

**MARQUETTE GENERAL HEALTH SYSTEM**

**Regional Medical Center**

**CONSENT TO PARTICIPATE IN AN INVESTIGATIONAL STUDY**

**TITLE: NSABP C-10 A Phase II Trial of 5-Fluorouracil, Leucovorin, and Oxaliplatin (mFOLFOX6) Chemotherapy Plus Bevacizumab for Patients with Unresectable Stage IV Colon Cancer and a Synchronous Asymptomatic Primary Tumor**

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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.

**Why have I been asked to take part in this study?**

You are being asked to take part in this study because you have cancer of the colon that has metastasized which means it has spread outside the colon. Your doctor currently considers the extent of cancer that has spread outside of the colon is too much to be safely removed at this time. The chemotherapy drugs used in this trial are well-accepted and approved for metastatic colon cancer, but the safety of giving these drugs to patients with the tumor still in the colon is not well known. You may or may not develop symptoms in the future from the tumor in your colon that will require surgery to remove part of your colon containing the tumor. You and your doctor have decided that you currently do not require surgery to control any symptoms from the tumor in your colon at this time.

**Who is conducting the study?**

The National Surgical Adjuvant Breast and Bowel Project (NSABP) is conducting this study.

**Why is this research study being done?**

The purpose of this study is to find out whether or not a combination of chemotherapy drugs is safe when given to patients who have not had their colon tumors removed by surgery. We also want to see if major surgery to remove the tumor in your colon can be safely avoided. Removing the colon when disease has spread outside the colon and cannot be entirely removed does not have proven benefit for patients with your stage of disease.

The chemotherapy drugs used in this study are 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (Eloxatin®). These drugs are commonly used to treat colon cancer. Bevacizumab (Avastin™) is a drug called a monoclonal antibody that has been shown to be helpful in treating colon cancer that has spread outside the colon. It is known as anti-angiogenic therapy because bevacizumab slows or stops angiogenesis (the growth of new blood vessels that feed a tumor). Tumors grow slower when they cannot make new blood vessels.

All of the drugs used in this study are approved by the Food and Drug Administration (FDA) for the treatment of your stage of colon cancer.

### **How many people will take part in the study?**

About 30 patients will take part in the first stage of this study. If the results of the first stage show that adding bevacizumab to 5-FU, leucovorin, and oxaliplatin is safe for treating patients who have not had their colon tumor removed, then about 60 additional patients will take part in the second stage of the study. All patients in the second stage of the study will receive the same treatment as the patients in stage 1.

About 90 patients from different cancer treatment centers 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 had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- medical history and physical exam
- blood tests
- urine test
- pregnancy test if you are a woman of child bearing potential
- chest x-ray or CT scan of your chest
- CT or MRI scan of your abdomen
- endoscopy (this procedure uses a scope to examine your colon)

*During the study:* If the tests and exams show that you can be in the study and you choose to take part, you will begin study therapy within 3 weeks after joining the study. You will receive the study therapy once every 14 days. The 14 days between the first day you receive your therapy and the next time you receive therapy is called a *cycle*.

You will receive all of the study drugs through a vein. To make this easier, a small tube will be placed in a vein in your chest. It will stay in place continuously for as long as you are receiving study therapy. Your doctor will tell you more about this.

On the first day of each cycle, you will receive bevacizumab. Your first bevacizumab treatment will take about an hour and a half. The second treatment will take about an hour. Other bevacizumab treatments usually take about half an hour. Immediately after receiving bevacizumab, you will be given leucovorin and oxaliplatin at the same time. This will take about 2 hours. Then you will receive the 5-FU over a few minutes followed by another dose of 5-FU that will be given to you over the next 46 hours using a small portable pump. The small size of the pump allows it to be attached to your clothing so that it can be used without limiting most of your movements and activities. You will wear this pump at home for the 46-hour period. This process will be repeated 14 days later.

The chemotherapy drugs and bevacizumab will continue as long as they are effective in treating your cancer and have not caused any serious side effects. Your doctor will talk with you about continuing or stopping this therapy.

