SCOTTSDALE HEALTHCARE
INSTITUTIONAL REVIEW BOARD

Consent to Participate in Research

Protocol Name: A Study to Compare the Study Drug, Erlotinib or Polyphenon E, to a Placebo (a substance that looks like a study drug but is not active) in Patients with Bladder Cancer That Has Been Removed.

Principal Investigator: Donald Lamm, MD
16620 N 40th St., Suite E
Phoenix, AZ 85032

Telephone #: 602- 493-6626

Sponsor: National Cancer Institute

Introduction

You are invited to consider taking part in this research study. We will be testing two medicines that we believe will reduce the risk of bladder tumor recurrence, Erlotinib (Tarceva®) and Polyphenon E. This form will describe the purpose and nature of the study, its possible risks and benefits, other options available to you, and your rights as a participant in the study. Please take whatever time you need to discuss the study with your physicians, hospital personnel and your family and friends. The decision to take part or not is yours. If you decide to take part, please initial each page, and sign and date the last line of this form.

Background and Purpose of the Study

We will be testing two new oral drugs for bladder cancer, and if you consent you will be taking either one of two experimental drugs; Erlotinib or Polyphenon E (green tea extract), or you will be taking a placebo (substance that looks like the study drug but is not active). Erlotinib is known to work by stopping an enzyme that helps tumors grow. Polyphenon E (green tea extract) may work by a number of ways, including stopping an enzyme that helps bladder tumors grow.

This is a 5-year study. The administration of the study drugs will last for 9 months and the next four years will involve follow-up visits. Depending on when you enter the study, the maximum number of visits will be 15 visits including the screening and study completion visits.

The main purpose of this study is to determine if either Erlotinib or Polyphenon E (green tea extract) will reduce the risk of bladder cancer recurrence and/or progression, and to find out the side effects (good or bad) that these drugs cause. Researchers will look at the tissue samples from your tumor and in the urine to find out what effect these drugs have on individual cancer cells. We will also look at your tissue samples to see if we can find a genetic link. If a genetic link can be found it may mean that your family members have an increased risk to develop bladder cancer. This information may be helpful or hurtful to your family members. You will not be given any genetic information unless you specifically request it on the last page of this form.

Erlotinib and Polyphenon E are investigational drugs that have been shown to shrink tumors in animals. Polyphenon E and other green tea extracts have been shown to prevent the development of several types of cancer, including bladder cancer, in animals. Erlotinib has been shown to shrink tumors in animals and has been studied in people with other cancers and seems promising, but it is not clear if it can improve results of standard treatment in those cancers.

The effects of Erlotinib or Polyphenon E in patients with bladder cancer are unknown.

Total Number of Participants

About 330 people will take part in this study nationally. People in the study are referred to as "participants." About 30 participants will enroll at this site.

General Plan of This Study

If you sign the consent form and agree to participate, we will ask you to do the following:
Screening Procedures
Before starting the study you will have tests and procedures performed within 3 weeks to decide if you are eligible for the study. The tests and procedures will include the following:

- A medical history, and medication history.
- A complete physical examination.
- A chest x-ray.
- A pulmonary (lung) function test (PFT) will be performed. You may have to go to Scottsdale Healthcare Shea to have this test done. PFT's measure your lung capacity. You blow into a machine, and it records how much air you take in and how fast you exhale it.
- A pulmonary test called a CT scan of the lungs may be performed if the lung test shows abnormal at screening and a lung specialist (pulmonologist) deems it necessary to rule out the presence of interstitial lung disease. Interstitial lung disease (ILD) is a broad category of lung diseases that includes disorders which are characterized by scarring of the lungs.
- Vital signs, including pulse, oral temperature, weight, height, and blood pressure
- Routine blood work, about 2-3 teaspoons of blood will be taken for this testing.
- A urine pregnancy test.
- Cystoscopy (a procedure done on an out patient basis, in which a doctor inserts a small tube-like instrument to look inside the bladder). This standard of care procedure includes bladder washings and urine collection. When we insert the cystoscope, we will gently "wash" the bladder with saline (water with a dash of salt), remove that saline and send it to the lab where it will be examined under a microscope for abnormalities.
- You will complete a risk factor questionnaire asking about your diet, life style, and behavior. You will need approximately 20 minutes to complete the questionnaire.
- The blood samples (about 2 teaspoons) we collect from you will be tested to evaluate genetic (inherited) factors that may be related to risk of cancer recurrence.

