# NCI Community Oncology Research Program – KC (NCORP-KC)

## N1048: A Phase II/III trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

***This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.***

**This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.**

You are being asked to take part in this research study because you have cancer of the rectum.

### WHY IS THIS RESEARCH STUDY BEING DONE?

The standard treatment for locally advanced rectal cancer involves chemotherapy and radiation, known as 5FUCMT, (the chemotherapy drugs 5-fluorouracil/capecitabine and radiation therapy) prior to surgery. Although radiation therapy to the pelvis has been a standard and important part of treatment for rectal cancer and has been shown to decrease the risk of the cancer coming back in the same area in the pelvis, some patients experience undesirable side effects from the radiation and there have been important advances in chemotherapy, surgery, and radiation which may be of benefit. The purpose of this study is to compare the effects, both good and bad, of the standard treatment of chemotherapy and radiation to chemotherapy using a combination regimen known as FOLFOX, (the drugs 5-fluorouracil (5-FU), oxaliplatin and leucovorin) and selective use of the standard treatment, depending on response to the FOLFOX. The drugs in the FOLFOX regimen are all FDA (Food and Drug Administration) approved and have been used routinely since 2002 to treat patients with advanced colorectal cancer.

This study is conducted by the Alliance, a national collaboration of researchers and physicians with different types of background and training who work together to plan and conduct clinical trials in cancer that will lead to improved treatment strategies that will decrease suffering and death. Alliance members come from major academic medical centers, community hospitals and community practice.

## HOW MANY PEOPLE WILL TAKE PART IN THE RESEARCH STUDY?

About 1120 people will take part in this study.

## 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 your study doctor.

- A history and physical exam, including your height, weight, pulse, blood pressure and temperature
- Routine blood tests (about 2 teaspoons of blood will be drawn)
- Pregnancy test (if applicable)
- Measurement of your rectal tumor by either MRI or endorectal ultrasound (ERUS)
- A CT scan of your chest, abdomen and pelvis to ensure that the cancer has not spread outside the pelvic area

### BEFORE THE STUDY TREATMENT BEGINS…

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care**.**

- Physical examination and interview
- Interview about recent and current symptoms (adverse events)
- A rectal exam performed by the colorectal surgeon who will operate on you
- A proctoscopy with biopsies performed by your colorectal surgeon or a gastroenterologist. A proctoscopy is similar to a colonoscopy or sigmoidoscopy but does not require examination of the entire colon so the preparation or "clean out" of your intestine is less extensive. Proctoscopy requires examination of just the lower part of the intestine known as the rectum.
- The biopsy sample of your rectal tumor will be studied by a pathologist to confirm the presence of rectal cancer. This may be performed even if you had a biopsy performed at another hospital.
- Blood and tissue samples will be collected that will help study investigators determine which if any patients can safely avoid radiation and which patients have especially good responses to the FOLFOX chemotherapy. The blood samples are required and about two teaspoons will be drawn. For patients in Group 1, these blood samples will be drawn within 14 days of beginning FOLFOX chemotherapy and before surgery. For patients in Group 2, these blood samples will be drawn within 14 days of beginning 5FUCMT chemoradiation and before surgery. The

tissue samples will be taken at the same time as the clinically recommended proctoscopy at baseline.

- Questionnaires about your day to day symptoms such as pain and constipation. You can choose whether you prefer to answer questions about your day to day symptoms using a confidential internet website or using a telephone voice response system. You will be asked to provide a telephone number and an active email address if you have one for contact. If you do not answer the questions as scheduled, you will receive an automated reminder call or email from the questionnaire coordinator. If there is no response to two successive reminders, an automatic email notification will be sent to the questionnaire coordinator who will then call you to discuss your symptoms.

**Treatment**

After completing these tests and procedures, you will be 'randomized' or assigned by chance to one of two study groups. A computer program will assign you to one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group. All of the study drugs used in both groups have been FDA-approved for the treatment of colorectal cancer.

