INSTITUTE: National Cancer Institute

STUDY NUMBER: 10-C-0132 PRINCIPAL INVESTIGATOR: Deborah Citrin, M.D.

STUDY TITLE: A Phase I Study of AZD6244 in Combination with Capecitabine and Radiotherapy in Locally Advanced Adenocarcinoma of the Rectum

Initial Review Approved by the IRB on 02/28/11
Amendment Approved by the IRB on 10/27/11 (F) Date Posted to Web: 11/15/11
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INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?
The purpose of this study is to find out what effects, good and/or bad, AZD6244 has on you and your rectal cancer. In some types of cancer such as yours, a protein called MEK is over active. This protein is important for cancer cells to be able to reproduce and survive. Because AZD6244 prevents MEK from working properly, it may keep your cancer cells from growing and living, so your cancer may shrink or its growth may slow down. In addition, it is possible that MEK can help tumor cells survive radiation treatments. Using AZD6244 may allow radiation to kill more tumor cells by preventing MEK from working properly. AZD6244 is an investigational or experimental anti-cancer agent that has not been approved by the Food and Drug Administration for use in patients with rectal cancer.

Why are you being asked to take part in this study?
You are being asked to take part in this study because you have rectal cancer that has spread outside the inner wall of the rectum or into lymph nodes in the pelvis that typically would require radiation and chemotherapy for treatment. You are being asked to participate because we are studying if AZD6244 can be delivered with chemotherapy and radiation for patients with the type for tumor that you have.

How many people will take part in this Study?
About 12 people will take part in this study. At the beginning of the study, patients will be treated with lower doses of the investigational drug. If the drug does not cause bad side effects, the dose will slowly be made higher as new patients take part in the study. The dose of AZD6244 will stay the same over the entire treatment for each patient. All patients will receive similar doses of radiation and capecitabine, a type of chemotherapy drug commonly used in the treatment of rectal cancer. A total of 18 patients are the most that would be able to enter the study.

Description of Research Study

What will happen if you take part in this research study?
Before you begin the study, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- *History and Physical examination*
- *CT scan of the chest, abdomen, and pelvis*
- *MRI or ultrasound of the rectal tumor*
- *Basic laboratory tests including blood counts and measurement of kidney function, liver function, and electrolytes in the blood.*
- *ECG (Electrocardiogram)*

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

- Radiation treatment planning and daily radiation treatments for six weeks
- Treatment with chemotherapy (capecitabine) taken as a pill during the radiation treatment
- Blood tests every week to check blood cell counts, blood electrolytes, and blood chemistries.
- Weekly visits with the radiation oncologist during treatment.
- Weekly ECG

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Treatment with AZD6244
- Sampling of two tablespoons of blood during the first three weeks of treatment and at one month after treatment

While you are in the study, you will need to keep track of the medicine you take with a medication diary. You will be given a form for the medication diary, and you will write in it each day. You will be treated with AZD6244 in addition to radiation, chemotherapy, and surgery which are the usual treatment for rectal cancer that has spread outside the rectum. This means that for one week before you start radiation and chemotherapy and during the rest of your treatment you will take AZD6244 capsules twice each day.

