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CONSENT FORM

CIRB C80405: A PHASE III TRIAL OF IRINOTECAN/5-FU/LEUCOVORIN OR OXALIPLATIN/5-FU/LEUCOVORIN WITH BEVACIZUMAB OR CETUXIMAB (C225) FOR PATIENTS WITH UNTREATED METASTATIC ADENOCARCINOMA OF THE COLON OR RECTUM

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CIRB C80405: A PHASE III TRIAL OF IRINOTECAN/5-FU/LEUCOVORIN OR OXALIPLATIN/5-FU/LEUCOVORIN WITH BEVACIZUMAB OR CETUXIMAB (C225) FOR PATIENTS WITH UNTREATED METASTATIC ADENOCARCINOMA OF THE COLON OR RECTUM

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 study because you have cancer of the colon or rectum which has spread and has not yet been treated.

Why is this study being done?

This study is being done to evaluate the effects (good and bad) of different regimens of chemotherapy. There are two common combinations of chemotherapy drugs used to treat your type of cancer: One uses 5-fluorouracil (also called 5-FU), leucovorin and oxaliplatin, and is also called “FOLFOX;” the other combination uses 5-FU, leucovorin, and irinotecan, this combination is also called “FOLFIRI.” At the present time, the Food and Drug Administration (FDA) has approved each of these as treatment for colon or rectal cancer.

The FDA has also approved the use of a drug called bevacizumab (or Avastin) in combination with these chemotherapy regimens. Bevacizumab plus either of these chemotherapy regimens is considered the standard of care for most patients.

Cetuximab is approved by the FDA for the treatment of colorectal cancer in patients who have developed progressive cancer following the use of irinotecan. Recent studies, however, have shown that people who have a mutation (an abnormality) in a gene in their tumor tissue called K-ras do not appear to benefit from treatment with cetuximab or other similar drugs.

The purpose of this study is to determine whether cetuximab plus chemotherapy is better than bevacizumab with chemotherapy in patients who do not have K-ras mutations in their tumor tissue.

How Many People Will Take Part in the Study?

As many as 2,900 people will take part in this study.

What Will Happen if I Take Part in the Research Study?

Before you begin the study . . .

Recent studies have shown that people who have a mutation (an abnormality) in a gene in the tumor tissue called K-ras do not appear to benefit from treatment with cetuximab or other similar drugs. For this reason, you will be asked to allow us to test your tumor sample to find out if it had the K-ras genetic mutation since this study is evaluating treatments that contain cetuximab.

This test can be done on tumor tissue that was removed at any time including at the time of diagnosis. The tissue will be sent to a laboratory at the Southwest Oncology Group. If the test shows that your tumor does not have a mutation in the K-ras marker, then you will be able to participate in this study. If the results of the test show that the K-ras marker has mutated in your tumor tissue, then you will not be able to enroll in this study. You and your doctor will then decide on the appropriate treatment strategy outside of this clinical trial.

We are also interested in determining whether the K-ras mutation can be detected in blood. Therefore, before it is determined whether you are eligible for the study, we would like to collect approximately 1 tablespoon of blood for research purposes only. This research blood test will not be used to determine your eligibility. The choice to provide this blood sample is up to you. This test is optional and no matter what you decide to do, it will not affect your care. Your blood sample will not be stored with your name on it and the greatest effort will be made to protect your privacy (more information about providing samples for research is included at the end of this form).

1) I agree that my blood may be used for the research study described above.

_____ Yes _____ No Initials _____

You will need to have the following additional 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.

- Medical history and physical examination;
- Blood tests, a pregnancy test, liver function tests, urinalysis;
- CAT or MRI scan, and chest X-ray.

If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in 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 one of the two groups. The two treatment groups are:

Group 1 (often called "Arm A") bevacizumab plus FOLFOX or FOLFIRI

Group 2 (often called "Arm B") cetuximab plus FOLFOX or FOLFIRI

You will receive either the combination of drugs called FOLFOX or FOLFIRI based on what your doctor advises is best for you. The decision of which chemotherapy will be used must be made prior to your enrollment in this clinical trial.

During the study . . .

Each treatment group will receive treatment over 8 weeks. This 8 week period is called “a cycle.” The treatment plans for each of the arms is listed below:

ARM A:

Order of infusion:	Week							
	1	2	3	4	5	6	7	8
Bevacizumab	X		X		X		X	
FOLFOX/FOLFIRI	X		X		X		X	

ARM B:

Order of infusion:	Week							
	1	2	3	4	5	6	7	8
Cetuximab	X	X	X	X	X	X	X	X
FOLFOX/FOLFIRI	X		X		X		X	

Arm A: If you are randomized to Arm A, you will first receive an infusion of bevacizumab by vein, followed by either the FOLFOX or FOLFIRI combination (see below). Your first infusion of bevacizumab will be over 90 minutes. Later infusions of bevacizumab will be given every two weeks, and may be given over a shorter time interval, depending on how you tolerate the infusions.