There will be two treatment groups in this study.
If you are in:

**Group 1** – You will receive FOLFOX chemotherapy once every two weeks. On the first day of the cycles (Day 1), you will be given leucovorin and oxaliplatin through a catheter placed in a vein in your arm (intravenously or IV) for 2 hours and also 5- fluorouracil IV via continuous infusion. This is one cycle; you will receive 6 cycles total over a period of 12 weeks.

After completing FOLFOX chemotherapy, you will have an MRI scan or endorectal ultrasound (ERUS) to examine the tumor and how it has changed. If the tumor has decreased in size by at least 20% from before you started chemotherapy, you will proceed directly to surgery. If the tumor has not shrunk in size by 20%, you will receive radiation with chemotherapy. This is exactly the same treatment that will be given to the patients in Group 2.

A pathologist will study the tumor removed during surgery using a microscope. If all borders of the tumor are normal and do not contain any tumor, this means that all the tumor could be removed during surgery and it is recommended that you receive six additional cycles of FOLFOX chemotherapy. If all borders of the tumor are not normal and contain some small amount of tumor, this means that the entire tumor could not be removed during surgery, and it is recommended that you receive chemotherapy and radiation therapy for 5.5 weeks after your surgery. The chemotherapy and radiation therapy that you will receive if all of the tumor could not be removed is exactly the same treatment that will be given to the patients in Group 2. After 5.5 weeks of chemoradiation (5FUCMT), additional cycles of FOLFOX or similar chemotherapy will be recommended for 4 cycles or 8 weeks.

**Group 2** – You will receive chemotherapy and radiation therapy for 5.5 weeks. You will be given either 5-fluorouracil IV via continuous infusion or Capecitabine doses taken orally twice daily, 5 days per week, on days of planned radiation therapy. If you are given capecitabine, please take two doses of capecitabine orally daily, one dose in the morning and one dose in the evening, about 12 hours apart on the days you receive radiation therapy. Please swallow the capecitabine tablet(s) whole with a full glass of water, about 8 ounces of water, within 30 minutes after a meal. Do not try to make up a missed or vomited dose, never double up on a dose and tell your doctor if you miss a dose.

After the chemotherapy and radiation therapy is completed, you will proceed directly to surgery.

After surgery, it is recommended that you receive FOLFOX chemotherapy once every two weeks. On the first day of the cycles (Day 1), you will be given leucovorin and oxaliplatin IV for 2 hours and also 5-fluorouracil IV by continuous infusion. This is one cycle; you will receive 8 cycles total over a period of 16 weeks. The FOLFOX chemotherapy is the same as for Group 1. What is different is the timing and when it is given – before or after surgery.
The following tables list the study procedures for each group:

## Group 1 Study Procedures

**Table 1. Group 1 Treatment schedule from FOLFOX chemotherapy to MRI/ERUS review of tumor size**

| Day/Time | What will happen |
|---|---|
| Day 1 of each FOLFOX chemotherapy cycle (Each cycle is 2 weeks, 6 cycles for a total of 12 weeks) | • A history and physical exam, including your weight, pulse, blood pressure and temperature<br>• Interview by a doctor and/or nurse about recent and current symptoms (adverse events)<br>• Routine blood tests<br>• Other tests may also be done if your doctor thinks they are needed.<br>• Complete the patient questionnaire about your symptoms by either a telephone voice response system or by an internet website; this will require less than five minutes at home.<br>• On the first day of the cycles (Day 1), you will be given leucovorin and oxaliplatin IV for 2 hours and also 5-fluorouracil IV via continuous infusion. This is one cycle; you will receive 6 cycles total over a period of 12 weeks. |
| Within 4 weeks after completion of FOLFOX chemotherapy | • A history and physical exam, including your weight, pulse, blood pressure and temperature<br>• Interview by your doctor and/or nurse about recent and current symptoms (adverse events)<br>• Rectal exam<br>• Proctoscopy<br>• Measurement of your tumor by either MRI scan or endorectal ultrasound (ERUS). Whichever test you had before starting treatment, will be the same as the test you have after the FOLFOX treatment. |

**Assignment to different treatments based on tumor size:** If the MRI or ERUS shows that the tumor has decreased in size by at least 20% from prior to chemotherapy, you will proceed directly to surgery within approximately 3 to 6 weeks; skip Table 2, go directly to Table 3.

