INFORMED CONSENT

PROTOCOL TITLE: RAD 0204 - A PHASE II STUDY OF EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITOR, ERLOTINIB, WITH PRE-OPERATIVE CHEMORADIATION FOR RESECTABLE ESOPHAGEAL CANCER

SPONSOR: University of Alabama at Birmingham Department of Radiation Oncology Genentech, Inc./OSI Pharmaceuticals

INVESTIGATOR: James A. Bonner, MD

SUBINVESTIGATORS: James Posey, MD; Martin J. Heslin, MD; Robert Cerfolio, MD; Nirag Jhala, MD; Kevin Raisch, PhD; Yufeng Li, PhD

PURPOSE OF THE STUDY

You have cancer of the esophagus and treatment is recommended. The standard treatment for cancer of the esophagus is radiation plus chemotherapy (5-fluorouracil and cisplatin) with or without surgery. At some institutions some patients are treated with surgery alone, but most of the patients are treated with radiation plus chemotherapy (5-fluorouracil and cisplatin). This is a new study using conventional chemotherapy (5-fluorouracil and cisplatin), a new anti-epidermal growth factor receptor chemotherapy agent (Erlotinib), radiation therapy, with or without surgery for the treatment of esophageal cancer. The purpose of this research study is to determine if conventional chemotherapy plus Erlotinib given with radiation therapy is more effective than conventional chemotherapy plus radiation therapy (without Erlotinib therapy) in treating cancer of the esophagus. The reason for this is that patients treated with conventional chemotherapy and radiation therapy with or without surgery still have a moderate chance of tumor recurring both in the esophagus and other parts of the body. Erlotinib is an investigational drug and is not FDA-approved for commercial use. Giving Erlotinib with conventional chemotherapy and radiation with or without surgery may decrease the recurrence rate. This point however has not been proven.

EXPLANATION OF PROCEDURES

Standard procedures that are part of regular cancer care and may be done even if you do not join the study:

Physical exams – by the medical oncologist, the radiation oncologist and the surgeon prior to study entry, weekly during radiation treatment by the radiation

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oncologist, by the surgeon, during the post-chemoradiation/Erlotinib treatment and prior to surgery, and during follow-up visits by the radiation oncologist, the medical oncologist and the surgeon.

Blood test – prior to study entry and before each cycle of chemotherapy.
CT scans of the chest and abdomen – prior to study entry and after completion of radiation, and during follow-up visits.
Endoscopic ultrasound – prior to study entry, then as needed after completion of radiation.
Biopsy of tissue – prior to study entry and at follow-up, if there is evidence of recurrence after completion of chemoradiation.
PET scan, Barium Contrast Upper GI exam, EKG, and Pulmonary Function Test are optional test your physician may decide are needed prior to treatment and at follow-up visits after completion of treatment.)

**Standard procedures that are part of regular cancer care and are being done because you are in this study:**

Physical exams – by the radiation oncologist every three (3) months after completion of radiation.
Blood test – weekly during radiation, and every three (3) months at follow-up visits.
Urine test – prior to study entry and then as needed.
CT scans of the chest and abdomen - approximately one (1) month after completion of radiation, then every three (3) months for two (2) years.
Bone Scan – may be required at study entry if one of your lab values, alkaline Phosphatase is elevated.
Bronchoscopy – if baseline evaluations suggest this procedure is needed for further evaluation of your disease and ability to receive radiation.
Nutritional assessment – prior to study entry.
Pregnancy test - *(females only)* to ensure you are not pregnant.

**Procedures being done because you are in this study:**

Biopsy of tissue – In addition to the biopsy taken before the start of your treatment, other biopsy will be performed on the day your radiation starts prior to any treatment.

**Erlotinib:**

An Erlotinib tablet will be taken orally each day (Monday through Sunday) starting 7 days (one week) before radiation and finishing on the last day of radiation on an empty stomach with 200 mL of water. You must not eat 2 hours before and 1 hour after taking Erlotinib.