Monitor Procedures

If at any time during the course of the study you experience symptoms such as fever, cough or shortness of breath, it is important that you see your doctor as soon as possible. In order to diagnose the cause of your symptoms, Doctor Lamm may order or do the following procedures and tests:

- A medical history, and medication history.
- A complete physical examination.
- A pulmonary (lung) function test will be performed at 3, 6, 9 and 12 months.
- A pulmonary test called a CT scan of the lungs will be performed.

At each study visit, you will be evaluated for any eye-related adverse events. If the study doctor finds any abnormal condition in your eyes, you will be referred for an eye examination.

Research Procedure

Randomization:
This is a randomized study. Randomization is a process similar to a 'flip of the coin'. Randomization means that you will be assigned to one of three study groups by chance. This means that you will have a 1 in 3 chance of being assigned to one of the following three groups:

1) 800mg of real Polyphenon E (green tea extract) plus Erlotinib placebo (a substance that looks like the study drug but is not active)

2) Polyphenon E placebo (a substance that looks like the study drug but is not active) plus 50mg –100mg of real Erlotinib

3) Polyphenon E placebo plus Erlotinib placebo (both placebos will look like the study drugs but will not be active).

Experience from a large number of clinical studies with Erlotinib in patients with cancer suggests that some side effects such as skin rash and diarrhea are common with higher doses, e.g., 150 mg per day and usually occur within the first 4 weeks of treatment (see Risks and Discomforts of Erlotinib below). To reduce both the frequency and possibly the severity of these side effects, Erlotinib will be given at a much lower dose, e.g., 50 mg per day for the first 6 weeks. This dose is only 1/3 of the usual starting dose of 150 mg per day used in current clinical trials in patients with cancer. If there are no significant side effects during the first 6 weeks, the dose of Erlotinib will be increased to 100 mg per day and continued for the 9 month duration of the treatment phase of the trial (as shown in the table below). Since neither you nor the study doctors and personnel will know to which group you have been assigned, participants in each study group will take part in increasing the dose of real Erlotinib or Erlotinib placebo (a substance that looks like the study drug but is not active).

Below is a chart of the dose schedule for each study group:

Study Group Assignment	Weeks 1-6	Weeks 7-39
Real Polyphenon E Plus Erlotinib placebo	Real Polyphenon E 800 mg (4 pills) Erlotinib placebo 50 mg (2 pills)	Real Polyphenon E 800 mg (4 pills) Erlotinib placebo 100 mg (1 pill)
Polyphenon E placebo Plus Real Erlotinib	Polyphenon E placebo 800 mg. (4 pills) Real Erlotinib 50 mg (2 pills)	Polyphenon E placebo 800 mg (4 pills) Real Erlotinib 100 mg (1 pill)
Polyphenon E placebo Plus Erlotinib placebo	Polyphenon E placebo 800 mg (4 pills) Erlotinib placebo 50 mg (2 pills)	Polyphenon E placebo 800 mg (4 pills) Erlotinib placebo 100 mg (1 pill)

If you experience significant side effects (e.g., rash) resulting from the study drug during weeks 1-6, study agent will be held until the side effects resolve. If you experience significant side effects resulting from the study drug during weeks 7-39, the Erlotinib dose will be decreased to 75mg.

