UR MEDICINE
MEDICINE of THE HIGHEST ORDER

NCT02466009

Consent Form

A Phase II Study of Regorafenib in Adults ≥ 65 Years with Metastatic Colorectal Cancer

Principal Investigators: Aram Hezel, M.D. and Supriya G. Mohile, M.D.

This consent form describes the research study, what you may expect if you decide to take part and important information to help you make your decision. Please read this form carefully.

The study staff will explain this study to you. Please ask questions about anything that is not clear before you agree to participate. You may take the consent form home to think about and discuss with family or friends.

- Being in this study is voluntary – it is your choice.
- If you join this study, you can change your mind and stop at any time.
- If you choose not to take part, your routine medical care will not be changed in any way.
- There are risks from participating and you should understand what these mean to you.

Introduction:

You are being asked to take part in this study because you are aged 65 or older and require treatment for colorectal cancer that has spread to other parts of the body (metastatic) and has not gotten better with other treatment.

This study is being conducted at the University of Rochester's James P. Wilmot Cancer Institute, Mayo Clinic (Mayo Clinic refers to Mayo Clinic in Rochester, Minnesota) and Fox Chase Cancer Center. At the University of Rochester, this study is being conducted by Dr. Aram Hezel and Dr. Supriya Mohile.

Purpose of Study:

The purpose of this study is to monitor the impact of a drug called regorafenib on quality of life and other issues relevant to the elderly. The study will also assess how well this drug controls cancer growth and extends life in patients aged 65 or older.

The standard treatment for metastatic colorectal cancer usually includes chemotherapy which can have side effects that are more difficult to tolerate for older patients with cancer.

Regorafenib (a non-chemotherapy option) was recently approved by the FDA for treatment of patients with your type of cancer that has grown on all standard chemotherapy agents.

This study is being done among elderly patients, whose cancer has grown on all chemotherapy agents or who are not able to tolerate chemotherapy, to measure the safety of regorafenib in the elderly population and to assess how well the drug controls cancer growth. Each subject will start at a slightly lower dose of regorafenib and this will then be increased to the full dose after 28 days depending on how the drug is tolerated by that individual. This study will use supportive care measures and close monitoring to help subjects tolerate regorafenib better.

Description of Study Procedures

If you decide to take part in this study, you will be asked to undergo some initial tests to ensure that you meet all the criteria necessary to take part in the study. Once you have completed your initial testing and meet the eligibility criteria, you will begin treatment.

Initially, you will be asked to take 120mg of regorafenib (3 tablets) each day for 21 days (3 weeks) in a 28-day cycle. After the first cycle, your study doctor will discuss the possibility of increasing the dose to 160mg (4 tablets) based on your health status. Treatment will continue as long as you are tolerating treatment and your colorectal cancer is either responding to treatment or remains stable.

During the study, you will have the following assessments:

- You will be asked about your medical history and current medications you are taking.
- You will have physical exams (including vital signs, blood pressure, weight, temperature)
- You will also undergo a Comprehensive Geriatric Assessment (CGA) before you begin the study, at 4 weeks and then every 3 months +/- 7 days while on study. These are being done to assess health areas specific to older cancer patients, taking into account demographic information, health conditions, quality of life, ability to perform basic daily activities, memory, physical performance (walking, leg strength, and balance), mood and social support. Several tests as well as questionnaires will be used to assess for any deterioration in these areas.

  These questionnaires can be completed at the study visit or given to you to take home, complete, and send back or mailed to you to be completed prior to the next visit.

- You will have routine blood work to look at your blood counts, liver and kidney function and your electrolytes. Approximately 6ml will be taken.
- You will have routine tumor scans to monitor the status of your cancer, usually a computed tomography (CT) scan or magnetic resonance imaging (MRI) scan.

Number of Subjects

Approximately 60 subjects from 3 study centers will take part in this research. Locally, about 20 subjects will participate.

Duration of the Study

Your participation in the study is expected to last between 6 and 12 months from the time you start treatment.

Risks of Participation

Regorafenib is a standard treatment for metastatic colorectal cancer. However, older patients may not tolerate the side effects of regorafenib. Everyone taking part in the study will be watched and supported carefully for any side effects.

Risks of Regorafenib

Drugs used for anti-cancer therapy are usually linked with undesirable side-effects. In the following section, side effects which have been so far detected in regorafenib studies with patients are described. You may experience none or some of these side-effects and they may be mild, moderate or severe and in some case, they may be life-threatening in nature or result in death. Many of the side effects disappear after study treatment is stopped. If you have any discomfort or experience any side effects, you must report these to your study doctor and/or study nurse. Your study doctor may then prescribe other medications to ease them or even interrupt or discontinue your use of regorafenib.