Arm B: If you are randomized to Arm B, you will first receive an infusion of cetuximab by vein, followed by either the FOLFOX or FOLFIRI combination (see below). The cetuximab will be given on the first day of your treatment for 2 hours as an infusion by vein. Each week after that you will receive cetuximab over 1 hour.

FOLFOX: If it is decided that you will take the FOLFOX combination, oxaliplatin will be given by vein over a period of 2 hours. Afterwards, (or at the same time) leucovorin will be given for 2 hours. 5-FU will then be given as a shot through your vein, followed by an infusion which will take about 2 days. This will be repeated every 2 weeks.

FOLFIRI: If it is decided that you will take the FOLFIRI combination, irinotecan will be given by vein over a period of 90 minutes. Afterwards, (or at the same time) leucovorin will be given for 2 hours. 5-FU will then be given as a shot through your vein, followed by an infusion which will take about 2 days. This will be repeated every 2 weeks.

You may also be asked to take a low dose of aspirin every day to try to prevent some bevacizumab complications (such as stroke or heart attack).

Tests and Procedures:

During the time that you are receiving the study treatment, you will need the following tests and procedures that are part of regular cancer care. However, if you are randomized to receive cetuximab, for the first 4 weeks of treatment some of these tests will be done more often because you are in this study:

- physical examinations (every 8 weeks),
- blood tests (about every 2 weeks),
- liver function tests (about every 2 weeks),
- urinalysis (every four weeks, only for patients receiving bevacizumab),
- CAT scans or MRI scans, and chest x-rays to monitor disease (every 8 weeks).

Your doctor may decide to continue your treatment for as long as the tumor does not grow and you are able to tolerate the treatment.

How Long Will I be in the Study?

You will be treated with this regimen of chemotherapy as long as there is evidence that your cancer is responding (that is, improving or stable). Treatment would also be stopped if you become too sick to receive the therapy, if your doctor believes another treatment is appropriate, or if you no longer wish to continue with the study. After the end of your treatment, the study doctor will continue to follow your progress every 2 months for up to 5 years and then every 6 months for up to 5 years.

The investigator and/or your doctor may decide to take you off this study:

- If your cancer grows
- If your health gets worse
- If there are other causes which prevent continuation of the study
- If another treatment option appears appropriate

Can I Stop Being in the 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 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.

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 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, 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 taking the drugs. 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.

Risks and side effects related to the treatments being studied include:

Arm A (Bevacizumab) with FOLFOX

LIKELY:

- Decreased number of white blood cells (neutrophils; may make you more vulnerable to infection which could be serious or even life threatening). Also see the Additional Information section below.
- Lower number of red blood cells (may make you short of breath, weak, fatigued or tired)
- Lower number of platelets (may result in easy bruising or bleeding)
- Darkening of the skin. This happens most often in the palms of the hands or along the vein where 5-FU is given. This is not harmful, but it could be permanent.
- Photosensitivity (exposure to sunlight can cause skin to be sensitive to sunburn)
- Diarrhea, which could lead to dehydration
- A sensation of pain or tingling in areas of the body that are exposed to cold air or cold liquid, such as your hands if placed in the refrigerator or your throat if exposed to a cold wind or drinking cold liquids (see the Additional Information section below).
- High blood pressure
- Temporary hair loss
- Nausea and/or vomiting
- Loss of appetite
- Headache
- Changes in fingernails
- Fatigue
- Taste changes

LESS LIKELY:

- Redness and sensitivity of the palms of the hands and soles of the feet
- "Pins and needle" and/or numbness sensation in the fingertips and toes which could be permanent.
- Protein in the urine, which may be a sign of kidney damage and could lead to kidney failure
- Kidney damage
- Blood in the urine or stool
- Watery eyes
- Cough, hoarseness, or runny or stuffy nose
- Shortness of breath

- Minor bleeding, including nose bleeds
- Blood clots in the legs, lung, brain, or abdomen which could lead to death
- Abnormal clotting and/or bleeding
- Destruction of red blood cells
- Abnormal heart rhythm (which may be serious)
- Hearing loss
- Inflammation in or around the ear
- Eye irritation
- Dry eye
- Swelling around the nerve responsible for sight
- Temporary vision problems sometimes caused by cold
- Belly pain
- Pain including chest pain not related to the heart
- Fluid collection in the abdomen
- Irritation or sores in the digestive tract anywhere from the mouth to the anus
- Constipation
- Blockage of the intestines and severe constipation
- Dry mouth
- Heartburn
- Difficulty swallowing
- Excess passing of gas
- Irritation of the pancreas which could cause belly pain
- Chills
- Swelling of the face and/or arms or legs
- Fever
- Difficulty walking
- Irritation at the site of the IV
- Reactions while drugs are being given, such as fever, chills, or nausea which can be severe
- Allergic reactions
- Infection
- Abscess (a type of infection) around the rectum
- Delayed wound healing
- Abnormal liver function as seen on a blood test: ALT, AST, alkaline phosphatase, bilirubin
- Abnormal blood test of bone health: Alkaline phosphatase
- Weight gain
- Weight loss
- Dehydration (when your body does not have as much water and fluid as it should)
- Increased blood sugar level
- Decreased blood sugar level
- Jaw stiffness
- Sleepiness
- Speech problems
- Restless, repetitive, or involuntary movements and rapid speech
- Weakness or paralysis of muscles
- Convulsion or seizure
- Anxiety
- Confusion

