

MARQUETTE GENERAL HEALTH SYSTEM

Regional Medical Center

CONSENT TO PARTICIPATE IN AN INVESTIGATIONAL STUDY

TITLE: A Randomized Phase II Clinical Trial Investigating Irinotecan Plus Cetuximab With or Without Anti-Insulin-Like Growth Factor-I Receptor Monoclonal Antibody (IMC-A12) for the Treatment of Patients with Metastatic K-RAS Wild-Type Carcinoma of the Colon or Rectum that has Progressed on Oxaliplatin and Bevacizumab Given as First-Line Therapy

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This is a clinical trial, which is a type of research study. You are being asked to take part in this study because you have colon or rectal cancer that has spread to other parts of your body and has not responded to the therapy you have already received. 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.

Who is conducting the study?

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation Research Program (FRP) is conducting the study. Marquette General Hospital is conducting the trial locally.

Why is this study being done?

This study is being done to compare the effects, good and/or bad, of giving patients with your type and stage of colon or rectal cancer the combination of a standard chemotherapy drug called irinotecan plus a drug called cetuximab (also called Erbitux[®]) with or without a third drug called IMC-A12. This study will include only patients who have tumors that were found by Esoterix Clinical Trial Services testing to be K-RAS wild-type.

- The main purpose of this study is to compare the effectiveness of the combination of irinotecan plus cetuximab to the combination of irinotecan plus cetuximab plus IMC-A12.

- Irinotecan is a chemotherapy drug commonly used to treat colon and rectal cancer. Chemotherapy drugs like irinotecan work by killing cancer cells directly. It is approved by the Food and Drug Administration (FDA) for use in your stage and type of cancer.
- Cetuximab is a type of drug called a “targeted therapy.” Cetuximab targets epidermal growth factor receptor (EGFR) on the cancer cell. Cetuximab attaches to EGFR on the surface of the cancer cell to block the cell's growth signal. This causes the growth of the cancer cell to slow down or stop and may reduce the size of the tumors.

Cetuximab is considered by the FDA to be an "investigational" drug in the FC-4/CP13-0708 study because it is still being researched for use in patients with your stage of cancer who have not yet received the chemotherapy drug irinotecan.

IMC-A12 is also an investigational drug. Like cetuximab, IMC-A12 is a targeted therapy, but it targets a different area on the cancer cell. IMC-A12 targets Insulin-like Growth Factor-I Receptor (IGF-IR) to interfere with the growth and survival of the cancer cell.

- Another purpose is to learn about the safety and side effects of the two combinations of drugs used in this study.
- This study will also help researchers to learn about how patients feel physically and emotionally during study treatment.

How many people will take part in the study?

About 100 people 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 and tests to find out if you can be in the study. These exams and tests are part of regular cancer care and may be done even if you do not join the study. If you recently have had any of the tests and exams listed below, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical exam
- Blood tests to check your blood counts and to check how well your kidneys and liver are working
- Blood test to measure the amount of albumin (protein) in your blood
- Blood tests to measure substances in your blood called tumor markers
- CT scan or MRI of your chest, abdomen, and pelvis
- Pregnancy test (if you are a woman of childbearing potential)

You will also need the following tests to make sure you are able to join the study. These tests are not part of regular cancer care and **are being done for the purpose of this study**.

- Blood test to measure the amounts of calcium, potassium, and magnesium in your blood
- Blood test to measure the amount of glucose (sugar) in your blood. You must not eat or drink anything but water for about 8 hours before this blood sample is taken.
- Urine test to check your kidney function
- Central K-RAS testing on your tumor sample (explained to you in a separate consent form)

If all exams, tests, and procedures listed above show that you can be in the study and if you choose to take part, you will be enrolled in the study and "randomized" to one of the two study groups to be described later in the consent form. 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 either group.