As of 31 March 2012, approximately 1200 patients have already received regorafenib in various studies. The following is a list of side effects that occurred for which there is a possibility that they were caused by regorafenib.

The most common side-effects (occurring in more than 1/10 of patients) of regorafenib include:

- Diarrhea
- Hair loss (alopecia)
- Headache
- High blood pressure (hypertension) – symptoms may include headache, dizziness, palpitations, blurred vision, ringing in the ears and nose bleeds
- Inflammation of lining of digestive tract (mucosal inflammation)
- Loss of appetite (anorexia)
- Feeling sick (nausea)
- Pain (e.g. in joints, muscles, abdomen, chest)
- Reduced numbers of red blood cells (hemoglobin decreased/anemia)) – symptoms may include feeling tired and weak, shortness of breath, increased heart rate, dizziness or lightheadedness, headache, chest pain, and pale skin.

- Skin changes including rash, painful reddening of the skin of hands and feet with or without blistering, redness, dryness and numbness/tingling (Rash, Palmar-plantar erythrodysaesthesia syndrome, Hand-foot skin reaction).
- Tiredness (Fatigue, Asthenia)
- Voice changes or hoarseness (Dysphonia)
- Vomiting
- Infection (CRP increased)
- Reduced numbers of cells that help the blood to clot (Thrombocytopenia)
- Bleeding, generally mild or moderate in severity, but which may be life-threatening or fatal (especially if it affects the lung, digestive tract or brain) (Hemorrhage/Hematoma, at any body site)
- Inflammation of the lining of the mouth which may cause mouth pain and sores (Stomatitis)
- Jaundice (a condition in which your skin and white part of your eyes turn a yellow color) (Hyperbilirubinemia)
- Fever (Pyrexia)
- Loss of weight

Less common side effects (occurring in 1/100 to 1/10 of patients) include:

- Reduced number of white blood cells (Leukopenia), which may make it hard for you to fight infections.
- Reduced function of thyroid gland (Hypothyroidism), which may cause symptoms including tiredness, depression, weight gain, cold intolerance, dry coarse hair, difficulty having bowel movements, dry skin, muscle cramps, high cholesterol, trouble with concentrating and swelling of the legs.
- Reduced levels of minerals in the blood including calcium, potassium, phosphorus and magnesium:
    - Symptoms of a low calcium level may include numbness and tingling in the hands and feet, muscle cramps, twitches and spasms, fatigue, confusion, disorientation and seizures
    - Symptoms of low potassium may include muscle weakness, cramping, leg discomfort, an irregular heart beat and confusion
- Increased levels of uric acid in the blood (Hyperuricemia)
- Shaky hands (Tremor)
- Changes in taste (Taste disorders)
- Dry mouth
- Heartburn and bringing up acid into the mouth (Gastroesophageal reflux)
- Inflammation of lining of stomach and bowel which may cause stomach pain and diarrhea (Gastroenteritis)
- Abnormal liver enzymes – symptoms may include feeling overly tired or weak, you may bruise or bleed more easily, abdominal pain, or yellowing of the skin or eyes
- Dry skin

- Muscle tightness and joint stiffness (Musculoskeletal stiffness)
- Increased losses of protein through urine which may be a sign that the kidneys are not functioning well (Proteinuria)
- Increased blood levels of pancreas enzymes called amylase and lipase (Amylase, Lipase increased)
- Reduced ability to form blood clots which may increase the tendency for bruising and bleeding (Abnormal International Normalized Ratio)
- Peeling rash (Exfoliative rash)

Uncommon side effects (occurring in 1/1000 to 1/100 of patients) include:

- Impaired blood supply to heart muscle which may cause life-threatening heart attack (Angina pectoris, Myocardial injury, Ischemia, Infarction)
- Severe blood pressure increase (Hypertensive crisis)
- Perforation (hole) in the digestive tract which may be fatal (Gastrointestinal perforation)
- Abnormal connection between the bowel and other organs which may need to be treated with an operation (Gastrointestinal fistula)
- Severe inflammation of the liver which may result in fatal liver failure (Severe liver injury)
- Nail disorder
- Multiple skin eruptions (Erythema multiforme)

Rare side effects (occurring in fewer than 1/1000 patients) include:

- Low grade skin tumors (Keratoacanthoma, Squamous cell carcinoma of the skin)
- Reversible (temporary) swelling in the rear part of the brain leading to headache, altered consciousness, fits(seizures) and visual symptoms (Reversible posterior leukoencephalopathy syndrome, RPLS)
- Serious reactions of the skin and/or mucous membranes which may include painful blisters and fever, including extensive detachment of the skin (Stevens-Johnson syndrome and toxic epidermal necrolysis)

<u>Special advice on side effects to watch out for:</u>

Severe liver inflammation is an uncommon but serious side effect which may result in fatal liver failure. If recognized early, it may be prevented from getting worse. There are several symptoms that may indicate something is wrong with the liver. They include jaundice (a yellowish pigmentation of skin and whites of the eyes), dark colored brown urine, excessive tiredness and unusual sleepiness, loss of appetite, confusion and disorientation. Your liver function will be regularly checked with blood tests, but if you notice these symptoms during your participation in this study, you should contact your study doctor immediately, so that a blood test can be done to check your liver function. The blood test will help your study doctor decide if it is safe for you to continue treatment, or if the drug should be temporarily or permanently stopped to prevent damage to your liver.

