INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0048 PRINCIPAL INVESTIGATOR: Udo Rudloff, M.D., Ph.D

STUDY TITLE: A Phase II Study of Lapatinib for the Treatment of Stage IV Melanoma Harboring ERBB4 Mutations

Continuing Review Approved by the IRB on 06/25/12
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Standard

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?

We have studied samples of melanoma tumors in the laboratory and have discovered that tumor cells from approximately 20% of melanoma patients contain a specific mutation (change) of a gene involved in making a protein called ERBB4 and changes in this gene have been associated with cancer. Lapatinib is a small molecule (drug) that is currently approved by the Food and Drug Administration (FDA) for the treatment of breast cancer. In the laboratory, lapatinib has been shown to significantly slow the growth of melanoma cells that contain this specific ERBB4 gene mutation.

Why are you being asked to take part in this study?

You have been diagnosed with metastatic melanoma and the only standard treatment available at this time that has been shown to cure melanoma in a small percentage of patients (about 5%) is aldesleukin (IL-2). A genetic analysis of your

tumor has demonstrated that your tumor contains the specific gene mutation we are studying and we want to test the effects lapatinib has on your cancer.

How many people will take part in this Study?

Up to 28 patients in several centers across the country may be enrolled in this study. The NIH Clinical Center will be the coordinating center for the study.

Description of Research Study

The purpose of this study is to determine if lapatinib can cause your tumor to shrink and to see how much lapatinib is in your blood after you have taken the lapatinib tablets (pharmacokinetics). We also want to measure how long the agent is able to keep your tumor from progressing. If you have a tumor that is easy to biopsy, we will ask you to have a biopsy after you have been taking the tablets for 2 weeks and again after you have taken the tablets for 12 weeks. This is to see if we can find genetic changes in your tumor. You may refuse to have biopsy and still participate in this study.

What will happen if you take part in this research study?

Before you begin the study
Prior to receiving the experimental treatment with lapatinib you will undergo many tests. These include imaging procedures, an EKG, and laboratory tests.

If you are a woman, you will undergo a pregnancy test. Women who are breast feeding or pregnant may not participate in this study because of the unknown effect on a fetus or nursing baby. We also ask that you practice an effective form of birth control while on this trial from at least 10-14 days prior to receiving the therapy, and for 4 months after being treated on this trial. Effective birth control methods include use of one of the following: abstinence, intrauterine device (IUD); hormonal (birth control pills, injections, implants); tubal ligation; cervical cap; or partner's vasectomy. If you think that you might be pregnant at any time during this trial, you should notify their doctor immediately.

During the study
Once we determine that you are eligible for treatment you will be given a 28-day supply of lapatinib in the form of a tablet. Each tablet contains 250 mg of the drug and you need to take 4 tablets a day; two tablets in the morning, approximately one hour before or after breakfast and 2 tablets in the evening, approximately one hour before or after dinner. The tablets should be taken approximately 10-12 hours apart, for a total of 1000 mg each day. You should not consume grapefruit or grapefruit juice while taking the study medications, as grapefruit may increase the risks for side effects. You should also discuss with your doctor all other medications you are currently taking, including herbal medicines, as some of these medicines may also interact with lapatinib in a harmful way.

You will be asked to keep a diary of the medicine that you are given and any side effects you may have during the study.

After the first 2 weeks, and every 2-4 weeks after that for the first 12 weeks, you will have laboratory tests repeated either at the NIH clinic or at home, to make sure you are tolerating the drug. If you do the tests at home, you will need to fax the results of the tests to Carole Webb, R.N. at 301-451-6933. After 4 weeks (28 days = 1 treatment cycle) you will return to the clinic for full evaluation and in addition to the laboratory tests, you will have scans repeated to determine if lapatinib is causing your disease to shrink or be controlled. If your disease has not progressed, you will continue to receive a new lapatinib supply every 28 days for up to 2 years (27 cycles). You will be asked to return to the

clinic at the end of every treatment cycle (4 weeks) for repeat labs and review of your medication diary. On certain visits (at the end of the first treatment cycle and every 2 cycles after that) you will also have repeat scans to evaluate your disease and to confirm that your tumor has not progressed.