**Endoscopic Biopsy:**
On the 8th day of taking Erlotinib (prior to beginning chemotherapy and radiation) you will undergo an endoscopic examination of your esophagus with an additional biopsy, exactly like the procedure and biopsy done at the time of your diagnosis of esophageal cancer. The purpose of this procedure and biopsy is to determine how your tumor has responded to the Erlotinib therapy given by itself. This information may provide information about the biology of your tumor that may help us better understand how Erlotinib works, and help us design more effective treatments for esophageal cancer in the future. As stated above, this procedure would not normally be done if you did not participate in this study. You will, therefore, not pay for the costs of this procedure and biopsy, which will be paid for by the study.

**Radiation Therapy:**

Radiation therapy will begin on day 8 of treatment and it is anticipated that chemotherapy and Erlotinib will precede radiation by up to 6 hours. The radiation therapy treatments will be given daily for 5 days per week, Monday-Friday. The duration of the radiation treatment will be approximately 5½ to 6 weeks (28 treatments if surgery is planned, or 30 treatments if your tumor has spread and the surgeon feels that surgery is not possible and will not improve your survival).

**Cisplatin and 5-Fluorouracil (5-FU):**

The 5-Fluorouracil (5-FU) and cis-platinum chemotherapy will begin on day 1 of weeks 2 and 6 of radiation therapy. Cisplatin will be given on day 1 of weeks 2 and 6 and 5-FU will be given over 4 days on weeks 2 and 6. An indwelling catheter (tube in the vein) will be placed if deemed necessary for safe administration of chemotherapy.

**Follow-Up Examinations:**

Approximately 2 to 4 weeks following the end of radiation therapy a CT scan of the chest and upper abdomen, and endoscopic ultrasound will be performed to evaluate the tumor response to chemotherapy, Erlotinib therapy and radiation.

**Surgery:**

If your surgeon feels that your tumor is confined to the esophagus and you are a good candidate for surgery during your initial evaluation, and no evidence of tumor spread is found and/or a good response to therapy is achieved, the surgery, esophagectomy, will be planned for 4 to 8 weeks after completion of chemoradiation. The surgical specimen (excised tumor) will be evaluated for pathological response to therapy under the microscope.

If obvious evidence of tumor progression exists, surgical excision of your tumor will not occur, and you will be followed for toxicity and survival. Plans for additional chemotherapy or radiation will be at the discretion of you and your oncologist(s).
If on initial evaluation your tumor is found to have spread to other parts of the body and/or you are not felt to be a good surgical candidate, you will not undergo surgery and plans for additional chemotherapy or radiation will be at the discretion of you and your oncologist(s).

You will be followed on protocol for a minimum of 2 years, with regularly scheduled CT scans, clinical evaluations, and laboratory work. If recurrent disease following surgery exists, you will be taken off protocol for consideration for other therapies that may help treat your tumor.

**Chemotherapy**
Chemotherapy is medicine, which will be given into your vein. You may have to be in the hospital as the treatment is given slowly over a period of four days. This chemotherapy may be given four times during the entire treatment.

*The drug combination will be cis-Platinum and 5-Fluorouracil.*
Cis-Platinum will be given through an intravenous (*in the vein*) tube over a few minutes in the morning. Because cis-Platinum can cause kidney damage, intravenous fluids may be needed to "flush" the kidneys. Mannitol, a drug that increases urine production, is given intravenously just prior to and after receiving cis-Platinum. So that your physician may better assess your kidney function during this time, you may be asked to save urine specimens and to keep a record of all fluids taken by mouth during the first 24-48 hours after cis-Platinum.

The second medicine is called 5-Fluorouracil (5-FU). It will be infused over a 4-day period. This medicine is less likely to cause side effects when it is given at a slow constant rate like this. After the first treatment, doses of drugs may be changed to fit your needs. Both 5-FU and cis-Platinum may cause nausea and vomiting. In order to minimize these side effects, Ondansetron or a similar anti-vomiting medication will be given either as a pill, shot or suppository prior to chemotherapy and every 3-4 hours thereafter as needed. Procedures will also include blood studies, x-rays, biopsy of the tumor, and any other tests that your physician feels are necessary.

**Erlotinib Therapy**
Erlotinib is an oral tablet that is taken each morning with at least 200 mL of water during the course of treatment. It will be taken before breakfast, and you must fast for 2 hours prior to and 1 hour after taking Erlotinib.