If the tumor has not decreased in size by at least 20% from prior to chemotherapy, you will receive chemotherapy and radiation therapy for 5.5 weeks as shown in Table 2 and then proceed to surgery approximately 5 to 8 weeks later as shown in Table 3.

**Table 2. Group 1 5FUCMT chemotherapy with radiation treatment**

| Day/Time | What will happen |
|---|---|
| Weekly during chemotherapy with radiation treatment (5FUCMT) | • Pulse, blood pressure and temperature<br>• Routine blood tests<br>• Other tests may also be done if your doctor thinks they are needed.<br>• Complete the patient questionnaire about your symptoms by either a telephone voice response system or by an internet website; this will require less than five minutes at home. |
| Every 2 weeks during chemotherapy with radiation treatment (5FUCMT) | • A history and physical exam, including your weight<br>• Interview by your doctor and/or nurse about recent and current symptoms (adverse events) |

**Table 3. Group 1 Surgery**

| Day/Time | What will happen |
|---|---|
| Surgery | • One blood sample for research purposes, this will be less than two teaspoons<br>• Other tests may also be done if your doctor thinks they are needed<br>• Pictures of the tumor to help ensure it is all removed<br>• Examination of tumor by pathologist |

**Assignment to different treatments based on tumor border:**
If all borders of the tumor are normal and do not contain any tumor, this means that all the tumor could be removed during surgery, and it is recommended that you receive six additional cycles of FOLFOX chemotherapy over a period of 12 weeks. During this time, the only required study procedure is an interview about recent and current symptoms (adverse events) during a routine clinical visit.

If all borders of the tumor are not normal and contain some small amount of tumor, this means that the entire tumor could not be removed during surgery and it is recommended that you receive chemotherapy and radiation therapy for 5.5 weeks followed by another 4 cycles of FOLFOX chemotherapy over a period of 8 weeks. During this time, the only required study procedure is an interview about recent and current symptoms (adverse events) during a routine clinical visit. If you receive chemoradiation (5FUCMT) before surgery, you will not receive chemoradiation (5FUCMT) again after surgery.

Following completion of FOLFOX chemotherapy, you will proceed to post-treatment observation, see Table 5. You will be monitored carefully by your doctors and will return for regular checkups. These checkups will include physical examinations, proctoscopy, blood tests and scans. This monitoring phase is the same for patients in Group 1 and Group 2.

## Group 2 Study Procedures

**Table 4. Group 2 Treatment schedule from 5FUCMT chemotherapy with radiation treatment to surgery**

| Day/Time | What will happen |
|---|---|
| Weekly during chemotherapy with radiation treatment (5FUCMT) | • Pulse, blood pressure and temperature<br>• Routine blood tests<br>• Other tests may also be done if your doctor thinks they are needed.<br>• Complete the patient questionnaire about your symptoms by either a telephone voice response system or by an internet website; this will require less than five minutes. |
| Biweekly during chemotherapy with radiation treatment (5FUCMT) | • A history and physical exam, including your weight<br>• Interview by your doctor and/or nurse about recent and current symptoms (adverse events) |
| Within 4 weeks after completion of chemotherapy with radiation treatment (5FUCMT) | • A history and physical exam, including your weight, pulse, blood pressure and temperature<br>• Interview by your doctor and/or nurse about recent and current symptoms (adverse events)<br>• Test to measure amount of CEA in your blood |
| Surgery (approximately 5-8 weeks after completing radiation therapy) | • One blood sample for research purposes, this will be less than two teaspoons<br>• Other tests may also be done if your doctor thinks they are needed.<br>• Pictures of the tumor to help ensure it is all removed<br>• Examination of tumor by pathologist |

After surgery, it is recommended that you receive 8 cycles or 16 weeks of FOLFOX chemotherapy.

Following completion of FOLFOX chemotherapy, you will proceed to post-treatment observation, see Table 5.

**If your cancer gets worse,** you will stop treatment. If at any time while you are on the study you or your doctor feel that the side effects of the drugs are too bad, you will stop treatment and go on to the monitoring phase.