Pharmacokinetics

Up to 10 patients, who live close by the NIH clinical center, may be asked to have blood drawn to measure the amount of lapatinib in their blood circulation. 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. If you agree to participate in this part of the study, you will have blood drawn before you take your morning tablets and 1, 2, 3, 4, 6, and 8 hours after your morning tablets on the day you start taking the tablets and again when you return for your follow up visit in about 4 weeks.

Please read the sentence below and think about your choice. After reading the sentence, circle and initial the answer that is right for you.

I agree to participate in the pharmacokinetics portion of this study which is for research purposes only.

Yes No Initials_____

Follow up and Evaluation

If your cancer continues to be better or stable after 27 cycles of therapy, you will be followed at the NIH every three months during the first 2 years, every 4 months during the third year and as clinically indicated after that.
If we find that your tumor is growing during lapatinib therapy, we will ask you to stop taking the drug and remove you from study. We will look for other investigational therapies you may be eligible for, or refer you back to the care of your local physician.

Study Chart

The treatment is given over 4-week periods of time called cycles. The 4-week treatment cycle will be repeated as long as you are tolerating the medication and your cancer is either stable or getting better. Each cycle is numbered in consecutive order. The chart below shows what will happen during cycle 1 and future cycles. This schedule indicates what will happen to you after you sign the consent and start the study.

Day	*What to do and what will happen to you*
Before starting study	• Complete history and physical examination • CT or other imaging studies • Laboratory tests • Echocardiogram • Pregnancy test (if female) • Evaluation of ERBB4 status
Cycle 1 (Days 1-28)	• Take lapatinib tablets twice a day • Complete medication and side effects diary • On day 14 (± 5 days), repeat laboratory tests (may be done at home or at the NIH) and have biopsy (optional) • PK studies
Prior to initiation of Cycle 2	• Physical examination • CT or other imaging studies as indicated • Laboratory tests • Review medication diary with research nurse
Cycles 2 and 3	• Take lapatinib by mouth every 12 hours (± 1 hour) and record in medication diary • On days 14 and 28 of cycle 2 and day 14 or cycle 3 (± 5 days), repeat laboratory tests (may be done at home or at the NIH)
Prior to initiation of Cycle 4	• Physical examination • CT or other imaging studies as indicated • Laboratory tests • Review medication diary with research nurse • Repeat biopsy (optional)
Cycle 4 through Cycle 27	• Take lapatinib by mouth every 12 hours (± 1 hour) and record in medication diary *At the end of every cycle:* • Physical examination • Laboratory tests • Review of medication diary with research nurse
At the completion of every 2nd Cycle (disease restaging)	• Physical examination • CT or other imaging studies as indicated • Laboratory tests • Review medication diary with research nurse
Follow-up	• Physical examination • CT or other imaging studies as indicated • Laboratory tests

Optional Biopsy

When tumor tissue is easily accessible and can be easily biopsied, we would like to request two additional biopsies, one after 2 weeks of therapy and one after 12 weeks of therapy. Biopsies are usually performed in the interventional radiology department using a CT imaging to locate the tumor. The biopsy to be performed is exclusively for research purposes and will not benefit you (refer to page 3). It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read the sentence below and think about your choice. After reading the 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. If you agree to have a tumor biopsy for research purposes, you will return to the NIH around 14 days after you start taking lapatinib (± 5 days) and again around 84 days after you start taking lapatinib (12 weeks, ± 5 days). Depending on the procedure, we may ask you to stay overnight to make sure you are ok.