You will need to take your study drug, by mouth, at the same time each day for 9 months. The study drug should be taken on an empty stomach at least 1 hour before breakfast, with at least 6-7 oz of water. You will have one teaspoon of blood drawn every three months for the first year to monitor the effects of the study drug, and subsequently as determined by your treating physician to follow these possible side effects. You will need to have standard cystoscopies (a procedure to look inside the bladder) every 3 months for 2 years. This is a procedure to view the inside of your bladder and urethra in great detail using a specialized endoscope (a tube with a small camera used to perform tests and surgeries). The procedure usually takes between 5 and 20 minutes, and you should be able to go home with the same means of transportation. This is standard care for patients with your type of bladder cancer.

You will need to stop taking study drug if your bladder cancer returns or if you experience side effects or if new scientific developments occur that indicate that this study drug is not in your best interest. Your doctor may also stop your study treatment if he/she feels that it is no longer in your best interest to continue.

<u>Visits 2 to 15 (Every 3 Months for the First 2 Years and Every 6 Months for the Next 3 Years)</u>

At each visit, you will be asked about any side effects that you may be experiencing. If you develop any new tumors in your bladder while you are on study, you will need to have them removed and you will be taken off the study drug. A urine pregnancy test will be performed on every visit for the first 2 years, and the cost will be covered by the sponsor. You will have two teaspoon of blood drawn every three months for the first year to monitor the effects of the study drug, and subsequently as determined by your treating physician to follow these possible toxicities. Genetic testing will be also performed on your blood samples to determine whether any genes associated with cancer can be identified. You will need to have standard cystoscopies every 3 months for 2 years. This is standard care for patients with your type of bladder cancer. Each

visit will last approximately 15 to 30 minutes.

A lung function test will be performed at 3, 6, and 12 months to monitor any changes in your lung. If changes occur, you will have a CT scan (a specialized X-ray that looks at organs in the body for abnormalities) of the chest for assessment. If a lung disease is confirmed, study drug will be discontinued.

If you experience side effects such as fever, coughing, short of breath, and it causes you to stop taking study drug for more than 2 weeks, you will be taken off of the study.

Your blood sample(s) will be used for the purpose of this research study only and will not be shared with any other investigators. Upon completion of the study, your sample will be destroyed.

How Your Treatment Will be Determined in This Study

You will be assigned to one of 3 research treatment groups. A computer will determine which group you will be in through a process that is much like picking a number out of a hat. Neither the researcher nor any of the participants will know who is in which group until the study ends. Your chance of being in any group is one in 3. In the event of an emergency, Dr. Lamm can obtain information about which group you are in and the treatment you are receiving. This process is called randomization.

Length of the Study for Each Participant

We expect that you will be in the study for 5 years.

Possible Benefits of Participating in the Study

You might lower the chance of bladder tumor recurrence. However, we cannot guarantee that you will experience medical benefits from participating in this study. Others may benefit in the future from the information we obtain while you are in this study.

Possible Side Effects and Other Risks of Participating in the Study

You may experience some side effects as a result of the experimental medicines and treatments you receive in this study.

Erlotinib:
The risks and side effects you might have with Erlotinib include those listed below that are reported with the higher dose of 150mg:

Common (greater than 21% of patients:

- skin rash, itching and dry skin (this may be treated with anti-acne antibiotics),
- diarrhea (this may be treated with anti-diarrhea medication). Rarely, diarrhea can be severe and cause dehydration, low blood pressure, impaired kidney function, and problems with blood chemistry requiring treatment in hospital.
- Tiredness.

Less common (5 to 20% of patients):

- headache, nausea and vomiting,
- loss of appetite,
- sore mouth,
- painful swallowing,
- anxiety,
- nose bleeds,
- cough,
- dry eyes,
- low red blood level (anemia),
- liver enzyme abnormality,
- dry mouth
- constipation,
- other infections.