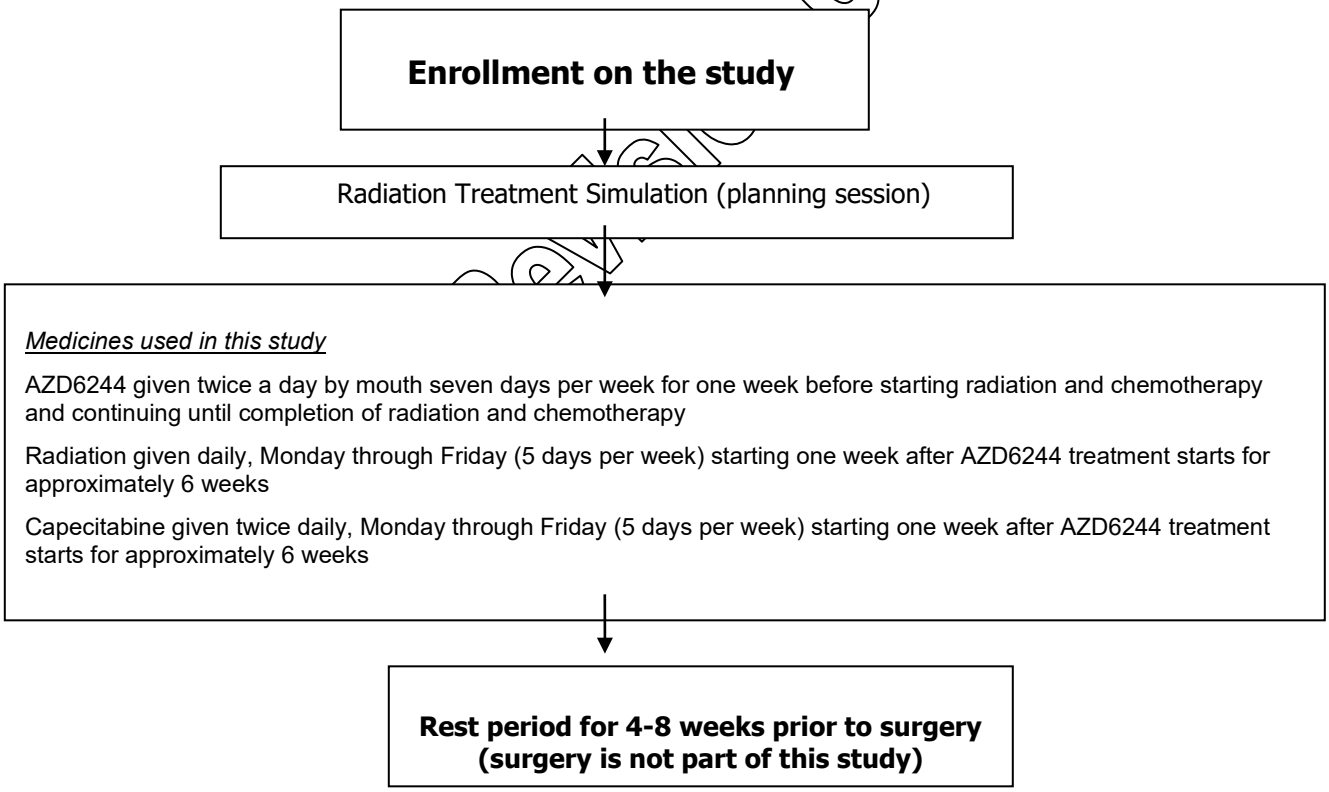
When you are finished taking AZD6244, you will continue to be seen every few weeks by the radiation oncologist. You will stop taking AZD6244 the same day you complete radiation and chemotherapy. You will undergo repeated physical examination, blood testing, and x-rays to see how your tumor responds to treatment and to make sure surgery is safe. Four to eight weeks after completing the treatment with AZD6244, radiation, and capecitabine you should undergo surgery to remove the rectal tumor and any lymph nodes near the rectum. This surgery is not part of the treatment delivered on this protocol. You may be eligible to receive surgery at NIH on other protocols.

You will be asked to take AZD6244 for approximately seven weeks including one week before your radiation and chemotherapy treatment and then continuing until the end of radiation and chemotherapy. After you are finished taking AZD6244, the study doctor will ask you to visit the office for a follow-up exam three weeks after you finish treatment to make sure you are not having side effects from the treatment. After treatment, you will also be asked to come for follow up visits every three months for the first year and then every year until you have been followed for three years. At these visits your doctor will examine you and ask questions to try to determine if you have any side effects from your radiation treatment. You will also need to have x-rays (CT scans) during these follow up visits to make sure that the tumor is gone.

Study Chart

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Study Copy



What does this study involve?

Standard of Care Treatment:
Treatments covered under this study may include capecitabine (a chemotherapy) and radiation to treat your cancer. These treatments will not be experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent.

Birth Control
If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:
- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study

Please talk to your doctor about these and other options.

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Risks or Discomforts of Participation
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 AZD6244. In some cases, side effects can be serious, long lasting, or may never go away.

What side effects or risks can I expect from being in this study?

Possible side effects from AZD6244:

Likely:
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Swelling of the arms and/or legs

- Fatigue or tiredness
- Acne
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

Less Likely:

- Lack of enough red blood cells (anemia)
- Belly pain
- Constipation
- Dry mouth
- Irritation or sores in the lining of the mouth
- Swelling of the face
- Fever
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Decreased number of a type of blood cell that helps to clot blood (platelet)
- Loss of appetite
- Decreased levels of a blood protein called albumin
- Decreased blood level of magnesium
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Difficulty sleeping or falling asleep
- Cough
- Shortness of breath
- Dry skin
- Itching
- High blood pressure

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Rare but Serious:

- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)

Capeciatabine and radiation are not experimental treatments for rectal cancer. The possible side effects of capecitabine are listed below. Your doctor will discuss these with you. It is important to let your doctor know if you develop these side effects because adjustments to your treatment may need to be made.