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_____

Alternative Approaches or Treatments

Other options for treatment of your cancer include:

- standard therapies
- experimental vaccines;
- experimental chemotherapies or biotherapies (such as ipilimumab or tremelimumab);
- other combination therapies; or
- getting no treatment; getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Risks or Discomforts of Participation

The primary risks involved in this study result from receiving lapatinib. Other possible risks relate to the biopsies. If new toxicities arise during the course of this study that are not in this consent, we will inform you of them.

Risk Profile of Lapatinib (CAEPR version 2.4, January 6, 2010)

Likely:

- Diarrhea
- Nausea or the urge to vomit
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

Less likely:

- Swelling or feeling of fullness and tightness in the abdomen (belly)
- Belly pain
- Heartburn
- Excess passing of gas
- Irritation or sores somewhere in the lining of the gastrointestinal tract
- Vomiting
- Fatigue or tiredness
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Increased blood level of a liver enzyme (ALT/SGPT)
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- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Taste changes
- Headache or head pain
- Loss of some or all of the finger or toenails
- Itching
- Acne
- Sudden reddening of the face and/or neck

Rare but Serious:

- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Liver failure
- Abnormal reaction of the body to substances, called allergens, that are contacted through the skin, inhaled into the lungs, swallowed, or injected (allergic reaction)
- Abnormal electrical conduction within the heart
- Inflammation (swelling and redness) of the lungs

Biopsy risks

The risks of a biopsy include bruising and discomfort at the biopsy site and rarely bleeding and infection. The biopsy may be performed using CT imaging to locate the tumor. If this is the case, you will receive additional radiation from the CT scan. This radiation exposure is **not** necessary for your medical care and is for research purposes only. The total amount of radiation you will receive in this study is from one or two CT scans. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving minimal risk and necessary to obtain the research information desired.

Using the standard way of describing radiation dose, from participating in this study, the most radiation you will receive will be a total of 1.2 rem to your kidneys. All other parts of your body will receive smaller amounts of radiation. Although each organ will receive a different dose, the amount of radiation exposure you will receive from this study is equal to a uniform whole-body exposure of 0.29 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation you will receive in this study is below the dose guideline established by the NIH Radiation Safety Committee for research subjects. This guideline is an effective dose of 5 rem (or 5,000 mrem) received per year.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem (or 300 mrem) per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. The dose that you will receive from participation in this research study is about the same amount you would normally receive in one year from these natural sources. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, *An Introduction to Radiation for NIH Research Subjects.*

Please tell your doctor if you have taken part in other research studies or received any medical care at the NIH or other places or hospitals that used radiation. This way we can make sure that you will not receive too much radiation. Consider x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors 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.

It is possible that the information obtained from your participation in this study may become valuable for commercial research and development purposes (including patentable inventions), which may be of significant benefit to society, the sponsor of this study, individual researchers, or other third parties. You will not receive direct financial benefit from such research and development.

Research Subject's Rights

The NCI Cancer Therapy Evaluation Program (CTEP) is the sponsor of this study. Your records may be reviewed by NIH organizations including the NCI and by organizations outside the National Institutes of Health, such as qualified representatives of the pharmaceutical collaborator that supplies the drugs for the study and representatives of the US Food and Drug Administration. Every effort will be made to protect your privacy in any recording or reporting of this information.

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 study treatment 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.
- Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the lapatinib to the NCI/CTEP for some reason. If this would occur, other possible options are:
  1. You might be able to get the lapatinib from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
  2. If there is no lapatinib available at all, no one will be able to get more and the study would close.

  If a problem with getting lapatinib occurs, your study doctor will talk to you about these options.
- 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.

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 progresses 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.

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.

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, qualified representatives of the pharmaceutical collaborator 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: Udo Rudloff, M.D., Ph.D. Building 10, Room 4-5950, Telephone: (301) 496-3098. 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 at 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.

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 JUNE 25, 2012 THROUGH JUNE 24, 2013.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____