After you have been assigned to one of the study treatment groups, you will begin your study therapy within 2 weeks. You will receive your study drugs on a specific schedule. This schedule will be repeated every 14 days. This 14-day period is called a *cycle*. The drugs and treatment schedules are as follows:

Study therapy – Group 1:

If you are randomized to Group 1, you will receive cetuximab and irinotecan through a vein on the first day of each cycle. It will take about 2 hours to receive the first dose of cetuximab. You will then be checked during the next hour for any signs of a reaction to the cetuximab. After 1 hour, you will then be given irinotecan over a period of 30 to 90 minutes. (Your doctor will decide how long the irinotecan treatment will take.) Also, for the first cycle only, you will be checked during the next hour following the completion of the irinotecan infusion to be sure you do not have a reaction to the irinotecan. Therefore, it will take about 4½ to 5½ hours to receive your first cycle of study therapy.

If you receive the first dose of cetuximab without problems, the second dose (second cycle) will be given over a 1½ hour time period, and irinotecan will be given to you over 30 to 90 minutes immediately following completion of the cetuximab. Therefore, it will take about 2 to 3 hours to receive your second cycle of study therapy.

If you receive the second dose of cetuximab without problems, all of the following doses will be given over a 1 hour period and irinotecan will be given to you over 30 to 90 minutes immediately following completion of the cetuximab. Therefore, it will take about 1½ to 2½ hours to receive all of the following cycles of study therapy.

You will continue to be treated with cetuximab and irinotecan once every 14 days as long as your cancer does not get worse and the drugs have not caused any serious side effects.

Study therapy – Group 2:

If you are randomized to Group 2, you will receive cetuximab, IMC-A12, and irinotecan through a vein on the first day of each 14-day cycle. The first dose of cetuximab will take about 2 hours to receive. You will then be checked for 1 hour for any signs of a reaction to cetuximab. After 1 hour, you will then receive IMC-A12 through a vein. This will take about 1 hour. Irinotecan will then be given to you over a period of 30 to 90 minutes. (Your doctor will decide how long the irinotecan treatment will take.) Also, for the first cycle only, you will be checked for an additional 1 hour following the completion of the irinotecan infusion to be sure you do not have a reaction to the irinotecan. It will take about a total of 5½ to 6½ hours for the first cycle of study therapy.

If you receive the first dose of cetuximab without problems, the second dose will be given over a period of 1½ hours. IMC-A12 will be given immediately following completion of the cetuximab and will take about 1 hour. Irinotecan will then be given over 30 to 90 minutes. Therefore, it will take about 3 to 4 hours to receive your second cycle of study therapy.

If you receive the second dose of cetuximab without problems, all of the following doses of cetuximab will be given over a period of 1 hour. IMC-A12 will be given immediately following completion of the cetuximab and will take about 1 hour. Irinotecan will then be given over a 30 to 90 minute period. Therefore, it will take about 2½ to 3½ hours to receive all of the remaining cycles of study therapy.

You will continue to be treated with cetuximab, IMC-A12, and irinotecan once every 14 days as long as your cancer does not get worse and the drugs have not caused any serious side effects.

A summary of study therapy for Group 1 and Group 2 is outlined below:

<p><u>GROUP 1</u></p> <p>Cetuximab</p> <p>+</p> <p>Irinotecan</p> <p>Given through a vein on Day 1 every 14 days</p>	<p><u>GROUP 2</u></p> <p>Cetuximab</p> <p>+</p> <p>IMC-A12</p> <p>+</p> <p>Irinotecan</p> <p>Given through a vein on Day 1 every 14 days</p>
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During study therapy:

You will have the following tests and exams. They are part of regular cancer care.

- Physical exam before every study treatment cycle
- Blood tests to check your blood counts and to check how well your kidneys and liver are working before every study treatment cycle
- CT scan or MRI of your chest every 6 weeks to see how your cancer is responding to the study therapy. Your study doctor may decide to use a chest x-ray as a substitute for a chest CT scan or MRI if you do not have any signs of cancer in your chest. (Regular cancer care only includes these tests every 12 weeks. The every 6-week schedule is being done for the purpose of this study.)
- CT scan or MRI of your abdomen and pelvis every 6 weeks to see how your cancer is responding to the study therapy. (Regular cancer care only includes these tests every 12 weeks. The every 6-week schedule is being done for the purpose of this study.)