- Depression
- Difficulty sleeping or falling asleep
- Bleeding in male or female organs
- Need to urinate often
- Difficulty emptying the bladder
- Hiccups
- Dry skin
- Skin rash
- Itching or hives
- Sudden reddening of the face and/or neck
- Excess sweating
- Hot flashes
- Low blood pressure
- Dizziness or fainting

RARE BUT SERIOUS:

- Clotted catheter or catheter infection
- Severe diarrhea that may be life threatening
- Allergic reactions (life-threatening breathing problems)
- Pneumonitis, meaning inflammation of the lungs that could lead to cough, or shortness of breath and in severe cases, could be fatal.
- Chest pain (angina)
- Heart attack
- Decreased heart function
- Stroke or TIA (mini-stroke)
- Throat tightness, shortness of breath, or a choking sensation (see the Additional Information section below)
- Failure of your liver to work correctly, or decreasing function of the liver (see the Additional Information section below)
- Severe infection (see the Additional Information section below)
- Fistula: An abnormal connection between organs in the body
- Bowel perforation and bowel anastomotic dehiscence: Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the belly. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events can be life-threatening. You should inform your doctors if you experience symptoms suggestive of bowel perforation, such as worsening or new pain in the belly or the rectum.
- Perforations in other places in the body, including the nose
- Stomach ulcers
- Clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells or cells that help to clot blood and kidney failure
- Kidney failure
- Severe or life-threatening internal or external uncontrolled bleeding, such as in the brain or lung
- Leaking from blood vessels in the brain (see the Additional Information section below).

- 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 and increases the risk of bleeding
- Inflammation of the gallbladder possibly associated with gallstones

Arm A (Bevacizumab) with FOLFIRI

LIKELY:

- Decreased number of white blood cells (neutrophils; may make you more vulnerable to infection which could be serious or even life threatening). Also see the Additional Information section below.
- Lower number of red blood cells (may make you short of breath, weak, fatigued or tired)
- Lower number of platelets (may result in easy bruising or bleeding)
- Darkening of the skin. This happens most often in the palms of the hands or along the vein where 5-FU is given. This is not harmful, but it could be permanent.
- Photosensitivity (exposure to sunlight can cause skin to be sensitive to sunburn)
- Diarrhea, which could lead to dehydration
- High blood pressure
- Temporary hair loss
- Nausea and/or vomiting
- Loss of appetite
- Headache
- Changes in fingernails
- Fatigue
- Taste changes

LESS LIKELY:

- Redness and sensitivity of the palms of the hands and soles of the feet
- Protein in the urine, which may be a sign of kidney damage and could lead to kidney failure
- Kidney damage
- Blood in the urine or stool
- Diarrhea during irinotecan infusion or shortly afterward associated with abdominal cramps, watery eyes, skin flushing and excessive production of saliva
- Irritation or sores in the digestive tract anywhere from the mouth to the anus
- Constipation
- Blockage of the intestines and severe constipation
- Heartburn
- Belly pain
- Pain including chest pain not related to the heart
- Skin rash
- Itching or hives
- Watery eyes
- Cough, hoarseness, or runny or stuffy nose
- Shortness of breath
- Minor bleeding, including nose bleeds
- Vaginal bleeding
- Dizziness or fainting
- Abnormal heart rhythm (which may be serious)
- Reactions while drugs are being given, such as fever, chills, or nausea which can be severe

- Allergic reactions
- Infection
- Abscess (a type of infection) around the rectum
- Delayed wound healing
- Blood clots in the legs, lung, brain, or abdomen which could lead to death
- Abnormal liver function as seen on a blood test: ALT, AST, alkaline phosphatase, bilirubin
- Abnormal blood test of bone health: Alkaline phosphatase
- Weight loss

RARE BUT SERIOUS:

- Clotted catheter or catheter infection
- Severe diarrhea that may be life threatening
- Allergic reactions (life-threatening breathing problems)
- Pneumonitis, meaning inflammation of the lungs that could lead to cough, or shortness of breath and in severe cases, could be fatal.
- Chest pain (angina)
- Heart attack
- Decreased heart function
- Stroke or TIA (mini-stroke)
- Fistula: An abnormal connection between organs in the body
- Bowel perforation and bowel anastomotic dehiscence: Bowel perforation occurs when an opening exists in the bowel wall allowing bowel contents to spill into the belly. Bowel anastomotic dehiscence is a breakdown in the surgical connection between two pieces of bowel. These events can be life-threatening. You should inform your doctors if you experience symptoms suggestive of bowel perforation, such as worsening or new pain in the belly or the rectum.
- Perforations in other places in the body, including the nose
- Stomach ulcers
- Clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells or cells that help to clot blood and kidney failure
- Kidney failure
- Severe or life-threatening internal or external uncontrolled bleeding, such as in the brain or lung
- Leaking from blood vessels in the brain (see the Additional Information section below).

Arm B (Cetuximab) with FOLFOX

LIKELY:

- Decreased number of white blood cells (neutrophils; may make you more vulnerable to infection which could be serious even life threatening)
- Lower number of red blood cells (may make you short of breath, weak, fatigued or tired)
- Lower number of platelets (may result in easy bruising or bleeding)
- Darkening of the skin. This happens most often in the palms of the hands or along the vein where 5-FU is given. This is not harmful, but it could be permanent.
- Soreness or painful ulcers in the mouth and/or throat (lasting a couple of days)
- Photosensitivity (exposure to sunlight can cause skin to be sensitive to sunburn)
- Diarrhea, which could lead to dehydration

- A sensation of pain or tingling in areas of the body that are exposed to cold air or cold liquid, such as your hands if placed in the refrigerator or your throat if exposed to a cold wind or drinking cold liquids (see the Additional Information section below).
- A skin rash that may resemble acne, involving mostly the face and chest. This may be severe.
- Skin rash
- Dry skin
- Hair loss
- Nausea and/or vomiting
- Loss of appetite
- Changes in fingernails
- Fatigue
- Fever
- Taste changes
- Headache

LESS LIKELY:

- “Pins and needle” and/or numbness sensation in the fingertips and toes which could be permanent.
- Kidney damage that could be severe (see the Additional Information section below)
- Low levels of magnesium or calcium in the blood, which may cause weakness and muscle cramps
- Depression
- Watery eyes
- Insomnia
- Dizziness or feeling of being unbalanced
- Abnormal clotting and/or bleeding
- Destruction of red blood cells
- Abnormal heart problems
- Hearing loss
- Inflammation in or around the ear
- Ringing in the ears
- Eye irritation
- Dry eye
- Swelling around the nerve responsible for sight
- Temporary vision problems sometimes caused by cold
- Swelling and redness of the eye and eyelids
- Belly pain
- Fluid collection in the abdomen
- Irritation or sores in the digestive track anywhere from the mouth to the anus
- Constipation
- Dry mouth
- Dry and cracking of the lips and corner of the mouth
- Heartburn
- Difficulty swallowing
- Excess passing of gas
- Stomach or intestinal bleeding, for example, blood in your stool

- Irritation of the pancreas which could cause belly pain
- Chills
- Swelling of the face and/or arms or legs
- Flu-like symptoms
- Infusion reactions with cetuximab, including fever, chills, and nausea which can be severe
- Allergic reaction
- Difficulty walking
- Irritation at the site of the IV
- Chest pain not heart-related
- Abnormal chemistry tests which may indicate abnormal liver function
- Weight gain
- Weight loss
- Dehydration (when your body does not have as much water and fluid as it should)
- Increased blood sugar level
- Decreased blood sugar level
- Pain in joints, back, bone, or muscle
- Jaw stiffness
- Sleepiness
- Speech problems
- Restless, repetitive, or involuntary movements and rapid speech
- Weakness or paralysis of muscles
- Convulsion or seizure
- Anxiety
- Confusion
- Difficulty sleeping or falling asleep
- Bleeding in male or female organs
- Need to urinate often
- Difficulty emptying the bladder
- Hiccups
- Excess sweating
- Itching or hives
- Skin ulceration
- Sudden reddening of the face and/or neck
- Hot flashes
- High blood pressure
- Low blood pressure
- Infection
- Fainting
- Cough, wheezing, or hoarseness

- Shortness of breath
- Stuffy or runny nose, sneezing

RARE BUT SERIOUS:

- Clotted catheter or catheter infection
- Severe diarrhea that may be life threatening
- Severe reactions during cetuximab infusions or severe allergic reaction: A fast heart rate, wheezing, low blood pressure, sweating, and swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications
- Inflammation of the lungs with shortness of breath and in severe cases, could be fatal.
- Heart problems (chest pain, heart attack, or heart failure) (see the Additional Information section below)
- Throat tightness, shortness of breath, or a choking sensation (see the Additional Information section below)
- Failure of your liver to work correctly, or decreasing function of the liver (see the Additional Information section below)
- Severe infection (see the Additional Information section below)
- 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 and increases the risk of bleeding
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung
- Inflammation of the gallbladder possibly associated with gallstones
- Stroke or TIA (mini-stroke)
- Severe bleeding from your tumor or other sites including the brain. In some cases, bleeding has resulted in death.
- Inflammation or irritation of the lining of the brain and spinal cord
- Fluid in the lungs
- Redness and sensitivity of the palms of the hands and soles of the feet