**When you are finished with surgery and treatment**
Your study doctor will need to evaluate you for up to five years after randomized; the post-treatment required study procedures are listed in Table 5. These monitoring tests are the same for patients in Group 1 and Group 2.

**Table 5. Post-treatment schedule for both Group 1 (FOLFOX chemotherapy) and Group 2 (5FUCMT chemotherapy with radiation therapy)**

| | |
|---|---|
| 9 months from randomization (± 1 month) | • A history and physical exam, including your weight, pulse, blood pressure and temperature<br>• Interview by your doctor about recent and current symptoms (adverse events)<br>• Routine blood tests<br>• Other tests may also be done if your doctor thinks they are needed. |
| Annually starting at 15 months from randomization until 5 years after randomization | • Colonoscopy performed at 15 months and 51 months after randomization (additional colonoscopies may be done at your doctors discretion)<br>• Proctoscopy (if colonoscopy not performed)<br>• CT Scan |
| Every six months starting at 15 months until 5 years after randomization | • A history and physical exam, including your weight, pulse, blood pressure and temperature<br>• Interview by your doctor about recent and current symptoms (adverse events)<br>• Routine blood tests<br>• Other tests may also be done if your doctor thinks they are needed. |
| Every 6 months for three years after surgery. | • Complete the patient questionnaire about your symptoms by either a telephone voice response system or by an internet website; this will require less than five minutes at home. |

After you have completed the follow-up visits, we would like to keep track of your medical condition for up to eight years after randomization. Keeping in touch with you and checking on your condition helps us look at the long-term effects of the study. We will ask you for your contact information in order to monitor your well-being over the long term.

## HOW LONG WILL I BE IN THE RESEARCH STUDY?

*We would like to keep track of your medical condition for a maximum of eight years after you begin this study to look for any long-term effects of the treatment in this study.*

Your study doctor may decide to take you off this study if your medical condition changes, or if the Alliance finds it must limit or stop the study. You may stop taking part in the study at any time. However, if you decide to stop taking part in the study, we want you to talk to the study doctor or your own doctor first.

## CAN I STOP BEING IN THE RESEARCH STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

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

You may have side effects while on the study. The chemotherapy, radiation and surgery treatments in this study all have well known side effects. None of these treatments is new and all have been administered to many patients. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop the study treatment. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

***You should talk to your study doctor about any side effects that you have while taking part in the study.***

**<u>Risks and side effects related to capecitabine</u>:**
**(Note: You may receive either capecitabine or 5-fluorouracil during radiation)**

**Likely risks related to capecitabine (***events occurring greater than 20 % of the time)*

- Diarrhea or loose stools
- Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (mucositis)
- Nausea

- Redness or sores of the palms of the hands or soles of the feet (palmar-plantar erysdysthesia or "hand-foot" syndrome)
- Dry skin (xerosis)
- Itching sensation (pruritis)

**Less likely risks related to capecitabine (***events occurring less than or equal to 20 % of the time)*

- Decreased red blood cells (anemia), the oxygen carrying cells, which could make you feel tired
- Decreased white blood cells (leukopenia), the infection fighting cells, which could put you at risk for infection
- Decreased number of platelets (thrombocytopenia), the blood clotting cells, which could put you at increased risk of bleeding
- Vomiting
- Stomach or abdominal pain
- Loss of appetite, not feeling hungry (anorexia)
- Constipation
- Heartburn
- Fatigue (feeling tired)
- Generalized weakness and loss of strength
- Hair loss
- Rash
- Red, sore eyes
- Fever
- Sensation of lightheadedness or vertigo (dizziness or a spinning sensation)
- Headache
- Pain, including joint, muscle, or bone pain
- Infection

**Rare but serious risks related to capecitabine (***events occurring less than 2-3 % of time)*

- Blood clots and/or bleeding
- Dehydration
- Abnormal liver function tests
- Heart attack
- Abnormal heartbeat

