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MED. REC. NO.: _____

NAME: _____

**OHSU Oregon Health & Science University
Consent Form**

IRB#: 4236

Protocol Approval Date: 06/10/2008

**Oregon Health & Science University
OHSU Cancer Institute Consent Form**

SUBJECT NAME: _____ **DATE:** _____

TITLE: Timing of Rectal Cancer Response to Chemoradiation

PRINCIPAL INVESTIGATOR: Charles Thomas, MD (503) 494-8756

CO-INVESTIGATORS:
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SPONSOR: University of California San Francisco (UCSF)

SUPPORTED BY: National Institute of Health (NIH)

INTRODUCTION:

You have been invited to participate in this research study because you have rectal cancer and are planning to have treatment for your cancer.

This is a clinical trial (a type of research study). Clinical trials include only subjects who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.



CO1450

IRB#: _____

MED. REC. NO.: _____

NAME: _____

WHY IS THIS STUDY BEING DONE?

The usual treatment for patients with your type of cancer includes radiation therapy and chemotherapy followed by surgery to remove the rectum. Chemotherapy and radiation are given at the same time, and the combined treatment is called chemoradiation.

Chemoradiation has been effective in treating rectal cancer. However, the optimum timing of the different parts (chemoradiation, surgery, and chemotherapy) has not been established. This study is being done to see when the best time to have surgery for your cancer is when standard chemoradiation and chemotherapy are given. It is believed that extending the interval between these different parts, and giving chemotherapy before surgery, may result in better outcomes for subjects with rectal cancer by allowing more time for the tumor to possibly continue to shrink.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

As many as 248 people will take part in this study which will be conducted at Oregon Health & Science University and other hospitals and universities across the United States and Canada. Of these subjects, about 4 will be enrolled at OHSU.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to the investigator.

- History and Physical Exam
- Chest x-ray
- CT (Computed Tomography – uses special x-ray equipment to produce pictures of inside the body) scan of your abdomen and pelvis – to determine the size and location of your tumor
- Proctoscopic exam - involves inserting a hollow tube into your rectum to evaluate your tumor.
- Endorectal Ultrasound (ERUS) uses a probe to produce an image of inside the rectum or Magnetic Resonance Imaging (MRI) uses a magnetic field to produce detailed pictures of inside the body to determine the size and location of your tumor
- Blood draw (approximately 3 teaspoons) - for standard blood tests
- Pregnancy test (if you are a woman of child-bearing potential)

During the study:

If the tests, exams and procedures show that you can participate in the study, you will be placed into one of the groups described below. No matter what group you are in you will receive

IRB#: _____

MED. REC. NO.: _____

NAME: _____

chemoradiation [radiation therapy and chemotherapy with Fluorouracil (5-FU)] for about 6 weeks. If you are in groups 2-4 you will receive more chemotherapy before surgery, but in different amounts and at different times depending on what group you are in.

Group 1: this group has been completed.

If you are in group 2: after chemoradiation you will receive 2 cycles (the second cycle will be given 2 weeks after the first) of chemotherapy starting about 4 weeks after chemoradiation, and then surgery about 11 weeks after finishing chemoradiation.

If you are in group 3: after chemoradiation you will receive 4 cycles (one cycle every two weeks) of chemotherapy starting about 4 weeks after chemoradiation, and then surgery about 15 weeks after finishing chemoradiation.

If you are in group 4: after chemoradiation you will receive 6 cycles (one cycle every two weeks) of chemotherapy starting about 4 weeks after chemoradiation, and then surgery about 19 weeks after finishing chemoradiation.

We will enroll patients into each group until we have met the required number of patients for that group (each group will have 62 patients). This way we will have results from the previous group before we move on to the next one. You are being asked to participate in Group _____.

You and the investigator will know which group you are enrolled in if you decide to participate in this study. Please ask the investigator if you have any questions about this kind of study.

Chemoradiation [Radiation therapy and Fluorouracil (5-FU)]:

Radiation therapy will be given to your whole pelvis once a day, 5 days a week for approximately 6 weeks. The first visit will take approximately 45 minutes, but the next visits will take approximately 10 minutes each.

You will also receive the chemotherapy drug Fluorouracil (5-FU). This is given continuously through a needle in a vein in your arm (intravenously) for 24 hours a day 7 days a week. 5-FU is administered through a small portable pump that you can wear on a belt and will be given through a special line called a PICC (Peripherally Inserted Central Catheter). In some cases, a port-a-cath is used instead of a PICC line. A port-a-cath is a device implanted just below the skin that allows access to a vein for the purpose of giving medications or drawing blood. Your oncologist will tell you whether or not you will be using a port-a-cath or a PICC line and will describe the procedure to you.