In addition to the listed side effects listed above, your study doctor may have updated information on side effects that occur with less frequency which he/she may discuss with you. You must understand that there may be side effects (including allergies) that are not yet known and you may have other side effects that have not been reported before. Therefore, you must notify your study doctor or one of the members of the study staff of any new symptoms that you may have, even if you are unsure whether they are due to the drug.

General considerations regarding other risks

As part of this study, you will have regular CT or MRI scans to monitor the status of your cancer and these scans are associated with some risks.

You will be exposed to radiation from CT scans. The amount of radiation you receive from these diagnostic tests is considered minimal. The dye injected in your vein during the CT scan may cause pain, burning sensation, hot flushes, and a severe allergic reaction, particularly in those with prior allergies to iodine. CT contrast solution can cause kidney damage, especially if you are diabetic, dehydrated or elderly.

The MRI scan uses a powerful magnetic field to generate images of the body. The magnet could move objects within your body that contain metal such as implants, clips or pacemakers. Certain magnetic imaging devices, such as 3T MRI machines, can demagnetize cochlear implants. If you have any of these items you should not participate in this study.

As explained above, blood samples will be taken during your clinic visits. The risk of blood drawing includes discomfort at the site of the blood draw with bruising, bleeding, infection and rarely, fainting and nerve damage.

Before taking part in the study, it will be necessary to stop taking some herbal drugs, any treatments used to treat cancer (whether they are marketed or experimental treatments) and some drugs that are used to stimulate the immune system. You will not be allowed to use these treatments during this study or within 30 days before the first dose of regorafenib.
Tell your study doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription or even over-the-counter medicines, such as vitamins or dietary supplements. Some medicines may affect the way regorafenib works or regorafenib may affect how other medicines work and cause serious side effects. Especially tell your study doctor if you are taking anything on this list:

- Some medicines to treat fungal infections (e.g. ketoconazole, itraconazole, posaconazole and voriconazole)
- Some medicines to treat bacterial infections (e.g. rifampicin, clarithromycin, telithromycin)
- Medicines typically used to treat epilepsy (seizures) (e.g. phenytoin, carbamazepine or phenobarbital)

- Methotrexate – a medicine typically used to treat cancer
- Digoxin – a medicine typically used to treat heart failure
- Warfarin or phenprocoumon – medicines typically used to thin your blood
- St. John's wort – a herbal treatment for depression (medicine obtained without a prescription)

You should not eat grapefruit, drink grapefruit juice or beverages containing grapefruit while taking regorafenib. This can affect the way regorafenib works.

You should always check with your study doctor before you start using any additional treatments during the study.

Fertility Risks

It is likely that regorafenib may have a potentially harmful effect on an unborn child. If you are a sexually active and possibly fertile man, you will be asked to use a medically approved method of birth control (contraception) during the treatment period and for at least 8 weeks after you finish taking your regorafenib. Check with your study doctor about what kind of birth control methods to use and for how long to use them.

If you plan to father a child during the study or within 8 weeks of the end of the study, you cannot take part in this study. If you think that your partner may be pregnant at any time while on this study, you must inform your study doctor immediately. You will be asked to take part in monitoring the outcome of the pregnancy and the study doctor will remain in contact with you to determine the conclusion of your pregnancy.

Benefits of Participation

You might not benefit from being in this research study. The potential benefit to you from being in this study might be that your cancer would be controlled.

New Study Findings

If we discover anything that might make you change your mind about continuing in the study, we will let you know.

Alternatives to Participation

Your other choices may include:

- Getting treatment or care without being in a research study
- Taking part in another research study
- Getting no treatment

If you decide that you don't want any more treatment, one of your options is called 'comfort care.' Comfort care includes pain medications and other support. It aims to maintain your

comfort and dignity rather than cure disease. Usually this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

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

Sponsor Support
The University of Rochester is receiving payment from Bayer, the company supplying the study drug regorafenib, for conducting this research study.

Costs
You and/or your health insurance company will be billed for parts of the study that are standard care for your disease. Standard of care tests, procedures and medications are those that you would undergo or receive as part of treatment for your condition whether you were participating in a research study or not. Your health insurance company may or may not pay for these charges. You will be responsible for all of the costs linked with this study that are related to standard care and are not covered by other payers (HMO, health insurance company etc.) such as co-pays, deductibles and other out-of-pocket expenses that you would normally be required to pay for the treatment of your cancer.