**<u>Risks and side effects related to 5-fluorouracil (5-FU):</u>**

**Likely risks related to 5-fluorouracil** (*events occurring greater than 20 % of the time)*

- Darkening of skin and nail beds, dry, flaky skin

- Decreased white blood cells, the infection fighting cells, which could put you at risk for infection
- Decreased number of platelets, the blood clotting cells, which could put you at increased risk of bleeding
- Nausea
- Vomiting
- Sores in mouth or on lips
- Thinning hair
- Diarrhea
- Brittle nails
- Increased sensitivity to sun

**Less likely risks related to 5-fluorouracil** ***(****events occurring less than or equal to 20 % of the time)*

- Darkening and stiffening of vein used for giving the drug
- Decreased appetite
- Headache
- Weakness
- Muscle aches

**Rare but serious risks related to 5-fluorouracil** *(events occurring less than or equal to 2-3 % of the time)*

- Difficulty walking
- Irritation of eyes
- Increased tearing of eyes
- Blurred vision

While you are being treated with 5-fluorouracil and after you stop treatment, do not have any immunizations (vaccinations) without first asking your doctor for approval. Try to avoid contact with people who have recently received the oral polio vaccine and check with your doctor about this.

**Risks and side effects related to leucovorin:**
Side effects that you may experience with this drug are uncommon. These, however, include an allergic reaction, varying from an itchy rash to breathing difficulties. Measures are available to help you if these should occur.

Leucovorin may interfere with the effects of anti-seizure medications such as phenobarbital, phenytoin, and primidone. When leucovorin is given together with a drug called 5-fluorouracil, it may increase its side effects.

**Risks and side effects related to oxaliplatin:**

**Likely risks related to oxaliplatin (***events occurring greater than 20 % of the time)*

- Nausea or the urge to vomit
- Vomiting
- Diarrhea
- Decrease in red blood cells (anemia), the oxygen carrying cells, which could make you feel tired
- Decreased number of platelets, the blood clotting cells, which could put you at increased risk of bleeding
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver enzyme (AST/SGOT)
- Fatigue or tiredness
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside brain and spinal cord) causing numbness, tingling and burning

**Less likely risks related to oxaliplatin (***events occurring less than or equal to 20 % of the time)*

- Abnormal blood clotting and/or bleeding
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Destruction of red blood cells
- Abnormally fast irregular heartbeat involving the upper chambers of the heart (atria)
- Abnormally fast regular heartbeat involving the upper chambers of the heart (atria)
- Period of very rapid and regular heartbeats that begins and ends suddenly
- Slow heartbeat; regular rhythm
- Fast heartbeat; regular rhythm
- Fast heartbeat usually originating in an area located above the ventricles
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Rapid heartbeat of one of the lower chambers (ventricle) of the heart; regular rhythm but potentially life-threatening, needs immediate attention
- Hearing loss
- Inflammation (swelling and redness) to the middle ear.
- Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). Commonly called "pink eye".
- Dry eye

- A situation in which one has temporary blindness of one eye, due to a blockage (or decreased blood flow) in the blood vessels leading to that eye
- Temporary vision problems caused by the cold
- Problem with eyelid
- Swelling around the nerve responsible for sight
- Belly pain
- Fluid collection in the abdomen
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Dry mouth
- Heartburn
- Difficulty swallowing
- Inflammation (swelling and redness) of the small and large bowel
- Inflammation (swelling and redness) of the esophagus (gullet or the tube that goes from mouth to stomach through which food passes)
- Excess passing of gas
- Inflammation (swelling and redness) of the stomach lining
- Bleeding in some organ(s) of the digestive tract
- Death of tissue somewhere in the digestive tract
- Sore (ulcer) somewhere in the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Inflammation (swelling and redness) of the pancreas
- Blockage of the small bowel
- Chills
- Swelling of the face
- Swelling of arms and/or legs
- Fever
- Limp or difficulty walking
- A condition in which both the liver and kidneys fail
- Inflammation (swelling and redness) or damage to the tissue where a drug was injected
- Chest pain (not heart-related)
- Liver failure
- Increase in size of the liver
- A condition in which there is blockage of the veins of the liver; leads to liver damage
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. This reaction may include hives, low blood pressure, wheezing, swelling of the throat and difficulty breathing.
- Infection