Post-chemoradiation chemotherapy (mFOLFOX-6):

The chemotherapy given after chemoradiation but before surgery is called modified FOLFOX-6 (mFOLFOX-6). This is a combination of three drugs, all given by vein (intravenously) through the PICC or port-a-cath: leucovorin, 5-FU, and oxaliplatin. Both leucovorin and oxaliplatin are

IRB#: _____

MED. REC. NO.: _____

NAME: _____

given over 2 hours. 5-FU is given once as a single, large dose that takes about 5 minutes and again as a 46-hour infusion.

Surgery:

After your last week of post-chemoradiation chemotherapy you will have an operation to remove your tumor.

Tests and procedures while you are on the study treatment:

While you are on study treatment, you will need the following tests and procedures at the times listed below. They are part of regular cancer care.

- Proctoscopic exam - depending on what group you are in, you will have a proctoscopic exam at the following times:
 - Group 2: Week 10
 - Group 3: Week 10 and 14
 - Group 4: Week 10, 14, and 18
- ERUS or MRI – depending on what group you are in, you will have an ERUS or MRI at the following times:
 - Group 2: Week 10
 - Group 3: Week 10 and 14
 - Group 4: Week 10, 14, and 18
- Physical exam – no matter what group you are in, you will have a physical exam during week 10, before surgery, and on an as-needed basis.
- Blood draw (approximately 3 teaspoons) for standard lab tests – no matter what group you are in, you will have blood drawn every week during chemotherapy and again before surgery.

When you are finished with the study treatment:

You will be followed for 30 days after the completion of the treatment. You will return to the clinic 2-3 weeks after your surgery for an assessment with the investigator. This is done as part of standard of care and is not done specifically for the study. About 1-2 weeks later you will be contacted via telephone by a member of the research team to see how you are feeling. After this you will be considered off of the study and no other follow-up will be required. After that you will be treated by your regular doctor as part of standard treatment.

Optional genetic study:

We would like to collect tumor tissue samples to look for genes and proteins that may be related to how your rectal cancer behaves or how you respond to treatment. In this optional portion of the study, you will be asked to provide tumor tissue samples for further investigation.

The research on your tumor samples will involve looking at the genetic material (known as DNA) and proteins to learn more about who will benefit from treatment for rectal cancer. Genes

IRB#: _____

MED. REC. NO.: _____

NAME: _____

are the units of DNA--the chemical structure carrying your genetic information--that determine many human characteristics such as the color of your eyes, your height, and whether you are male or female.

Your tumor tissue samples will not be used in future research and your entire genetic makeup will not be determined from your samples. These samples will be stored until the study is completed, and any samples remaining after that time will be destroyed.

You can still be in the main study if you choose not to participate in the optional genetic study. If you choose to participate in the optional genetic study, the following will be collected.

- **Biopsy sample:** a portion of your tissue removed as part of your initial diagnosis.
- **Surgical pathology sample:** a portion of your tissue that will be removed during the surgery portion of this study.

If we are not able to obtain a biopsy sample before you begin the study treatment, you may be asked to undergo a proctoscopic exam in order to collect a tissue sample for research purposes. This procedure for the optional portion of the study is voluntary. If you are willing to undergo a proctoscopic exam for the purpose of obtaining a tissue sample for research, there will be no additional charge to you or to your insurance company.

Because these samples will be collected before or during regular study visits there will be no added time required to take part in this in this portion of the study.

A code number will be assigned to you, your tumor tissue samples and information about you. Only the investigators named on this consent form, as well as Karin Avila, Clinical Research Coordinator at UCSF, will be authorized to link the code number to you. Other investigators who may receive samples of your tumor tissue for research will be given only the code number which will not identify you.

All other parties including employers, insurance companies, personal physicians, and relatives will be refused access to the information or to the samples, unless you provide written permission, or unless we are required by law to do so.

You will have the opportunity to make a decision about this optional genetic study at the end of this consent form.

If you have any questions regarding this study now or in the future, contact Dr. Charles Thomas at (503) 494-8756. Please see the study chart below for more information.