Arm B (Cetuximab) with FOLFIRI

LIKELY:

- Decreased number of white blood cells (neutrophils; may make you more vulnerable to infection which could be serious even life threatening)
- Lower number of red blood cells (may make you short of breath, weak, fatigued or tired)
- Lower number of platelets (may result in easy bruising or bleeding)
- Darkening of the skin. This happens most often in the palms of the hands or along the vein where 5-FU is given. This is not harmful, but it could be permanent.
- Soreness or painful ulcers in the mouth and/or throat (lasting a couple of days)
- Photosensitivity (exposure to sunlight can cause skin to be sensitive to sunburn)
- Diarrhea, which could lead to dehydration
- A skin rash that may resemble acne, involving mostly the face and chest. This may be severe.
- Skin rash
- Dry skin
- Hair loss
- Nausea and/or vomiting

- Loss of appetite
- Changes in fingernails
- Fatigue
- Fever
- Taste changes
- Headache

LESS LIKELY:

- Low levels of magnesium or calcium in the blood, which may cause weakness and muscle cramps
- Diarrhea during irinotecan infusion or shortly afterward associated with abdominal cramps, watery eyes, skin flushing and excessive production of saliva
- Depression
- Watery eyes
- Dry eye
- Swelling and redness of the eye and eyelids
- Insomnia
- Dizziness or feeling of being unbalanced
- Inflammation of the outside of the ear
- Ringing in the ears
- Belly pain
- Constipation
- Dry mouth
- Dry and cracking of the lips and corner of the mouth
- Heartburn
- Chills
- Swelling of the arms or legs
- Flu-like symptoms
- Infusion reactions with cetuximab, including fever, chills, and nausea which can be severe
- Chest pain not heart-related
- Allergic reaction
- Infection
- Weight loss
- Dehydration (when your body does not have as much water and fluid as it should)
- Pain in joints, back, or muscle
- Fainting
- Cough, wheezing, or hoarseness
- Shortness of breath
- Stuffy or runny nose, sneezing
- Itching or hives
- Skin ulceration
- Low blood pressure

RARE BUT SERIOUS:

- Clotted catheter or catheter infection
- Severe diarrhea that may be life threatening
- Severe reactions during cetuximab infusions or severe allergic reaction: A fast heart rate, wheezing, low blood pressure, sweating, and swelling of the throat, and face rash may occur within a few minutes of starting treatment. They can be handled with medications.
- Inflammation of the lungs with shortness of breath and in severe cases, could be fatal.
- Heart problems (chest pain, heart attack, or heart failure) (see the Additional Information section below)
- Inflammation or irritation of the lining of the brain and spinal cord
- Fluid in the lungs
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung
- Redness and sensitivity of the palms of the hands and soles of the feet

Unanticipated side effects may occur which have not been reported. If you have any unusual symptoms, report them immediately to your doctor.

Reproductive risks: You should not conceive a baby while on this study and for at least six months after you stop taking bevacizumab and for at least two months after you stop taking cetuximab, because the drugs may affect an unborn baby. It is important you understand that you need to use birth regulation (regulation highly effective: abstinence, IUD, birth control pills, tubal ligation or partner's vasectomy and less effective: condom, diaphragm or cervical cap) while on this study. Check with your study doctor about what kind of birth regulation (regulation highly effective: abstinence, IUD, birth control pills, tubal ligation or partner's vasectomy and less effective: condom, diaphragm or cervical cap) methods to use and how long to use them. Some methods might not be approved for use in this study.

Additional Information about Risks

Additional information about the risks of oxaliplatin:

Exposure to cold (oxaliplatin): When receiving oxaliplatin, the nerves that affect your throat may be affected and cause a strange sensation when swallowing cold liquids. You should avoid cold beverages while you are participating in this study. You may also notice a tingling and numbness or pain in your hands and feet that worsen on exposure to cold. Extra layers of clothing (gloves, mittens and warm socks) may help these symptoms be less severe.

If you should develop **throat tightness, shortness of breath, or a choking sensation**, contact your doctor immediately. In the patients treated with this drug, there have been 11 patients (of more the 50,000 who have be treated with oxaliplatin) who got lung problems such as cough, shortness of breath, or trouble breathing. This caused scar tissue in the lungs and these events can be life threatening.

Inflammation of the nerves can become worse during the time you are receiving treatment, and the risk of developing it increases with the amount of oxaliplatin you receive. This inflammation usually goes away.