Infrequent (fewer than 5% of patients)

- eye changes with blurred vision and corneal (front surface of the eye) damage,
- inflammation or infection of the skin,
- inflammation of the uterus (womb) with vaginal bleeding,
- fever,
- kidney damage,
- irritation of the stomach or bowel that may lead to ulcers or bleeding,
- dehydration,
- fall in blood counts that can lead to bleeding, and
- irritation of the chest/lungs that may lead to fever, cough, and shortness of breath. This may be severe and life threatening. Please tell your doctor if you have any problems breathing, shortness of breath, cough, or fever. Erlotinib will be stopped while the cause of these problems are investigated and will be permanently stopped if these problems are due to inflammation of the lungs caused by Erlotinib. Most of the participants who developed this serious pulmonary side effect had primary lung cancer or the cancer had spread to the lungs from a tumor that originated outside of the lungs.

With and investigational drug such as Erlotinib additional unexpected and sometimes serious side effects are possible.

If you are taking or are prescribed a blood thinner at any time during the study, it is essential that you inform your doctor immediately. Being treated with the study drug, Erlotinib, at the same time as you are taking a blood thinner called coumadin or warfarin may increase the risk of bleeding. Until more information is known about this, your physician will follow you closely with blood tests to monitor the situation. If ou are seeing another doctor at another clinic who prescribes your blood-thinners, it is important that you inform him/her as well.

Abnormal elevation of values in liver function tests have bee seen in patients receiving Erlotinib. If you are taking another medication that has the potential to cause liver damage, you should have liver function tests.

Your doctor will watch you closely to see if you have side effects. When possible, other drugs will be given to you to make these side effects less serious and uncomfortable. Many side effects go away shortly after treatment is stopped but in some cases effects can be serious, long-lasting or permanent.

If you experience serious side effects that require treatment between regular clinic/hospital visits, it is important that you make every effort to return to the clinic/hospital where Erlotinib was given. If you need immediate treatment and are unable to return to the clinic/hospital where Erlotinib was given, your study doctor should be contacted as soon as possible.

Pregnancy
Women who are pregnant or breast feeding should not receive Erlotinib. It is recommended that a negative pregnancy test be confirmed before administration of study drug to those who may possibly become pregnant. Both sexually active men and women should use effective contraceptive methods to prevent the possibility of fathering a child or becoming pregnant while receiving study drug. If you are a female of child-bearing age, you must have a urine pregnancy test to determine if you are pregnant or not. This test will be paid for by the study sponsor. Should you become pregnant or planning to have a child during the course of this study, you must immediately notify your study physician.

Polyphenon E:
There is no safety information available on Polyphenon E (Green Tea Extracts) from large, controlled clinical studies. There has been a single case report where a powdered green tea started an asthma episode in an asthma patient who worked at a green tea factory. There have been reported side effects of nausea and bloating when taking Polyphenon E in participants in a small clinical study sponsored by the National Cancer Institute. That study showed that 800 mg. of Polyphenon E per day is safe and well tolerated.

Cystoscopy:
You may feel slight discomfort as the cystoscope is passed through the urethra into the bladder. You will feel uncomfortable (a strong need to urinate) when the fluid has filled the bladder.

You may notice a small amount of blood in your urine following this procedure. If the bleeding continues after three voids (urinations), contact your health care provider.

There is also a chance of infection. If you develop pain, chills, fever, or reduced urine output, contact the study doctor immediately.

Blood draws
There are possible side effects, which can occur from having blood drawn. You could possibly develop a bruise, redness, or soreness at the site where the needle was put in to draw your blood. You may briefly feel the prick of the needle when it is inserted into your vein. You may feel dizzy or faint when your blood is drawn. IF YOU HAVE EVER FAINTED WHILE HAVING YOUR BLOOD DRAWN – YOU SHOULD INFORM THE PERSON DRAWING YOUR BLOOD BEFORE THE PROCEDURE STARTS.

We will take reasonable safeguards to minimize known and potential risks but unknown

and/or unanticipated side effects might occur. Most side effects go away when the drug is stopped, but lung inflammation could be long lasting when the study drugs are stopped.

Who Can Participate

This study is designed for former smokers with bladder cancer that has not invaded the muscle wall of the bladder. Participants must have their bladder tumor removed but be at a high risk (estimated to be at least 50%) for tumor recurrence.