IRB#: _____

MED. REC. NO.: _____

NAME: _____

SUMMARY OF STUDY EXAMS AND PROCEDURES

Procedure	Screening	Week 1-6	Week 7-9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22-23	Week 24	Week 25	Week 26-27	Week 28
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CO1450

²Group 2 ³Group 3 ⁴Group 4

IRB#: _____

MED. REC. NO.: _____

NAME: _____

Medical history and physical exam	X			X						X ²				X ³			X ⁴		
Chest x-ray	X																		
CT scan	X																		
Proctoscopic exam	X			X				X ^{3,4}			X ⁴								
ERUS/MRI	X			X				X ^{3,4}			X ⁴								
Chemoradiation		X																	
Blood tests	X	X		X	X	X	X	X ^{3,4}	X ^{3,4}	X ^{3,4}	X	X ⁴	X ⁴	X ⁴	X ^{3,4}			X ⁴	
Pregnancy test	X																		
Chemotherapy				X		X		X ^{3,4}		X ^{3,4}		X ⁴		X ⁴					
Surgery											X ²				X ³			X ⁴	
Follow-up														X ²			X ³		X ⁴
OPTIONAL tumor biopsy	X																		
OPTIONAL pathology sample											X ²				X ³			X ⁴	

IRB#: _____

MED. REC. NO.: _____

NAME: _____

SUBJECT ACCESS TO GENETIC INFORMATION

The results of these studies will not be made available to you because the research is still in an early phase and the reliability of the results is unknown.

HOW LONG WILL I BE IN THE STUDY?

You will be in the treatment phase of the study for up to seven months. About 30 days after you finish the study treatment you will come back to the clinic for a follow-up visit to see if your cancer has come back or if you have any other health problems. However, the investigator may take you off this study if your cancer does not improve, if any new areas of cancer develop, if you become pregnant, if you have serious side effects, if you do not follow instructions, or if the investigator determines that it is in your best interest.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the investigator if you are thinking about stopping or decide to stop.

It is important to tell the investigator if you are thinking about stopping so that he or she can discuss what follow-up care and testing you might need for your safety.

You will be told if we learn anything in doing this study that might make you want to change your mind about continuing to be in the study.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, the investigators do not know all the side effects that may happen. Side effects may be mild or very serious. The investigator may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to the investigator about any side effects that you have while taking part in the study.

The chemoradiation treatment used in this study is considered standard of care for your type of cancer, and you will be receiving it whether you participate in the study or not. Chemoradiation often cause side effects, but these side effects are not specifically due to the study. They will be discussed with you by your medical oncologists and radiation oncologists.

Below is a list of side effects that are associated with the drugs that make up mFOLFOX-6 (post-chemoradiation chemotherapy). Although mFOLFOX-6 is approved by the FDA in the treatment of colorectal cancer, it is not commonly used after chemoradiation in rectal cancer patients. This is a combination of three drugs, all given by vein (intravenously) through the PICC or port-a-cath: leucovorin, 5-FU, and oxaliplatin. Both leucovorin and oxaliplatin are given over 2 hours. 5-FU is given once as a single, large dose that takes about 5 minutes and again as a 46-hour



IRB#: _____

MED. REC. NO.: _____

NAME: _____

infusion. Therefore, it is possible you may experience different or more severe side effects from mFOLFOX-6.

For the following side effects, "likely" events are expected to happen to more than 20% of subjects, "less likely" events will probably happen to about 20% of subjects, and "rare but serious" events will happen to less than 1-2%.

Risks and side effects related to Fluorouracil (5-FU):

Likely:

- Mouth and throat sores
- Diarrhea
- Heartburn
- Nausea
- Vomiting
- Loss of appetite
- Hair loss (which may be complete)
- Skin irritation
- Itchy skin rash (all over the body and at the location of the PICC or port-a-cath)
- Discoloration of nails and skin
- Photosensitivity (an allergic reaction to the sun that may cause a rash)
- Numbness, tingling and painful blistering on the palms of the hands or soles of the feet

Less likely:

- Dry skin
- Ulcers in the digestive tract
- Muscle weakness
- Low blood calcium levels (may cause muscle soreness or a "pins and needles" type of sensation in the muscles)

Rare but serious:

- Low blood pressure
- Chest pain
- Your heart beating too fast (also called tachycardia)
- Your heart beating too slow (also called brachycardia)
- Myocardial ischemia, which occurs when the arteries in your heart become partially blocked and your heart does not get enough blood
- Decrease in bone marrow function (causes a decrease in the number of white blood cells and platelets in the blood, which can lead to an increased risk of infection and easy bruising or bleeding)

IRB#: _____

MED. REC. NO.: _____

NAME: _____

Risks and side effects related to Oxaliplatin:

Likely:

- Nausea
- Vomiting
- Fatigue
- Loss of appetite
- Neurological problems, such as: numbness, tingling, and weakness or pain in the arms and legs or elsewhere on the body
- Altered taste
- Abdominal pain and cramping
- Diarrhea
- Constipation
- Inflammation or infection of the bowel wall
- Decreased red blood cell count (also called anemia) can cause fatigue and shortness of breath
- Decreased platelet count can cause bleeding and may require blood transfusions

Less likely:

- Rash
- Loss of taste
- Sores in the mouth or throat
- Decreased white blood cell count can lead to susceptibility to infection that can be life threatening
- Sensation of difficulty in breathing or swallowing that may be worsened by drinking cold beverages or exposure to cold air

Rare but serious:

- Cough and shortness of breath due to inflammation and scarring or fibrosis (formation of tissue containing fibers) of the lung
- Liver injury
- Confusion
- Stroke

Risks and side effects related to Leucovorin:

Rare but serious:

- Allergic reaction, such as:
 - Skin rash
 - Hives
 - Itching
 - Wheezing

The combination of 5-FU and leucovorin may frequently cause diarrhea, mouth sores, nausea, vomiting, fatigue, hair loss, loss of weight and occasionally a skin rash.

Risks and side effects related to surgery:

Likely:

- Bleeding
- Infection
- Inability to control your bowels

Less likely:

- Rectal stricture (scar tissue that may narrow your rectum)
- Urethral injury (injury to the urinary tract which could lead to urinary problems such as incontinence or impotence)
- Rectovaginal fistula (an opening between the rectum and vagina)

For blood draw: We will draw blood from a vein in your arm. You may feel some pain when your blood is drawn. There is a small chance the needle will cause bleeding, a bruise, or an infection.

For MRI: The magnetic resonance imaging (MRI) machine is a powerful magnet. This magnet may cause any metal in your body to move. If you know of any metal in your body, you will need to tell the investigator right away. Otherwise, there are no known risks of MRI. Some individuals with claustrophobia (fear of closed spaces) may find the MRI equipment too confining. In that case, you can request to be removed from the scanner and this will be done immediately. The MRI scanner makes a loud thumping sound. You may be asked to wear protective earplugs during scanning. The dye that is injected into a vein in your arm for the scan is well tolerated. Some people feel dizzy or queasy or get a headache with it or notice a cold feeling near the injection site. There is a rare chance of having an allergic reaction to the dye that very rarely can be serious and life threatening.

For x-rays: In this study, you will be exposed to radiation during the chest x-ray. While we cannot be sure any dose of radiation is entirely safe, the amount you will be exposed to in this study is not known to cause health problems.

For CT scans: In this study, you will be exposed to radiation during the CT scan. Although the amount to which you will be exposed is higher than from a typical x-ray, the risk of harmful effects from these exams is very small.

For Tumor Biopsy (only if you decide to participate in the optional genetic portion of the study): If we are unable to obtain a biopsy sample before you begin study treatment and you agree to having another biopsy performed for purposes of the study, there may be additional risks. The risks of a tissue biopsy via proctoscopy include bleeding and infection.

IRB#: _____

MED. REC. NO.: _____

NAME: _____

For pregnancy/risk to fetus (For Women): The drugs in this study can affect a fetus or a nursing infant. You should not become pregnant or nurse your baby while on this study. If you are sexually active and are at risk of getting pregnant, you and your male partner(s) must use a method of birth control that works well or you must not have sex. The investigator will talk to you about the types of birth control that are acceptable. You will have to use birth control or abstain the whole time you are in this study. If you become pregnant during the research study, please tell the investigator and your doctor immediately.

For pregnancy/risk to fetus (For Men): The drugs in this study can damage sperm. You should not father a child while on this study. If you are sexually active and are at risk of causing a pregnancy, you and your female partner(s) must use a method of birth control that works well or you must not have sex. The investigator will talk to you about the types of birth control that are acceptable. You will have to use birth control or abstain the whole time you are in this study. If a female partner becomes pregnant during the research study, please tell the investigator and ask your partner to tell her doctor immediately.

Delayed surgery: **The longer waiting period is done specifically for the study and is not considered standard of care.** By having additional chemotherapy before surgery, you may experience additional and/or severe toxicities. Depending on the nature and severity of these toxicities, your treatment could lead to a delay in surgery. **In addition, there is a risk that the tumor will grow during the longer waiting period before surgery. If the investigator or your doctor discovers that the tumor has not responded to the chemoradiation (the size is the same or larger compared to the tumor before chemoradiation) you will have surgery immediately.** If your surgery is delayed for more than 6 weeks after the last day that you receive pre-operative chemotherapy, you will be taken off study and treated according to standard of care.