- Test that shows a problem in blood clotting
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Increased blood level of a liver enzyme (GGT)
- Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
- Decreased number of a type of white blood cell (lymphocyte, neutrophil/granulocyte,) or total number of white blood cells (leukocytes)
- Weight gain or loss
- More acid than normal in the blood
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Increased blood sugar level
- Increased blood level of uric acid, a waste material from food digestion
- Decreased levels of a blood protein called albumin
- Decreased blood level of calcium
- Decreased blood sugar level
- Decreased potassium, magnesium, sodium, and/or phosphate
- Joint, back, bone and/or muscle pain
- Difficulty or limitation in ability to open mouth
- Loss of muscle coordination; awkward, uncoordinated walking; unsteadiness when walking
- Sleepiness
- Dizziness (or sensation of lightheadedness, unsteadiness or giddiness)
- Taste changes
- Speech problems
- Restless, repetitive, or involuntary movements and rapid speech
- Headache or head pain
- Bleeding in the brain
- Decreased blood flow to the brain which may lead to stroke
- A malfunction of the nerves within the head and neck
- Paralysis of facial muscles due to problems with the nerves that supply them
- Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)
- Convulsion or seizure
- Anxiety, feelings of dread or danger
- Confusion
- Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
- Difficulty sleeping or falling asleep
- Blood in the urine

- Bleeding in the kidney
- Need to urinate often
- Difficulty emptying the bladder
- Presence of blood in a fallopian tube (tube between ovary to uterus [womb])
- Bleeding from somewhere in the reproductive organs (e.g., vagina, testes)
- Bleeding in the prostate
- Bleeding in the spermatic cord (a structure resembling a cord that suspends the testis within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)
- Stuffy or runny nose, sneezing
- Bleeding in the respiratory tract
- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Hiccups
- Inflammation (swelling and redness) of the lungs that may cause difficulty breathing and can be life-threatening
- Scarring of the lungs that can cause shortness of breath and interfere with breathing
- Changes in the blood vessels in the liver
- Voice change
- Hair loss
- Dry skin
- Excess sweating
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives
- Sudden reddening of the face and/or neck
- Hot flashes
- High blood pressure
- Low blood pressure
- Inflammation (swelling and irritation) of a vein; blood clot
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung.
- Bleeding with a decreased number of blood cells that help to clot blood (platelets)

**Rare but serious risks related to oxaliplatin (***events occurring less than 2-3 % of the time)*

- Formation of blood clots in small blood vessels around the body that leads to a low platelet (a type of blood cell that helps to clot blood) count

- Gas in the intestinal (bowel) wall
- Inflammation (swelling and redness) of the gallbladder possibly associated with gallstones
- Sudden decrease of kidney function
- Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs
- Swelling and redness of the skin on the palms of the hands and soles of the feet

**Risks and side effects related to the radiation therapy:**

**Likely risks related to radiation therapy** *(events occurring greater than 20 % of the time)*

- Short-term reddening and drying of the skin in the area receiving radiation
- Fatigue (feeling tired)
- Hair loss around the area receiving radiation

**Less likely risks related to the radiation therapy (***events occurring less than or equal to 20 % of the time)*

- Nausea
- Vomiting
- Headache

**Rare but serious risks related to the radiation therapy** *(events occurring less than 2-3 % of the time)*

- Decreased white blood cells, the infection fighting cells, which could put you at risk for infection
- Decreased number of platelets, the blood clotting cells, which could put you at increased risk of bleeding
- Damage to the intestines that could require surgery to repair
- Tumors caused by radiation

Although every effort will be made to minimize the risk of side effects, the possibility that they may occur cannot be eliminated. Side effects resulting from radiation therapy, when used in combination with chemotherapy, can be severe, or in rare cases, fatal. These side effects may be long-lasting or even permanent.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. The radiation and some of the drugs used in the study may make you unable to have children in the future

For more information about risks and side effects in your individual situation, ask your doctor.