**RISKS AND DISCOMFORTS**

Side effects of the treatments are:

**Radiation Therapy**
Common side effects include reddening of the skin and hair loss in the treatment area, tiredness, and sore throat causing difficulty with swallowing. Rare complications include esophageal stricture (*tightening*), fistula or perforation (abnormal openings), as well as radiation pneumonitis (*scarring of the lungs*) and myelitis (*nerve damage*).
Chemotherapy

5-Fluorouracil (5-FU) may cause nausea, loss of appetite, vomiting, diarrhea with cramping or bleeding, skin rash, tiredness, headache, confusion, inflammation of the fingers and toes, mouth sores, sore throat, reversible hair loss, chest pain, increased sensitivity to sunlight, skin, nail or vein darkening or thickening, and a depression of the bone marrow (the blood forming organ) which increase the risk of anemia, infection, or bleeding. If the bone marrow is depressed extensively, transfusions may be required to correct the problem. Escape of drug from the injection site may cause chronic ulceration of the skin or severe local reaction. It is also possible that changes may occur in the sperm of males, which might produce birth defects in future children. Additional, more serious side effects, which rarely occur, include chest pain with some damage to the heart, loss of coordination or balance, or other manifestations of brain or nerve damage.

Cisplatin

Cisplatin frequently causes loss of appetite, nausea, vomiting, hearing loss, loss of taste, damage to kidneys, and bone marrow suppression (which can lead to anemia, infections, bruising or bleeding or, rarely acute leukemia). Other less common but serious side effects include numbness and tingling of fingers and toes, loss of coordination, seizures, allergic reactions, chemical abnormalities of the blood (high uric acid or low magnesium), facial swelling, involuntary shaking, decreased vision, muscle cramps or spasms. There is a risk of leukemia, which is cancer of the blood and bone marrow, when cisplatin is given with other anticancer drugs.

Other unforeseeable or unexpected risks may occur.

Reproductive Risks:

It is unknown what effects this medication (treatment) may have on an unborn child. For this reason, you will be asked to practice an effective method of birth control while participating in this study. Reliable methods of birth control are considered to be: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), Depo Provera, Norplant, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable method involves the careful use of condoms and a spermicidal foam or gel and/or a cervical cap or sponge. You should not nurse your baby while on this study. We encourage you to ask your doctor about counseling and more information about preventing pregnancy.

Pregnant and breastfeeding women will be excluded from the study and pregnancy tests will be performed for all women of childbearing potential.

Female participants should immediately notify the investigator if they become pregnant during the study. Male participants should also notify the investigator if he fathers a child during the study.
Male participants should not father a child for the duration of the study and should use an acceptable method of birth control such as condom and spermicide or vasectomy.

Your doctor(s) will closely monitor your condition. In order for him/her to recognize and treat all these undesirable side effects early, repeated blood tests, x-rays and other history and physical examinations will be required.

As part of the evaluation of your therapy, you will permit your doctors, or their designated nurses to withdraw samples of your blood during the course of treatment. Possible side effects include minimal discomfort from needle punctures, possible hematoma (black and blue marks), and rare instances of fainting. On the days blood is drawn, two or three samples may be required, each sample amounting to less than two teaspoons.

**Erlotinib Therapy**

Erlotinib frequently causes an acne-like skin reaction (folliculitis) which generally occurs 8 to 10 days after taking the first dose. It can be treated with topical ointments, but usually resolves gradually after approximately 2 weeks, despite continued Erlotinib therapy. Diarrhea also occurs commonly in patients taking Erlotinib. Most episodes are mild to moderate in severity and onset generally occurs during weeks 3 to 4 of therapy. Symptoms are usually self-limited, or managed successfully with nonspecific measures, such as loperamide. Erlotinib-associated diarrhea usually does not worsen with continued treatment. Other less commonly reported side effects include mild headaches, which are relieved by analgesic medications, mild jaundice, which resolves spontaneously despite continued Erlotinib use, mucous membrane disorder (sores or ulcerations of the linings of your nose, mouth, and gastrointestinal tract), and corneal irritation, especially in people who wear contact lenses. If you wear contact lenses and choose to participate in this study, you should use artificial tears to keep your eyes moist and be examined regularly by your eye doctor (approximately every month) while taking Erlotinib.