In some cases, the combination of oxaliplatin and 5-FU can cause a severe infection often associated with **diarrhea**. This infection is serious and can be life threatening. Contact your physician immediately if you are experiencing severe diarrhea (more than 7 or 8 times per day), fever, as well as numbness or tingling in your hands, feet or throat, or weakness.

A few patients treated with oxaliplatin have developed a condition known as “**Tumor Lysis Syndrome.**” Tumor Lysis Syndrome is a complication that can occur when cancer cells are destroyed by treatment. The destruction of cells may damage the kidneys and change calcium levels in the body. This complication may lead to the need for kidney dialysis usually on a temporary basis. You may also develop a condition associated with the dysfunction of your kidneys called Hemolytic Uremic Syndrome. This syndrome can be serious and may lead to seizures, problems with the central nervous system, or coma.

Very rarely, liver damage that can lead to **chronic liver disease** has been associated with oxaliplatin when used with 5-FU. Liver disease may appear as the enlargement of the liver and/or the spleen, abnormal blood flow to the liver, and/or enlarged blood vessels in your esophagus.

Platinum drugs like oxaliplatin have been known to cause **leukemia** in a small number of patients. It is not known whether risk of future development of leukemia is a side effect of oxaliplatin. One case of leukemia and one case of myelodysplastic syndrome, a condition which could lead to leukemia, have been seen following oxaliplatin chemotherapy, although it is not certain that oxaliplatin caused these blood disorders.

Additional information about the side effects of bevacizumab:

Neutropenia (**decrease in white blood cells**) is a common side effect of chemotherapy drugs. This may happen more often when bevacizumab is added to chemotherapy. In some studies of bevacizumab plus chemotherapy, there was also an increase in fever with neutropenia and infections. Rarely, these infections resulted in death.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS is a medical condition related to **leakiness of blood vessels in the brain** and can cause confusion, blindness or vision changes, seizure, and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening and may have long-term effects on brain function.

Additional information about the side effects of cetuximab:

Rare incidents of heart problems such as chest pain, decreased heart function, and injury to the heart muscle have been observed in clinical trials with cetuximab in combination with 5-FU-containing regimens. Heart problems are already known to occur with 5-FU; but we do not know at this time whether the addition of cetuximab to 5-FU increases the risk of these problems.

If you are a woman and become pregnant or suspect you are pregnant while participating on this study, you should inform your physician immediately. Because the risk of toxicity of these agents in nursing infants is also unknown, breastfeeding should be discontinued.

For more information about risks and side effects, ask the study doctor at the number listed on the cover page.

Are There Benefits to Taking Part in the Study?

Taking part in this study may or may not make your health better. While doctors hope that adding cetuximab to FOLFOX or FOLFIRI will be more useful against cancer compared to bevacizumab and FOLFOX or FOLFIRI alone, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these drugs as a treatment for cancer. 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, which may involve using combinations of the drugs used in this study or different drugs
- Taking part in another study
- 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:

- The Cancer and Leukemia Group B (CALGB)
- The Southwest Oncology Group (SWOG)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Bristol-Meyers Squibb pharmaceutical company, the makers of cetuximab.

The Cancer Trials Support Unit (CTSU) may also view your records if you are participating in this trial through one of their institutions.

The Cancer and Leukemia Group B have received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state, or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services or for purpose of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

What are the costs of taking part in this 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. 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.

Bristol-Meyers Squibb is supplying the cetuximab at no cost to you. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the cetuximab.

If, during the study, cetuximab becomes approved for use in your type of colon or rectal cancer, you and/or your health plan may have to pay for drug needed to complete this study.

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 study?

It is important that you tell your study doctor 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 the number listed on the cover page.

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 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.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.

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.

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:

(name) _____ (title) _____
(address) _____ (phone number) _____.

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 study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor at the number listed on the cover page.

For questions about your rights while taking part in this study, call the MultiCare Health Institutional Review Board (a group of people who review the research to protect your rights) at 253-403-3877.

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

RELATED STUDIES

Please note: The following section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say “no” to taking part in any of these additional studies.

Diet and Lifestyle Study

The study investigators would like to ask you to fill out a questionnaire about your diet and daily activities within the first month of your treatment. This questionnaire should take about 30 minutes to complete, and can be filled out during one of your chemotherapy sessions. When you are presented with the questionnaire, you may choose whether or not you would like to fill it out.

- 2) I choose to take part in the Diet and Lifestyle study and agree to complete the diet and lifestyle questionnaire:

_____ Yes _____ No Initials _____

Medical Costs Study

In addition to the studies described above, the researchers would like to obtain information about the costs of your medical care and prescription medication.