## ARE THERE BENEFITS TO TAKING PART IN THE RESEARCH STUDY?

Taking part in this study may or may not make your health better. While doctors hope that FOLFOX chemotherapy prior to surgery will enable some patients to avoid radiation therapy to the pelvis, this is not yet known. There is no proof yet that the 5FUCMT chemoradiation can be safely omitted for patients whose rectal cancers shrink by more than 20% from FOLFOX. The possible benefit to you would be avoiding the frequent visits to receive radiation or some long term effects of radiation. However, there is no proof of this, and we do not yet know if the risks outweigh the benefits.

We do know that the information from this study will help doctors learn more about using FOLFOX chemotherapy versus 5FUCMT chemoradiation prior to surgery. This information could help future cancer patients.

## WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS RESEARCH STUDY?

You do not have to be in this study to receive treatment for your cancer.

**Your other choices may include:**

- Getting treatment or care for your cancer without being in a study. The standard care for rectal cancer patients is what is described for Group 2
- Taking part in another study

Other choices that are not recommended because your rectal cancer has been found at a stage where it has the potential to be cured include:

- Getting no treatment
- 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, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

## WILL MY 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. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- North Central Cancer Treatment Group (NCCTG)
- Alliance
- Institutional Review Boards
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a service sponsored by the NCI to provide greater access to cancer trials

A description of this clinical trial will be made available on http://www.ClinicalTrials.gov as required by US Law. This website will not include information that can identify you. At the most, the website will include a summary of results. You can research this website at any time.

## WHAT ARE THE COSTS OF TAKING PART IN THIS RESEARCH STUDY?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Most of the treatments in this study are part of routine care. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Your health plan/insurance company will not be asked to pay for any of the research tests, or for the questionnaires about your quality of life and symptoms.

You will not be paid for taking part in this study.

*For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at*

http://cancer.gov/clinicaltrials/understanding/insurance-coverage

*You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.*

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

It is important that you tell your study doctor, _____ *[investigator's name(s)];* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

**WHAT ARE MY RIGHTS IF I TAKE PART IN THIS RESEARCH STUDY?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**WHO CAN ANSWER MY QUESTIONS ABOUT THE RESEARCH STUDY?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the NCI Community Oncology Research Program - Kansas City Institutional Review Board (a group of people who review the research to protect your rights) at 913-948-5588.

You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).

**Self-Reporting of Symptoms Study**

*We want to know your view of how your life has been affected by cancer and its treatment. This "Self Reporting of Symptoms" part of this study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.*

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

For the Self-Reporting of Symptoms part of the study, you will be asked to answer questions about your symptoms from home using a secure website or using an automated telephone system. You will be asked to answer questions at your first visit, once every

week during your pre-operative treatment, and then once every 6 months for three years after your surgery. It takes about 5 minutes to answer questions each time. You will be shown how to use the secure website or automated telephone system by a member of the study staff at your first visit. This demonstration will take 10-20 minutes. Each time you are scheduled to answer questions, you will receive an automatic e-mail or telephone reminder depending on whether you are using the secure website or automated telephone system.

Just like in the main study, your personal information will be kept private and questionnaires will be coded using a study ID number and not with your name.

**USE OF BIOLOGICAL SAMPLES IN RESEARCH**

**Blood Samples**

Research blood samples will be drawn at the same time as the required blood tests for this study; no additional blood draws are necessary to obtain the research blood samples. About 2 tablespoons of blood will be drawn each time for these research studies.

The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

**Tissue Samples**

We will use tumor tissue from the proctoscopy you have at the beginning of the study and from your surgery specimen to understand why some tumors respond better to chemotherapy and/or radiation treatments than others. This research is not designed specifically to help you, but the research might help people who have rectal cancer and other diseases in the future. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

The research blood and tumor tissue samples will be sent to Alliance laboratories at The Ohio State University in Columbus Ohio which has a secure tissue storage facility that has worked with many similar research studies sponsored by the National Cancer Institute (NCI). Ohio State will prepare tiny samples of blood that may be sent to research scientists whose work has been reviewed by the study investigators and the NCI. This includes laboratories at Memorial Sloan-Kettering Cancer Center in New York City. The purpose of these research tests is to better understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. Also, scientific tools will allow researchers to look at your whole DNA, not just one part or one gene. This kind of research can provide information to researchers about the development of cancer and response to treatment. Because the information gained in these genetic studies can be very useful to the research community, the National Institutes of Health (NIH) has

requested that these data be placed in a central database housed at the NIH. The National Cancer Institute is part of the NIH. The goal is to speed up the process for discovery of new treatments, prevention, and diagnosis of disease. Researchers must get approval from the NIH before they can access the research results and health-related information from your specimen. All information will be coded with a unique number. Researchers will not have access to your name or identity; they will only see coded information.