**Endoscopy and Repeat Biopsy**

You will receive sedation by vein prior to inserting the endoscope into your esophagus by way of mouth. Due to the sedation you will not likely experience pain or discomfort during the procedure, however, your throat may be sore for a few days following. Unlikely risks from the biopsy include infection and bleeding. The procedure and biopsy are done under sterile conditions to minimize these risks.

**Risk of Death:** In a recently completed study of Lung cancer in the United States using Erlotinib or a dummy tablet (placebo) in combination with other cancer drugs (chemotherapy), it was discovered that the number of side effects and serious side effects in the study was about the same between patients taking either the Erlotinib or the placebo tablets. However, when serious side effect occurred, they were more likely to have lead to death for the patients who took Erlotinib plus chemotherapy as compared to those who took the placebo plus chemotherapy. The treating doctors suspected that many of the deaths were caused directly by their patient's lung cancer.
getting worse, or due to events such as pneumonia. The reason why the Erlotinib patients were more likely to die of serious side effects than placebo patients is not entirely clear.

**BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. Possible benefits are shrinkage of your tumor and an increase in your survival. Personal benefit may not result from taking part in this study, but knowledge may be gained that will benefit others.

**SIGNIFICANT NEW FINDINGS**

You have been told that should your disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in your best interest, or should your physician feel that this treatment is no longer in your best interest, the treatment would be stopped. Further treatment would be discussed.

**ALTERNATIVE TREATMENTS**

Alternative treatments, which could be considered for your cancer, include surgery alone, chemoradiation or chemoradiation followed by surgery without Erlotinib therapy. An additional alternative is no further therapy, which would probably result in continued growth of your tumor.

Your doctor can provide detailed information about your disease and the benefits of the various treatments available. You should feel free to discuss your disease and your prognosis with the doctor. The physician involved in your care will be available to answer any questions you may have concerning this program.

**CONFIDENTIALITY**

The information gathered during this study will be kept confidential to the extent of the law.

Records of your progress while on the study will be kept in a confidential form at The University of Alabama at Birmingham. The confidentiality of the central computer records is carefully guarded. During required reviews, representatives of the Food and Drug Administration (FDA), Genentech, Inc./OSI Pharmaceuticals-representatives, and UAB's Institutional Review Board (IRB) may have access to medical records, which contain your identity. However, no information by which you can be identified will be released or published.

Information relating to this study, including your name, medical record number, date of birth and social security number may be shared with the billing offices of UAB and UAB-affiliated entities so that claims may be submitted for payment to your insurance

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company for standard care, non-study related clinical services and procedures provided to you during the course of this study.

If you receive services in University Hospital as part of this trial, this informed consent document will be placed in and made part of your permanent medical record at this facility.

WITHDRAWAL WITHOUT PREJUDICE

Participation in this study is voluntary. You are free to withdraw your consent to participate in this treatment program at any time without prejudice to your subsequent care. Refusal to participate will involve no penalty, or loss of benefits. You are free to seek care from a physician of your choice at any time. If you withdraw from the study, you will continue to receive care.

COSTS OF PARTICIPATION IN THE RESEARCH

The study drug, Erlotinib, will be provided to you by the drug manufacturer, Genentech, Inc./OSI Pharmaceuticals, at no charge for the duration of the study. Cisplatin and 5-FU are commercially available and will be billed your insurance company in the usual manner. The tumor marker analysis on the biopsy and surgical specimen, which may not be covered by your insurance company, will be provided at no cost to you.

You or your insurance company will be charged for standard medical care and/or hospitalization for the treatment of your cancer.

Your physician will explain any procedures related solely to research, which would not otherwise be necessary. Some of these procedures may result in added costs and some of these costs may not be covered by insurance. Your doctor will discuss these with you.

PAYMENT FOR PARTICIPATION IN THE RESEARCH

No compensation for participation will be given.

PAYMENTS FOR RESEARCH RELATED INJURIES

UAB and the drug manufacturer, Genentech, Inc./OSI Pharmaceuticals, have made no provision for monetary compensation in the event of injury resulting from the research and in the event of such injury, treatment is provided, but is not provided free of charge. You will not be provided with reimbursement for medical care nor will you receive other compensation.
QUESTIONS

For more information concerning the research and research-related risks or injuries, you can notify Dr. James Bonner, the principal investigator, at UAB Department of Radiation Oncology, (205)-975-0224. For more information concerning any of the procedures, you may contact Lisa Clemons, R.N. at (205) 975-2880 or Susan Suter, RN at (205) 975-0868.

