation therapy (RT)[C] | | X----------X | | | | | | | |
| Pre-study procedures including Informed consent, Demographics, Medical history, and Height | X | | | | | | | | |
| Concurrent meds | X | X----------X | | | | | | X | X |
| Physical exam, Vital signs, Weight | X | X | X | X | X | X | X | X | X |
| An assessment of how you perform everyday tasks and activities | X | X | | | | X | | X | X |
| Blood draws for complete blood count and general health status | X | X | X | X | X | X | X | X | X |
| EKG (as indicated) | X | | | | | | | | |
| Blood draws for research study (mandatory) | | | X[b] | X[b] | | X[b] | | | |
| Side effects evaluation | | X----------X | | | | | | X | |
| Mandatory collection of a sample from your surgery | | | | | | | | | X[a] |
| Medical imaging scans to look at your tumor | X | | | | | | | | X[c] |
| Digital rectal exam and proctoscopic or sigmoidoscopic exam | | | | | | | | | X[d] |
| Pregnancy test | X | | | | | | | | |

A: IPdR: Dose as assigned; take by mouth once a day everyday throughout the duration of RT (Weeks 1-6). On days when you will also get radiation treatment, the IPdR dose should be taken between 30 minutes and 2 hours before radiation begins. These doses can be taken at home.

B: Capecitabine: Dose as assigned; take by mouth twice a day on days of RT (taken Monday morning through Friday evening each week of RT)

C: You will receive RT on Monday to Friday for 6 weeks (Weeks 1-6) and will receive a total of 28 doses

a: Specimen removed by the surgeon during this surgery will be examined by a pathologist, and the pathologist will check if there are any rectal cancer cells still left.

b: Blood for research studies will be drawn on Day 8, prior to taking your IPdR dose; and then at 30 min, 1 hour, 2 hour, and 4 hours after taking your IPdR dose. On Day 21 and Day 35, blood will be drawn at 1-2 hours after taking your IPdR dose.

c: You will need to come in for this scan at 6-10 weeks following completion of therapy (within the 2 weeks before you have surgery).

d: Your surgeon will perform a digital rectal exam and either a proctoscopy or sigmoidoscopy as part of your pre-operative examination (within the 2 weeks before you have surgery)