You will also need the following tests that are not part of regular cancer care and **are being done for the purpose of this study:**

- Blood tests to measure the amounts of glucose (sugar), calcium, potassium, magnesium, and albumin (protein) in your blood before every study treatment cycle
- Pregnancy test (if you are a women of childbearing potential) within 72 hours prior to receiving the first dose of study therapy

- Because it is not part of regular cancer care to have chest x-rays, CT scans, or MRIs done every 6 weeks, the tests done at the **every other 6-week time point are being done for the purpose of this study.**
- If you are in Group 2, you will have blood samples collected to check for antibodies against IMC-A12. Antibodies are proteins made by the body to fight foreign substances. A blood sample will be collected before your first dose, 4th dose, and 7th dose of IMC-A12 to check if your body has made antibodies against IMC-A12. You may also have blood samples collected if you have a reaction to IMC-A12. These blood samples will be sent to a lab at ImClone (the company that makes IMC-A12).

A laboratory at ImClone will test your blood samples. Neither you nor your doctor will receive the results of this testing. The testing will not affect your therapy or care during the study. There is no benefit to you from this testing. These samples are for research only; they are not necessary for your care. There will be no cost to you for this testing.

This testing will help ImClone to evaluate the safety of IMC-A12 for patients like you. ImClone will not be able to identify you because the blood samples they receive will be coded. The blood samples will be destroyed after the testing is complete. They will not be used by ImClone or the NSABP FRP for any other purpose.

After study therapy has stopped:

Beginning about 4-6 weeks after you stop receiving study therapy, you will have the following tests and exams that are part of regular cancer care:

- Examination by your doctor or other healthcare professional to see how you are doing. Your study doctor will continue to report your health status to the NSABP FRP about every 6 weeks.

You will also need the following tests that are not part of regular cancer care and **are being done for the purpose of this study:**

- Blood tests to measure the amount of glucose (sugar) in your blood at 4-6 weeks after you stop study therapy. If the results are higher than normal, you will have additional blood tests every 6 weeks until the amount of glucose returns to normal.
- Blood tests to measure the amounts of calcium, potassium, and magnesium in your blood at 4-6 weeks after you stop receiving study therapy
- CT scan, MRI, or x-ray of your chest every 6 weeks as long as your cancer does not get worse
- CT scan or MRI of your abdomen and pelvis every 6 weeks as long as your cancer does not get worse
- Collection of a blood sample to check for antibodies to IMC-A12 (only if you are in Group 2) at 4-6 weeks after you stop receiving study therapy

Quality of life questionnaires

You will be asked to take part in a quality of life study. We want to learn about your view of how your life is affected by the study treatment and its side effects. This quality of life study will collect information from you about how you are feeling physically and emotionally during your study therapy. We also want to learn how you are able to carry out your day-to-day activities. You will be asked to complete 3 questionnaires. Each one will take about 5 to 10 minutes to fill out. You will be given one questionnaire before you are enrolled in the study, one after Cycle 3, and one after completing your study therapy. If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

How long will I be in the study?

You will continue to receive your study therapy unless your cancer gets worse or you or your doctor decides that you should stop. If you stop receiving study therapy, the NSABP FRP would like to continue to keep track of your medical condition about every 6 weeks for the rest of your life.

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 that any risks from the study therapy 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 will be most helpful for you.

You can choose to withdraw in one of two ways. In the first way, you can stop your study treatment, but still allow the study doctor to report your health status to the NSABP FRP. In the second, you can stop your study treatment and request that no new information be reported to the NSABP FRP.

Can anyone else stop me from being in the study?

Your study doctor may stop you from taking part in this study at any time if he or she believes it is in the best interest for your health; if you do not follow the study rules; or if the study is stopped by the NSABP FRP.

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 do not know all the side effects that may happen. Side effects may be mild or very serious. Your healthcare team may give you medicines to help lessen side effects. Many side effects may go away soon after you stop taking the study therapy. 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 irinotecan (Group 1 and Group 2):**Likely**

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

- Diarrhea can happen the day that you receive irinotecan (either during treatment or shortly after) and may be accompanied by a runny nose, increased saliva, watery eyes, visual changes, sweating, abdominal cramps, slower heart rate, or flushing can also occur. Diarrhea can also occur several days after you receive irinotecan and may last for several days.
- Nausea
- Vomiting
- Loss of or decrease in appetite
- Weight loss
- Constipation
- Sores or inflammation in the lining of the mouth and/or throat
- Infection
- Decreased white blood cell count (may lead to infection)
- Decreased red blood cell count (may lead to tiredness, shortness of breath)
- Decreased platelet count (may lead to increased bruising or bleeding)
- Weakness/fatigue
- Temporary hair loss