In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

In order to obtain this information, you will be asked to complete a questionnaire on your first visit, which will take about 5-10 minutes to complete. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is complete the costs of medical care and prescription medication questionnaire. You may change your mind about completing the questionnaire at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

- 3) I choose to take part in the medical costs study and agree to complete the medical costs questionnaire:

_____ Yes _____ No Initials _____

Consent Form for Use of Tissue and Blood for Research

About Using Tissue for Research

As part of this research study, we would like to request your permission to study cells from your tumor. The tumor samples were previously obtained when your disease was first diagnosed or when you had surgery. These tumor samples will be used in a laboratory to investigate colorectal cancer.

The researchers would like to keep some of the tissue that was left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. [This NCI information sheet is available at <http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.html>]

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have 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.

In addition, the researchers would like to investigate whether substances in your blood (sometimes called tumor markers) are related to the way that your body responds (or doesn't respond) to the chemotherapy you receive in this trial. These tumor markers are inherited through your family, and could be passed to your children. These are also called genetic studies.

The researchers would also like to collect additional samples of your blood. Approximately 5 teaspoons of additional blood at the beginning of the study, after 8 weeks of therapy, and at the end of the study would be collected. Also, in order to study how cetuximab might cause allergic reactions, the researchers would like to collect an additional teaspoon of blood following any allergic reaction you might have. These additional tubes of blood would only be collected from patients randomized to receive cetuximab.

Things to Think About

The choice to let us keep the left over tissue 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 tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Cancer and Leukemia Group B 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 tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

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

Benefits

The benefits of research using tissue 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 is the 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 Choice

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

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

4) My tissue and blood may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.

_____ Yes _____ No Participant _____ Date _____

5) My tissue and blood may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease and heart disease).

_____ Yes _____ No Participant _____ Date _____

6) Someone may contact me in the future to ask me to take part in more research.

_____ Yes _____ No Participant _____ Date _____

Genetic studies on blood cells:

The researchers would like to investigate whether substances in your blood are related to the way that your body responds (or doesn't respond) to the chemotherapy you receive in this trial. These tumor markers are inherited through your family, and could be passed to your children. These are also called genetic studies.

Blood taken before treatment will be used to learn how certain genes influence the effectiveness and side effects of cetuximab and bevacizumab. In order to study the genes the DNA must be removed from your blood sample. DNA is the substance that makes up your genes. Genes are the units of inheritance that are passed down from generation to generation. They are responsible for eye color, hair color, blood type, and hundreds of other traits.

There are specific risks associated with genetic studies. To help you make your decision, additional information about participation in genetic studies is included at the end of this consent form. This information identifies how your personal information will be protected by the Cancer and Leukemia Group B and its researchers.

Blood taken for these studies will be done only once at the time you enter the study. About 1 tablespoon of blood would be taken.

7) I agree that my blood may be used for the genetic research studies described above.

_____ Yes _____ No Initials _____

Safeguards of Confidentiality in Studies Involving Genes (genetic studies):

It is possible to use blood samples to study many different kinds of genes. The Cancer and Leukemia Group B recognizes this possibility and will take the following steps to protect your privacy and to protect you from having your sample tested for any genetic changes not directly related to cancer:

- Blood samples will be stored at a Cancer and Leukemia Group B laboratory. The Cancer and Leukemia Group B Statistical Center will perform all analyses of data and store all study results. Your blood sample will not be stored with your name on it. Instead, it will be labeled with a special Cancer and Leukemia Group B identification number. The only location where your name and special identification number will be stored together is at the Cancer and Leukemia Group B Statistical Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy.
- Information about your participation in this study and results of any tests performed on your sample will be kept only at the Cancer and Leukemia Group B Statistical Center at Duke University. This information will not be made available to your doctors or to individual researchers at Cancer and Leukemia Group B. Test results from this study will not be put in your medical records. All study information, including test results, is stored under conditions that limit access in order to protect the privacy of the people participating in this study.
- Your blood will be used only for the study of genes involved in cancer.
- There are no absolute legal protections against discrimination on the basis of genetic information. However, there are legal precautions including new federal and state laws (in most states) that are designed to protect against discrimination on the basis of genetic information. Since neither you nor your physician will be notified of the results of this test, it is unlikely that any discrimination could take place.

The same precautions to protect your privacy will be in place for such future studies. Future investigators will receive blood samples with the special Cancer and Leukemia Group B identification number only, and your blood sample will not be identified with your name. These future investigators must apply to the Cancer and Leukemia Group B and have their research project reviewed and approved by the Cancer and Leukemia Group B.

If you decide now to give a sample of blood and then change your mind at any time about participating in the study, just contact your institution and let them know that you do not want the researchers to use your sample. The results from these studies may be published, but individual patients will not be identified in the publications.

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) or TTY: 1-800-332-8615

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/>

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

Signature

I have been given a copy of all 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.