During the study you will need to have the following tests and procedures. They are considered part of regular cancer care unless noted otherwise.

**During study therapy:**

- a brief exam by your nurse or doctor before every cycle of therapy
- blood tests before every cycle of therapy
- urine tests before every other cycle of therapy (If your urine test contains an abnormal amount of protein, you will then need to collect your urine for 24 hours. If you need to do this, your study doctor or nurse will let you know what you need to do.)
- Scans of your chest and abdomen when your study doctor feels it is necessary to check whether your tumor is responding to therapy

**After study therapy ends through year 5 of being in the study:**

- a physical exam every 3 months by your study doctor or other doctor taking care of you
- Scans of your chest and abdomen when your doctor feels it is necessary to check whether your tumor is responding to therapy

**How long will I be on the study?**

You will continue to receive chemotherapy and bevacizumab unless your cancer gets worse or you or your doctor decide you should stop. We would like to keep track of your medical condition for 5 years even if you stop the chemotherapy drugs and bevacizumab before the end of the 5 years.

Your doctor may stop the study drugs if one of the following happens:

- the study treatment does not work for your cancer;

- you develop a serious side effect that you cannot tolerate or that cannot be controlled with other medications;
- your health gets worse;
- your doctor decides you should receive a different type of therapy;
- you are unable to meet the requirements of the study (for example, you cannot receive the drugs as prescribed or cannot return for follow-up visits);
- new information about the study drugs or other treatment for colon cancer becomes available.

### **Can I stop being in the study?**

Yes, you can decide to stop at any time. Tell the 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 drugs 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. You can choose to withdraw in one of two ways. In the first, you can stop your study treatment, but still allow the study doctor to follow your care. In the second, you can stop your study treatment and not have any further contact with the study staff.

### **Can anyone else stop me from being in the study?**

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 by the NSABP.

### **What side effects or risks can I expect from being in the study?**

Patients with colon cancer that has spread beyond the colon, but for whom the colon cancer remains in place may or may not develop symptoms (bleeding, perforation [hole in the bowel wall], obstruction) related to the colon tumor. If symptoms develop requiring urgent or emergent surgery, a surgeon will be contacted and you will be able to undergo necessary surgery if you so choose.

You may have side effects while being on the study. 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. Your doctor may also decide that it is necessary to delay or change your study therapy. Many side effects go away soon after you stop taking the drugs. In some cases, side effects can be serious, long lasting, or never go away. *There is also a risk of death.*

You should talk with your study doctor about any side effects you may have while taking part in the study.

### ***Risks and side effects related to the chemotherapy (5-FU, leucovorin, and oxaliplatin)***

#### ***Likely effects***

These side effects occur in **25% or more** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Diarrhea
- Nausea
- Vomiting
- Abdominal pain or cramps
- Sores in mouth, throat, and the esophagus, which is the tube that goes from the mouth to the stomach
- Low white blood cell count (may make you more likely to get infections)
- Low platelet count that may lead to bleeding
- Low red blood cell count (anemia) (can cause tiredness, weakness, and shortness of breath)
- Cough
- Nail changes
- Skin darkening
- Time away from work
- Infection
- Fatigue
- Nerve problems that are usually temporary, but some may be long-lasting. These may be made worse by exposure to cold temperature and cold objects
  - Pain, tingling, burning, or numb feeling (pins and needles) in hands, feet, or area around mouth or throat, which may cause problems walking or performing the activities of daily living.
  - Trouble swallowing or saying words, jaw tightness, odd feelings in the tongue, chest pressure, or a feeling of not being able to swallow or breathe without having any physical reason for this.
- Temporary hair loss

These side effects occur in **10 - 24%** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Loss of appetite
- Fever
- Changes in blood tests that may indicate liver injury