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

- Skin rash
- Difficulty sleeping
- Dehydration
- Fever
- Blood tests that show changes in liver function
- Swelling of the arms and legs
- Upset stomach
- Abdominal pain or cramping
- Headache
- Back pain
- Dizziness
- Blood clot in a blood vessel (could be life-threatening)
- Shortness of breath
- Cough

Less likely

This side effect occurs in **3-9%** of patients receiving irinotecan:

Low blood pressure

Rare but serious

These side effects occur in **less than 3%** of patients receiving irinotecan:

- Heart problems (including irregular heartbeats, chest pain, and possibly heart attack or heart failure)
- Inflammation of the pancreas
- Severe diarrhea with a low white blood cell count that can result in death
- Inflammation of the bowel (may cause ulcers, bleeding, obstruction, or infection)
- Bowel perforation (occurs when an opening develops in the bowel allowing bowel contents to spill into the abdomen. This can lead to a life threatening infection and will require surgery to repair).
- Allergic reaction (including chills, rash, hives, itching, flushing, swelling, low blood pressure, wheezing, and shortness of breath)
- Severe lung problems (including shortness of breath, inflammation, and damage that could be permanent)
- Kidney failure

Risks and side effects related to cetuximab (Group 1 and Group 2):**Likely**

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

- Skin rash. One of the most common side effects of cetuximab is a mild to moderate skin rash that often looks like acne. The rash often appears on the face, upper chest, and back but can affect any area of the skin. You may have dry skin, itching, or pain with the rash. You will need to limit your time in the sun while receiving cetuximab and for 2 months after your last dose because sunlight can make the rash worse. Your study doctor or nurse will talk to you more about how to care for your skin. The rash usually goes away after cetuximab has stopped.
- Nausea
- Vomiting
- Constipation
- Diarrhea
- Abdominal pain or cramping
- Weakness/fatigue
- Fever
- Infection
- Headache
- Decreased magnesium in the blood
- Decreased potassium in the blood

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

- Shortness of breath
- Cough
- Nail changes (including redness and swelling of the nail folds of the fingers and toes and possible nail loss)
- Reaction to the infusion (including fever, chills, rash, hives, itching, flushing, swelling, low blood pressure, hoarseness, shortness of breath, wheezing, sweating)
- Swelling of the arms and legs
- Dehydration
- Decrease in appetite
- Back pain
- Infection
- Difficulty sleeping
- Sores or inflammation in the lining of the mouth and/or throat

Less likely

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

- Eye problems (such as increased tearing, redness, itchiness, dry eyes, sensitivity to light, blurred vision, and eye infection)
- Decreased red blood cells (may lead to tiredness, shortness of breath)
- Weight loss
- Heartburn
- Temporary hair loss
- Depression

Rare but serious

These side effects occur in **less than 3%** of patients receiving cetuximab:

- Severe lung problems (including shortness of breath, inflammation, and damage that could be permanent)
- Severe skin infection
- Rare cases of sudden death have occurred in patients with cancer of the head and neck who received radiation therapy and cetuximab. These patients also had a history of heart-related problems. The relationship of these events to cetuximab is not known.
- Severe allergic reaction which could be life-threatening
- Blood clot that may be life-threatening
- Kidney failure

Risks and side effects related to IMC-A12 (Group 2):**Likely**

This side effect occurs in **10-24%** of patients receiving IMC-A12:

Too much glucose (sugar) in the blood

Less likely

These side effects occur in **3-9%** of patients receiving IMC-A12:

- Nausea
- Loss of appetite
- Weight loss
- Swelling of the arms and legs
- Kidney damage
- Skin condition which includes irritation, swelling, redness, itching and thick, dry silvery scales on the skin (also known as psoriasis)
- Skin problems including rash, acne, itching, and dryness
- Hair loss
- Numbness, tingling, prickling and burning in the hands and feet
- Discolored stools
- Dizziness
- Reaction to the infusion (including fever, chills, rash, hives, itching, flushing, swelling, low blood pressure, hoarseness, shortness of breath, wheezing, sweating)
- Increased burping
- Fatigue
- Headache
- Decreased red blood cell count (may lead to tiredness, shortness of breath)