Signature of Patient or
Patient's Legal Representative: _____ Date: _____

Printed Name of Legal Representative (if any): _____

Representative's Authority to Act for Patient: _____

Signature of Person Obtaining Authorization: _____

Printed Name of Person Obtaining Authorization: _____

Authorization to Use or Disclose (Release) Identifiable Health Information For Research

Participant's Name: _____

Birthdate: _____

1. What is the purpose of this form?

The Cancer Trials Support Unit (CTSU) is an organization that does research to learn about the causes of cancer, and how to prevent and treat cancer. Researchers would like to use your health information for research. This information may include data that identifies you. Please carefully review the information below. If you agree that researchers can use your identifiable health information, you must sign and date this form to give them your permission.

2. What health information do the researchers want to use?

The researchers want to abstract and use the portions of your medical record that they will need for their research. If you enter a CTSU research study, information that will be used and/or released may include your complete medical record, and in particular, the following:

- the history and diagnosis of your disease
- specific information about treatments you received
- information about other medical conditions that may affect your treatment
- medical data, including laboratory test results, tumor measurements, CT scans, MRIs, X-rays, photographs of radiation therapy target areas, and pathology results
- information on side effects (adverse events) you may experience, and how these were treated
- long-term information about your general health status and the status of your disease
- tissue and/or blood samples, associated data related to the analysis of the samples

You may request a blank copy of the CTSU data forms from the Northwest CCOP to learn what information will be shared.

3. Why do the researchers want my health information?

The Northwest CCOP will collect your health information and share it with the CTSU if you enter a Cooperative Group research study, or to evaluate your eligibility for a study. The CTSU researchers will use your information for the following cancer research study(ies). You are being asked to take part in a study known as: CIRB C80405: A PHASE III TRIAL OF IRINOTECAN/5-FU/LEUCOVORIN OR OXALIPLATIN/5-FU/LEUCOVORIN WITH BEVACIZUMAB OR CETUXIMAB (C225) FOR PATIENTS WITH UNTREATED METASTATIC ADENOCARCINOMA OF THE COLON OR RECTUM.

4. *Who will be able to use my health information?*

The Northwest CCOP will use your health information for research. As part of this research, they may give your information to the following Groups taking part in the research. The Northwest CCOP may also permit staff from these Groups to review your original records as required by law for audit purposes.

the Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials

National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the research group coordinating this study.

The company that makes the study drugs and are supporting the study.

NCI US (National Cancer Institute in the United States)

Therapeutic Products Program of Health Canada (because it oversees the use of drugs in Canada)

The Northwest CCOP

public health agencies and other government agencies (including non-U.S.) as authorized or required by law

other people or organizations assisting with CTSU research efforts and the Food and Drug Administration

central laboratories, central review centers, and central reviewers. The central laboratories and review agencies may also give your health information to those groups listed above.

5. *How will information about me be kept private?*

The CTSU will keep all identifiable health information confidential to the extent possible, even though they and other federal research groups are not subject to the same federal privacy laws governing clinical centers. The CTSU will not release identifiable health information about you to others except as authorized by this form, or required by law. If your identifiable health information must be shared with other organizations, the privacy laws that govern those organizations would apply.

6. *What happens if I do not sign this authorization form?*

If you do not sign this authorization form, you will not be able to take part in a research study for which you are being considered.

7. *If I sign this form, will I automatically be entered into the research study?*

No, you cannot be entered into any research study without further discussion and separate consent. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a separate research consent form.

8. What happens if I want to withdraw my authorization?

You can change your mind at any time and withdraw this authorization. This request for withdrawal must be made in writing. Beginning on the date you withdraw your authorization, no new identifiable health information will be used for research. However, researchers may continue to use the health information that was provided before you withdrew your permission.

If you sign this form and enter the research study, but later change your mind and withdraw your authorization, you will be removed from the research study at that time.

To withdraw your authorization, please contact the person below. She will make sure your written request to withdraw your authorization is processed correctly.

Karyn Hart, RHIT, CCRP
Program Coordinator
Northwest CCOP
315 Martin Luther King Jr., Way
Tacoma, WA 98405
(253) 403-1461

9. How long will this authorization last?

If you agree by signing this form that researchers can use your identifiable health information, this authorization has no expiration date. However, as stated above, you can change your mind and withdraw your permission at any time.

10. What are my rights regarding my identifiable health information?

You have the right to refuse to sign this authorization form. You have the right to review and/or copy records of your health information kept by the Northwest CCOP. You do not have the right to review and/or copy records kept by the CTSU or other researchers associated with the research study.

Signatures

I agree that my identifiable health information may be used and disclosed for research purposes described in this form.

Signature of Patient or Patient's Legal Representative: _____ Date: _____

Printed Name of Legal Representative (if any): _____

Representative's Authority to Act for Patient: _____

Signature of Person Obtaining Authorization: _____

Printed Name of Person Obtaining Authorization: _____