#### *Less likely effects*

These side effects may occur in **3-9%** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Gastrointestinal ulcers and bleeding
- Bowel wall changes (that may require hospitalization)
- Constipation
- Intestinal blockage
- Flu-like symptoms such as fevers, chills, and muscle aches
- Watery eyes
- Nasal stuffiness
- Allergic reaction (including itching, hives, skin rash, fever, chills, muscle stiffening, sinus congestion, or swelling or puffiness of the face, especially eyelids)
- Fever with a low white blood cell count
- Blood clots
- Dizziness
- Dehydration
- Shortness of breath
- Headache
- Rash
- Blood tests that may indicate kidney damage
- Blistering, peeling, redness, swelling, tingling, numbness, and/or pain of the palms of hands and bottoms of feet
- Inflammation of the veins
- Taste changes
- Changes (high or low) in blood pressure
- Pain in muscles, bones, joints
- Mood changes (including depression)
- Weight loss
- Hot flashes/flushing
- Hiccups
- Eye problems (including redness or

- Rapid heartbeat
- Difficulty sleeping
- Irritation
- Involuntary movements

*Rare but serious effects*

These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving 5-FU, leucovorin, and oxaliplatin:

- Confusion or memory loss
- Slurred speech
- Poor coordination and balance
- Changes in the lungs (including inflammation, thickening, scarring, and possible lung failure)
- A breakdown of red blood cells and kidney failure known as the hemolytic uremic syndrome
- Skin and tissue damage in the area surrounding the catheter where the chemotherapy drug is injected
- Severe allergic reaction including shortness of breath, low blood pressure, wheezing, chest tightness and severe breathing problems
- Liver damage that may be permanent, including a serious form called "veno-occlusive disease" which can cause swelling of the abdomen, painful swelling of the liver, yellowing of the skin
- Problems with hearing
- Visual changes (including blindness usually lasting less than a minute)
- Heart attack or chest pain
- Irregular heartbeat
- Clots that form in the blood and use up the substances needed to stop bleeding

Diarrhea that occurs at the same time as low white blood cell counts can lead to very serious, life-threatening infection. On rare occasions, this can be fatal. Diarrhea can also be a sign of other serious intestinal problems. It is very important that you tell the study staff if you are having diarrhea so they can watch over your condition. You may need to be hospitalized to receive supportive care.

### ***Side effects of bevacizumab***

#### *Likely effects*

These side effects occur in **25% or more** of patients receiving bevacizumab:

- Nose bleeds
- High blood pressure
- Protein in the urine

These side effects may occur in **10-24%** of patients receiving bevacizumab:

- Watery eyes
- Bleeding, infection, or bowel perforation (hole in the bowel wall) following major surgery
- Skin and nail changes (including dryness, itching, rash, discoloration, ulcers, or peeling)
- Sores in mouth and/or throat
- Taste changes
- Mild to moderate bleeding in the gastrointestinal tract (serious and life-threatening bleeding events were rare)
- Shortness of breath

Complications following surgery for patients requiring surgery while receiving bevacizumab have been noted to be more common than for patients not receiving bevacizumab before surgery. If you require emergency surgery, you would be at increased risk of complications following surgery to treat your colon tumor. Any major surgery required for treatment of other conditions may also be associated with increased complications. We recommend stopping bevacizumab for at least 28 days before any elective major surgery.

#### *Less likely effects*

These side effects may occur in **3-9%** of patients receiving bevacizumab:

- Gastrointestinal upset (which may include gas, heartburn, constipation, diarrhea, nausea, vomiting, or loss of appetite)
- Abdominal pain
- Abnormally slow bowel contraction
- Headache
- Pain in the chest area
- Low white blood cell count (may make you more likely to get infections)
- Changes in blood tests that indicate possible kidney damage
- Low red blood cell count (anemia) (can cause tiredness, weakness, and shortness of breath)
- Allergy-type symptoms like stuffy nose and sneezing
- Weight loss
- Confusion
- Poor coordination and balance
- Cough
- Frequent urination
- Vaginal spotting or bleeding
- Voice changes (hoarseness)
- Blood clots in veins
- Tiredness/weakness
- Flu-like symptoms, such as fevers, chills, muscle aches, joint pain and stiffness

- Low platelet count that might interfere with clotting
- Low sodium and/or potassium levels that might make you feel weak or dizzy