Rare but serious

These side effects occur in **less than 3%** of patients receiving IMC-A12:

- Leukoencephalopathy which is the destruction of the outer myelin sheath (fatty coating that covers the nerve cells of the brain). This may affect brain function, and for example, may cause changes in brain scans, vision changes, or cause difficulty with walking.
- Nephrotoxicity (kidney poisoning)
- Fever
- Dehydration (reduction of water content)
- Bacteremia (bacteria infection in the blood)
- Electrocardiogram QT corrected intervals prolonged (heart rhythm change)

Reproductive risks: Women may experience changes in their menstrual periods and changes in their ability to get pregnant related to treatment with the drugs used in this study. Because the drugs in this study can be harmful to an unborn baby, both female patients and partners of male patients should not conceive a baby while receiving study therapy and for at least 2 months after the last dose of any of the drugs used in this study. Both male and female patients should ask for

more information about preventing pregnancy. If you become aware that you or your sexual partner is pregnant during the course of your participation in this research study, you should tell your study doctor as soon as possible. Women should also not breastfeed a baby while on this study and for at least 2 months after the last dose of any of the drugs used in this study.

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

What are my responsibilities?

- Keep your study appointments. If you cannot keep an appointment, contact your study doctor or research study staff to reschedule as soon as you know that you will miss the appointment.
- Tell your study doctor or research staff about any medications you are taking.
- Tell your study doctor or research study staff about any side effects, doctor visits, or hospitalization that you may have whether or not you think they are related to the study therapy.
- Tell your study doctor if you have been in a research study in the last 30 days or are in another research study now. While participating in this research study, you should not take part in any other research project without approval from your study doctor. This is to protect you from possible injury arising from such things as extra drawing of blood samples, possible incompatibility between research drugs, or other hazards.

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 these drugs will be effective in treating colon and rectal cancer, 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
- Taking part in another study
- Getting no treatment, which means that your care will focus on keeping you comfortable rather than slowing the cancer growth

Talk to your study 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 National Surgical Adjuvant Breast and Bowel Project (NSABP) Foundation Research Program (FRP);
- ImClone Systems Incorporated, the company providing support for the FC-4/CP13-0708 study;
- Chesapeake Research Review, Inc., which is a Research Ethics Review Board that reviews this study);
- International Drug Development Institute (IDDI), the company that will analyze the data for this study;
- your local Institutional Review Board (IRB), a group of people who review the research study to protect your rights; and
- government agencies including the U.S. 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?

You and/or your health plan/insurance company will need to pay for some 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.

Tests and drugs for which there is no charge in this study:

- Cetuximab will be provided by ImClone Systems Incorporated at no cost for the FC-4/CP13-0708 study. However, you or your insurance company will need to pay for the costs of the supplies and for the personnel who give you the drug.
- IMC-A12 will be provided by ImClone Systems Incorporated at no cost to patients randomized to Group 2. However, you or your insurance company will need to pay for the costs of the supplies and for the personnel who give you the drug.
- There will be no charge for tests and exams that are "not part of regular cancer care and **are being done for the purpose of this study.**" These tests and exams are described in earlier sections of this consent form.
- As described to you in a separate consent form, there will be no charge to you or your insurance company for the collection, shipping, or K-RAS testing of your tumor sample required for the FC-4/CP13-0708 trial.

Irinotecan is available commercially, and you or your insurance company will be responsible for its cost. You or your insurance company will also need to pay for costs of the supplies and for the personnel who give you the drugs.

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

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.

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 906-225-3922.

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. There are no plans to pay for medical treatment through the study.

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.

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 study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ at 906-225-3922.

For questions about your rights while taking part in this study, call the Patient Advocate at Marquette General Hospital at 906-225-3183.

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

Signatures

I have been given a copy of all fifteen pages of this form. I have read the consent form or it has been read to me. This information was explained to me and my questions were answered. I agree to take part in this research study.

Date

Patient's signature

Print name of patient

Date

Signature of person
conducting the informed consent discussion

Print name of person
conducting the informed consent discussion