If the results of these studies of your genetic makeup were to be released through a breach of confidentiality, this could affect your ability to get insurance or to get or keep a job.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

You may or may not personally benefit from being in this study. However, by serving as a subject, you may help us learn how to benefit patients in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose not to be in this study.

Instead of being in the study, you have these options:

- Get treatment or care for your cancer without being in a study.

IRB#: _____

MED. REC. NO.: _____

NAME: _____

- Take part in another study.
- Receive no treatment.

If you decide that you do not want any further active treatment for your rectal cancer, one of your options is called “comfort care.” Comfort care means that your doctor will offer you medication to help control your pain, together with any other treatment and support you need to help you maintain your overall comfort and dignity. It is often possible for this comfort care to be provided at home.

If you think that comfort care is something you might prefer, feel free to discuss it with family and friends, any spiritual advisor, and your doctor.

Please talk to your regular doctor about these and other options.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

Efforts will be made to keep your personal information in your medical record confidential. We cannot guarantee total privacy. Your personal information may be disclosed if required by law. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the OHSU Cancer Institute, the OHSU IRB, the National Cancer Institute (NCI), the University of California San Francisco Clinical Trial Office, Karin Avila (Clinical Research Assistant at UCSF), and the Food and Drug Administration (FDA).

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Some of the tests, drugs and procedures in this study are part of the regular treatment for your condition. These would be performed or given to you even if you were not in this study. The costs for these tests, drugs and procedures will be billed to your insurance. If you are uninsured, you will be billed for them. You will be responsible for any costs your insurance does not cover. The tests, drugs and procedures that are considered standard of care and which will be billed to your insurance include: chest x-ray, abdominal CT scan, proctoscopic exam, ERUS, MRI, radiation therapy, 5-FU, mFOLFOX-6, surgery, blood draws, pregnancy tests, and physical exams.

You will not be responsible for the tests and procedures that are not considered standard of care. These include the proctoscopic exam to obtain tumor tissue (if necessary) and the genetic tests on your tumor tissue samples that are part of the optional portion of the study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

If you believe you have been injured or harmed while participating in this research and require immediate treatment, contact Dr. Charles Thomas at (503) 494-8756.

IRB#: _____

MED. REC. NO.: _____

NAME: _____

You have not waived your legal rights by signing this form. If you are harmed by the study drugs or procedures, you will be treated. Oregon Health & Science University does not offer to pay for the cost of the treatment. Any claim you make against Oregon Health & Science University may be limited by the Oregon Tort Claims Act (ORS 30.260 through 30.300).

Oregon Health & Science University is also subject to the Oregon Genetic Privacy law (ORS 192.531 through ORS 192.549) and its requirements concerning confidentiality and the legal remedies provided by that law for breach of its requirements. You have not waived your legal rights by signing this form. For clarification on this subject, or if you have questions, please call the OHSU Research Integrity Office at (503) 494-7887.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

You do not have to join this or any research study. If you do join, and later change your mind, you may quit at any time. If you refuse to join or withdraw early from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled.

Your health care provider may be one of the investigators of this research study, and as an investigator is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another doctor who is in no way involved in this project. You do not have to be in any research study offered by your physician.

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a revised consent form if this occurs.

If you choose to withdraw from the study, the investigator will discuss what alternative follow up care and testing would be most helpful for you.

We will give you a copy of this signed form.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

Dr. Charles Thomas (telephone: 503-494-8756) has offered to answer any questions you may have about this study. You will be informed of any new findings developed during the course of this research study that may change the way you feel about being in the study.

If you have any questions regarding your rights as a research subject, you may contact the Oregon Health & Science University Research Integrity Office at (503) 494-7887.

IRB#: _____

MED. REC. NO.: _____

NAME: _____

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at 1-800-4CANCER or TTY 1-800-332-8615.

IRB#: _____
MED. REC. NO.: _____
NAME: _____

SIGNATURES:

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No" and place your initials on the line. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to the investigator.

1. I choose to take part in the optional genetic portion of the study.

Yes _____ No _____

2. I am willing to undergo a proctoscopy to obtain a tissue sample for this optional genetic portion of the study in the event that a tissue sample from a previous biopsy is not available.

Yes _____ No _____

Your signature below indicates that you have read this entire form and that you agree to be in this study.



Subject signature

Date

Signature of person obtaining consent

Date

Print name of person obtaining consent

Date