The most common side effects of capecitabine are:

Diarrhea
Nausea and/or vomiting
Sores in the mouth and throat (stomatitis)
Upset stomach
Loss of appetite
Fatigue
Too much water loss from the body (dehydration)
Painful tingling rash on the hands and feet

Other types of rash
Decrease in blood counts (especially white blood cell count)
Itchy skin
Hair loss
Nail problems
Tiredness or weakness
Headache
Fever
Pain
Trouble sleeping
Changes in taste
Pain (muscle, back, joint, chest)

Some additional aide effects may occur with radiation to the pelvic area. These side effects are listed below. Your doctor will discuss these with you. It is important to let your doctor know if you develop these side effects because changes may need to be made to your treatment. The short term side effects of radiation tend to go away a few weeks after treatment is completed.

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Likely short term side effects of radiation
Skin irritation in the area radiated (pelvis)
Fatigue
Diarrhea
Hair loss in the area treated with radiation

Less Likely short term side effects of radiation:
Burning with urination or urgent urination
Decrease in blood counts
Pain in the pelvis area

Some side effects of radiation can happen many months or years after treatment. It is impossible to predict who will develop long term side effects. Your doctor will discuss these risks with you. The possible long term side effects of radiation to the pelvis can include:

Common: increased tendency to develop gas or diarrhea, more frequent or urgent bowel movements, infertility
Uncommon: bleeding from the rectum, bleeding from the bladder, scarring of the vagina in females, decreased sexual function in males
Extremely rare: injury to the hips that could result in a fracture of bone, life threatening tumor caused by radiation.

Potential Benefits of Participation
Are there benefits to taking part in this study?
The aim of this study is to see if AZD6244 in combination with radiation and chemotherapy will cause your tumor to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the

future who have cancer. While doctors hope AZD6244 will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about AZD6244 as a treatment for cancer. This information could help future cancer patients.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive all treatment on this study at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH. Any medicine used as part of the study (AZD6244 and capecitabine) and medicines used to treat side effects of the study will be provided at no charge to you.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs even if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

The National Cancer Institute and the Pharmaceutical Company (Astra-Zeneca) that makes AZD6244 may inspect and copy patient's research records for quality assurance and data analysis.

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Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease grows during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped. If the investigational treatment is stopped, you may continue to receive chemotherapy and radiation to complete your treatment if the investigator thinks it is safe. You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process *http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf*. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Optional Biopsy

You are being given the option of having a biopsy before and twice during the course of your treatment. Your doctor will remove some small pieces of tumor from the rectum to do some research tests. This procedure will be performed under mild sedation if required so that you will be more comfortable during the procedure. The results of these tests will not be used to plan your care. This tissue will be used to allow us to test the effects of AZD6244 on the tumor.

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.

The choice to undergo these biopsies is up to you. No matter what you decide to do, it will not affect your care. 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.

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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. We may also be able to tell better how AZD6244 affects tumors by looking at the biopsy tissue. Biopsies can result in pain that usually goes away within a day or two of the biopsy. In addition, there is a small risk of infection or bleeding after the biopsy.

Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I agree to have the tumor biopsy for the research tests in this study.

Yes No Initials_____

Optional Studies

We would like to keep some of the tissue, blood, and urine that are collected for future research. These specimens will be identified by a number and not your name. The use of your specimens will be for research purposes only and will not benefit you. It is also possible that the stored specimens may never be used. Results of research done on your specimens will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your tissue, blood, and urine 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, blood, and urine. Then any tissue, blood, and urine that remain will be destroyed.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My tissue, blood, and urine specimens may be kept for use in research to learn about, prevent, or treat cancer.

Yes No Initials_____

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

Yes No Initials_____

3. Someone may contact me in the future to ask permission to use my specimen(s) in new research not included in this consent.

Yes No Initials_____

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OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Deborah Citrin, M.D., Building 10, CRC B2-3500, Telephone: 301-496-5457. If you have any questions about the use of your tissue for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

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COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 28, 2011 THROUGH FEBRUARY 27, 2012.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____