The study drug regorafenib will be provided by the study sponsors at no cost to you. Procedures that are done only for the study, such as the Comprehensive Geriatric Assessments will be paid for by the study and will not be billed to you or your insurance company.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

Payments
You will not be paid for participating in this study.

Circumstances for Removal from Study
There are some cases where you could be removed from the study without your consent. You may be withdrawn from the study if your disease becomes worse or if your study doctor feels that staying in the study is harmful to your health. You may be withdrawn from the study if you do not keep appointments for study visits, if you experience a treatment delay, or if you cannot complete study activities.

You also may decide that you no longer wish to participate in this research study. If you decide you would like to stop being in this study, we ask that that you notify your study doctor or study coordinator of your decision to stop participation. You will be asked to complete one additional end-of-study visit for safety follow-up.

Study Completion

To ensure your safety after you have stopped the study drug, you will be asked to return approximately 30 days after your last dose to complete an end-of-study visit which will include physical exam, review of medical history and current medications, and end-of-study blood work (approximately 6ml will be taken).

If you come off treatment due to progression of your cancer, information about any other cancer therapies you may receive and how they work for you will be monitored until the study closes.

If you come off treatment early for any other reason other than the progression of your cancer, information about your health status and cancer will be collected until the study closes.

Compensation for Injury

If you are directly injured by the drug(s) being studied, or by medical procedures needed because of this study, and you receive medical care for the injury, you may need to pay for that care. You will be reimbursed for reasonable and necessary medical costs for such care, but you might not be reimbursed for care covered and paid for by a third party like your health insurance provider, or costs such as required co-payments or deductibles related to that coverage. No other funds have been set aside to pay for such things as lost wages or expenses due to a current underlying illness or condition.

If your research injury is paid for by the University or Sponsor, we will collect your name, date of birth, gender, and Medicare Health Insurance Claim Number or Social Security Number to determine your Medicare status. This information will be used only in accordance with the law. If you are a Medicare beneficiary, information about the study you are in, and any payments made related to your injury, will be reported to the Centers for Medicare & Medicaid Services (CMS), in accordance with CMS requirements. This information will not be used for any other purpose.

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes

The University of Rochester makes every effort to keep the information collected from you private. In order to do so, we will limit access of research information collected on this study to include only trained research personnel assigned to this study. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the University of Rochester Medical Center (URMC) and Affiliates Notice of Privacy Practices, please ask the investigators for one.

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to this study
- Results of medical tests

Who may use and give out information about you?

- The study doctor and study staff
- URMC and Affiliates

Your information may be given to:

- The University of Rochester, including the Institutional Review Board that oversees the research.
- Other University of Rochester physicians involved in your clinical care.
- The Sponsor of this study (Bayer) and the people or groups it hires to help perform this research.
- Federal and State agencies (such as the U.S. Food and Drug Administration (FDA), the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research. They may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about you private.
- A group that oversees the data (study information) and safety of this research.

Why will this information be used and/or given to others?

- To do the research
- To study the results
- To see if the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

How long will this permission be valid?
This permission will last indefinitely.

May I cancel my permission to use and disclose information?
Yes. You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?
Yes. If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
No. There is a risk that your information will be given to others without your permission.

Results of Research testing and documenting study participation:

- Results of research testing and information about your participation in this study will be included in your electronic health record. The study team may be notified if you receive other health care services at URMC and Affiliates.
- Individuals who have a reason to access your electronic health record in the University of Rochester Medical Center and its Affiliates (Strong Memorial Hospital, Highland Hospital, URMC primary care and specialist physician offices, etc.) will have access to the results of testing performed as part of this research study and will know that you participated in this research study.

More Information
A description of this clinical trial will be available on the internet at http://www.ClinicalTrials.gov as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Contact Persons
For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact:

Dr. Aram Hezel at **585-275-5863 (24 hours)**

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420628, Rochester, NY 14642, Telephone (585) 276-0005 or (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process;
- In the event the study staff could not be reached

Voluntary Participation

Participation in this study is voluntary. You are free not to participate or to withdraw at any time, for whatever reason, without risking loss of present or future care you would otherwise expect to receive. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

Signature/Dates

After reading and discussing the information in this consent form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to you;
- Other options you may have instead of being in the study;
- How your personal information will be protected;
- What to do if you have problems or questions about this study.

Subject Consent

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I will receive a signed copy of this form for my records and future reference.

Study Subject: _____ Print Name

Study Subject: _____ Signature

_____ Date

Person Obtaining Consent

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form for their records and future reference. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read consent before signing.

_____ Print Name and Title

_____ Signature

_____ Date