**Blood and Tumor Tissue:**

We ask you for permission to keep leftover blood and leftover tissue for future research. Future research means that today we do not know what the important research questions are but that your information might be useful to help answer questions that turn out to be important in the future. No materials will be released for research until a careful review has been performed to ensure that materials are used for legitimate research. Allowing leftover specimens of your tumor tissue, blood or stored copies of your scans to be used for future research is completely optional.

**MRI/CT scans**

We would like to keep copies of the MRI and/or CT scans from the study for future research. If you say no to this, then copies of your scans will be destroyed at the end of the study monitoring period.

**THINGS TO THINK ABOUT**

The choice to let us keep your samples (blood and/or tissue) and scans for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your samples can be kept for research, you can change your mind at any time. You or your physician will need to write to: Data Manager for N1048, Alliance Statistics and Data Center, Mayo Clinic, 200 First Street Southwest, Rochester, Minnesota 55905. Then any samples that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While Alliance may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes samples are used for genetic research (about diseases that are passed on in families). Even if your samples are used for this kind of research, the results will not be put in your health records.

Your samples will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future.

**Benefits**

The benefits of research using samples include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

**Risks**

The greatest risk to you from the use of your samples is the possible release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

**Making Your Choices**

Please read each sentence below and think about your choice. After reading each sentence, mark "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My MRI and/or CT scans may be kept for use in research to learn about, prevent, or treat cancer.

   ☐ Yes ☐ No Please initial here: _____ Date: _____

2. My MRI and/or CT scans may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   ☐ Yes ☐ No Please initial here: _____ Date: _____

3. My blood samples may be kept for use in research to learn about, prevent, or treat cancer.

   ☐ Yes ☐ No Please initial here: _____ Date: _____

4. My blood samples may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   ☐ Yes ☐ No Please initial here: _____ Date: _____

5. My tissue samples may be collected and stored for use in research to learn about, prevent, or treat cancer.

   ☐ Yes ☐ No Please initial here: _____ Date: _____

6. My tissue samples may be collected and stored for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your samples destroyed at any time, contact your study doctor. If you say NO, your tissue/blood/scan materials will be destroyed at the end of the study.

7. I would like to be contacted by study investigators with a summary of results of the study.

☐ Yes ☐ No Please initial here: _____ Date: _____

Alliance has the right to end storage of the samples without telling you.

## HOW DO OUTSIDE RESEARCHERS GET MATERIALS FOR FUTURE RESEARCH?

Researchers from universities, hospitals, and other health organizations do research using patient materials. They may call Alliance and ask for samples for their studies. The Alliance team which includes patient representatives looks at the way that these studies will be done, and decides if any of the samples can be used. After insuring that the researchers and the studies that they are proposing are valid, Alliance may send materials and some information about you to the research teams. This will not include your name, address, phone number, social security number, or any other identifying information. If you allow your samples to be given to outside researchers, it will be given to them with a code number. If researchers outside Alliance use the samples for future research, and want to contact you, they will have to first contact Alliance researchers. If necessary, we would contact you and ask you for your permission and willingness to be contacted.

***Please read the following statements and mark your choice:***

1. I permit Alliance to give my stored samples (blood or tissue) for use in future research to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

## WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237).

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/
- For NCI's general information about cancer in Spanish, go to http://www.cancer.gov/espanol

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. This may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

Signature

I have been given a copy of all 24 pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

**Printed Participant Name: _____**

**Participant Signature: _____**

**Date: _____**

**Printed name of person obtaining informed consent: _____**

**Signature of person obtaining informed consent:_____**

**Date _____**