Blood clots in your arteries may cause stroke or heart attack or other problems. Several studies comparing chemotherapy with bevacizumab to chemotherapy alone have been done in patients with advanced cancers. Side effects of each study were looked at together. Problems due to blood clots in arteries were seen in about 2% of patients receiving chemotherapy alone, and about 4.5% of patients receiving bevacizumab with chemotherapy. Patients who were 65 or older, or those with past problems with blood clots in their arteries, appeared to be at greatest risk. Problems due to blood clots in the arteries were seen in about 2.9% of patients 65 or older receiving chemotherapy alone, and about 8.5% of patients 65 or older receiving bevacizumab with chemotherapy. Patients who were both 65 or older and reported a history of past problems with blood clots in their arteries appeared to be at even higher risk, although further study is required before an estimate of the risk can be provided. These conditions can be life-threatening or fatal.

#### *Rare but serious effects*

These side effects are **rare but serious**, occurring in **less than 3%** of patients receiving bevacizumab:

- Bleeding in various parts of the body leading to disability (including stroke) or death (especially in lung cancer patients). *You should report any abnormal bleeding to your study doctor.*
- Bowel perforation, which is an abnormal opening in the bowel wall allowing bowel contents to spill into the abdomen. This problem can lead to a life-threatening infection and usually requires surgery to repair.
- In addition to bowel perforation, perforation of other organs or tissues.
- Fistula (an abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected) may occur, for example, between the gastrointestinal tract and the skin or between the gastrointestinal tract and the vagina. A rare type of fistula, tracheo-esophageal fistula, which is an abnormal connection between the trachea (windpipe) and the esophagus (the tube that connects the mouth of the stomach) has been reported.
- Risk related to wound healing: There have been reports of patients receiving bevacizumab who developed problems with healing of their surgical wounds. These problems can include a delay in wound healing, failure of a wound to heal or spontaneous opening of a wound. These problems can lead to a life-threatening infection and could require surgery to repair. While you are receiving bevacizumab, your doctor will temporarily stop your bevacizumab therapy prior to any surgery to avoid possible problems with wound healing. If you need surgery for any reason while on bevacizumab, tell your doctor.  
There have also been a few reports of patients receiving bevacizumab in other trials who developed complications with wound healing due to skin problems such as leg ulcers. These wound healing problems have been associated with infections that can take a long time to heal. Therefore, if you develop any skin problems, such as open sores or wounds, tell your doctor.
- Allergic reaction including fever, chills, rash, hives, flushing, low blood pressure, swelling, and shortness of breath

- Reaction to the bevacizumab infusion including: fever, chills, hives, rash, joint pain, shortness of breath, low or high blood pressure, muscle stiffening, and sweating may occur during the infusion and last about 24 hours
- Kidney damage
- Coughing up blood
- Heart problems (including irregular heartbeat, changes in blood pressure, fluid collections surrounding the heart, chest pain, and possibly heart attack or heart failure)
- Infection
- Lung problems
- Reversible changes in liver function tests that may indicate liver damage
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) is a medical condition related to leakiness of blood vessels in the brain. RPLS can cause headaches, confusion, vision changes or blindness, and seizure, as well as changes in brain scans. This condition is usually temporary but in very rare cases, it is potentially life-threatening and may have long-term effects on brain function.
- Severe high blood pressure that can have an effect on brain function and can be life-threatening
- High blood pressure of the blood vessels in the lungs.

*Risks related to fertility and pregnancy:* You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Men and women should continue to take precautions for at least 3 months after their last dose of bevacizumab. Women should not breastfeed a baby while on this study. Both male and female patients should ask about counseling and more information about preventing pregnancy. Female patients who feel they might be pregnant, even though they practiced birth control, must notify the study doctor immediately.

For more information about risks and side effects, ask your study doctor.