If you have questions about your rights as a research participant, you may contact Ms. Sheila Moore, Director of the Office of Institutional Review Board for Human Use (IRB). Ms. Moore can be reached at 205-934-3789 or 1-800-822-8816, press the option for an operator/attendant and ask for extension 4-3789 between the hours of 8:00 a.m. and 5:00 p.m. CT, Monday through Friday.

LEGAL RIGHTS

You are not waiving any of your legal rights by signing this consent form.

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TISSUE AND BLOOD TESTING

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor samples were stored in the pathology department. You are being asked for permission to use the tumor biopsy, a blood sample and remainder of the tumor to examine tumor marker levels in the cancer cells, which may predict how well the tumor will respond to the experimental agent, Erlotinib, used in this study. The purpose of this evaluation in cancer cells is to correlate patient response to therapy including Erlotinib, with tumor marker levels. Since this tissue was removed at the time of surgery or biopsy, the permission to use your tissue will not involve any additional procedure or expense to you. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like yours responds to treatment, can be identified.

Initial your choice below:

__________________________ YES, I AGREE TO ALLOW MY REMAINING TUMOR AND BLOOD SAMPLES TO BE USED FOR FUTURE CANCER RESEARCH.

__________________________ NO, I DO NOT AGREE TO ALLOW MY TUMOR AND BLOOD SAMPLES TO BE USED FOR FUTURE RESEARCH.

__________________________________________________________
Participant Signature

__________________________________________________________
Date

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SIGNATURES

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study and that you have read or had read to you all the information on this form. You will be given a signed copy of this form.

Signature of Participant or Legally Authorized Representative

Signature of Physician or Investigator

Signature of Witness

Signature of Person Obtaining Consent (If other than investigator)
University of Alabama at Birmingham
AUTHORIZATION FOR USE/DISCLOSURE OF HEALTH INFORMATION
FOR RESEARCH

You are being asked to sign this form to serve as authorization for UAB to use and release your health information for research. Participation in research is voluntary. If you choose to participate in the research, you must sign this form so that your health information may be used for the research. Once this information has been disclosed, it may be subject to redisclosure and no longer be protected by federal privacy regulations.

Participant Name: ___________________________ UAB IRB Protocol Number: F020925001
Research Protocol: RAD 0204 - Phase II Study of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor, Erlotinib, with Pre-operative Chemoradiation For Resectable Esophageal Cancer Principal Investigator: James A. Bonner, MD
Sponsor: Department of Radiation Oncology

Persons/organizations providing the information (check all that apply):

☑️ University Hospital
☒ Kirklin Clinic/Health Services Foundation ("HSF")
☐ The Children's Hospital of Alabama
☐ Other: ________

☑️ UAB Clinics: ☑️ Callahan Eye Foundation Hospital ("CEFH")
☐ Jefferson County Department of Public Health

Description of health information to be provided: All medical information and personal identifiers including past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of whatever kind related to or collected for use in the research protocol.

Persons/organizations receiving the information: The physicians, nurses and staff working on the research protocol (whether at UAB or elsewhere); other operating units of UAB, HSF, Children’s, CEFH and the Department of Public Health, as necessary for their operations; the IRB and its staff; the sponsor of the research and its employees; and outside regulatory agencies such as the Food and Drug Administration.

Authorization Expiration: Completion of Research Protocol

Authorization Revocation: You or your legally authorized representative must read and initial the following:

Initials: ________ I understand that I may revoke this Authorization at any time by notifying the Director of the IRB, in writing, referencing the Research Protocol and IRB Protocol Number. If I revoke this Authorization, it will not have any effect to the extent UAB took action in reliance on the Authorization and any research data generated prior to revocation may still be used by the researcher.

Signature of participant: ___________________________ Date: __________

OR

Signature of legally authorized representative: ___________________________ Date: __________

Printed name of participant’s representative: ___________________________

Relationship to the participant: ___________________________

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