### **Are there benefits to taking part in this study?**

Taking part in this study may or may not allow you to avoid a major surgery to remove the cancer in your colon. Because cancer had spread to areas outside your colon, removing the colon cancer alone is not considered a curative surgery. By avoiding this major surgery, you may avoid the pain, recovery time, and potential complications associated with elective removal of your colon cancer. We believe that the information from this study will help doctors learn more about the safety of these drugs for patients who have not had their colon tumor removed and their cancer has spread outside their colon. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment.

Talk with 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 inspect and/or copy your research records for quality assurance and data analysis include:

- the National Surgical Adjuvant Breast and Bowel Project (NSABP)
- your local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and
- government agencies, including the National Cancer Institute (NCI) or its authorized representatives, the Food and Drug Administration (FDA), and the Office for Human Research Protections (OHRP). These agencies may review the research to see that it is being done safely and correctly.

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

All of the drugs in this study are available commercially and you or your insurance company will be responsible for their cost.

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer in this study. 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.

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.

### **Institutional Funding:**

Funds are provided from the study sponsor to Marquette General Hospital on a per patient basis to help with the institution's costs of participating in this study.

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

It is important that you tell your study doctor, \_\_\_\_\_ (*insert 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 \_\_\_\_\_ (*insert 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 as a study participant?**

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.

### **Whom can I call if I have questions or problems?**

In the event that physical injury occurs as a result of this research, facilities for treatment of injury will be available; however, you will not automatically be provided with reimbursement for medical care or other compensation. For more information concerning the research and research-related risks or injuries, you can notify Dr. \_\_\_\_\_, or his/her associates, who may be reached by phoning the office at (906) 225-3922. During the evenings, weekends, or holidays you may phone Marquette General Health System at (906) 228-9440, and request to speak with the medical oncologist on call. You can also call the Patient Advocate at Marquette General Health System at (906) 228-9440, if you have any questions, comments, or concerns about the study or your rights as a research subject.

### **Where can I get more information?**

- You may call the National Cancer Institute's (NCI's) Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

- You may also visit the NCI Web site at <http://cancer.gov>
- For the NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials>
- For the NCI's general information about cancer, go to <http://cancer.gov/cancerinfo>
- You may also visit the NSABP Web site at <http://www.nsabp.pitt.edu>

### **WHOM DO I CALL IF I HAVE PROBLEMS OR QUESTIONS?**

In the event that physical injury occurs as a result of this research, facilities for treatment of injury will be available; however, you will not automatically be provided with reimbursement for medical care or other compensation. For more information concerning the research and research-related risks or injuries, you can notify Dr. \_\_\_\_\_, or his/her associates, who may be reached by phoning the office at (906) 225-3922. During the evenings, weekends, or holidays you may phone Marquette General Hospital at (906) 228-9440, and request to speak with the oncology physician on call. You can also call the Patient Advocate at Marquette General Hospital at (906) 228-9440, if you have any questions, comments, or concerns about the study or your rights as a research subject.

**VOLUNTARY CONSENT:**

You certify that you have read the preceding or it has been read to you and that you understand its contents. Any questions you have pertaining to the research or research related injuries have been and will be answered by Dr. \_\_\_\_\_ or his/her associates, who may be reached by phoning the office at (906) 225-3922. During evenings, weekends, or holidays you may phone Marquette General Hospital at (906) 228-9440, and request to speak with the medical oncologist on call. Any questions you have concerning your rights as a research subject will be answered by the Patient Advocate at Marquette General Hospital, who may be reached by phoning (906) 228-9440. You will be given a copy of this consent form.

**Your signature below means that you have freely agreed to participate in this investigational study.**

\_\_\_\_\_  
Patient's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of person conducting  
Informed consent discussion

\_\_\_\_\_  
Date

**I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the patient indicated, and that any questions about this information have been answered.**

\_\_\_\_\_  
Investigator's Signature

\_\_\_\_\_  
Date

**Your signature below means that you do not wish to participate in this investigational study.**

\_\_\_\_\_  
Patient's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of person conducting

\_\_\_\_\_  
Date

Informed consent discussion

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Investigator's Signature

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Date

Amendment #2 approved 8/8/07  
Amendment #3 approved 2/13/2008