Your suitability for this study will be determined by medical tests and by medical history, physical exam, chest x-ray, and lung function tests.

Who Cannot Participate

The medicines and procedures used in this study may be unsafe for an unborn baby, a nursing infant, sperm, and eggs. Therefore, women and men who participate in this study must agree to use an appropriate and effective method of birth control throughout the study period and for at least 3 months after the last day of the study. These methods should be discussed with Dr. Lamm. If you do become pregnant during the study or if you father a child during the study, you should immediately notify Dr. Lamm at 602-493-6626. In addition if you are already pregnant or are breast-feeding, you cannot participate in this study.

You cannot participate in this study if you:

- had prior chemotherapy or radiation treatments,
- have other cancers,
- have other significant medical or psychiatric condition,
- a history of asthma or interstitial lung disease,
- normally drink more than 5 cups of green tea daily
- take medications that may interfere with the study agents (your doctor will describe these)
- a history of exposure to metal dust or wood dust in your work or home environment,
- have a history of a connective tissue disease such as scleroderma, or rheumatoid arthritis,
- have significant eye abnormality, or if you are using contact lenses.

Other Treatment Options

If you do not participate in this study, the following options are available to treat your illness/condition: Standard treatment, which would include removal of any tumors, as well as treatment with chemotherapy or immunotherapy such as BCG given into the bladder. BCG is a vaccination to prevent tuberculosis. You could also choose to have no treatment, or periodic follow-up cystoscopies. Green Tea, but not the study preparation, is available without participating in the study.

Confidentiality of the Data Collected During the Study

Every effort will be made to keep your medical records confidential, as well as other

personal information that we gather during this study. Please see the attached "Authorization to Share Protected (personal) Health Information (PHI) in Research."

Whenever data from this study are published, your name will not be used.

Individuals from the Scottsdale Healthcare IRB, Scottsdale Healthcare, the U.S. Food and Drug Administration, the investigators at UCLA, the National Cancer Institute, and the companies that make Erlotinib and polyphenon may look at medical and research records related to this study, both to assure quality control and to analyze data. We will disclose personal information about you to others as required by law.

Every tissue or fluid sample contains genetic information. The genetic information we obtain from your blood sample may identify you, and give us information about your parents and ancestors. We have learned from past research that we are not always able to predict problems that may arise because of the research. You should be aware that possible problems related to genetic testing include insurance or employment discrimination, but we will take every precaution to maintain your confidentiality now and in the future. We may learn that there is a genetic link to your cancer, and this may be helpful or hurtful to members of your family. We will not give you any information we learn about your parents and ancestors, but it may be helpful for us to study members of your family. We will not contact your relatives without your permission. You will not be given any genetic information we may find unless you specifically request it on the last page of this form.

Electronic Data Security

Information about your participation in this study is stored in a computer and we will take the following precautions to protect it from unauthorized disclosure, tampering, or damage: Only authorized users will have access.

New Findings

Throughout the study, we will tell you about new information we receive about treatments that may be appropriate for you, about the treatments under research in this study, and any information that may affect your interest in remaining in the study.

Costs to You for Participating

Erlotinib and Polyphenon E (green tea extract) are investigational drugs and will be supplied to you at no cost. Routine blood tests will be billed to your insurer; other blood tests done specifically for this study, the pulmonary function test, the possible CT chest scan, and a possible eye examination will be paid for by the study. Your periodic, routine cystoscopies (a procedure done on an out patient basis, in which a doctor inserts a small tube-like instrument to look inside the bladder) will also be billed to your insurer. (Standard, routine procedures are those that would be billed to your insurer for the medical care you would receive if you were not on the study).

It is possible that your insurance will not pay for all the standard treatments and tests you will receive if you participate in this research. That is because many insurance companies, HMOs, and health benefit plans do not cover the cost of standard treatments that are provided as part of a research study. If that happens, you will be

responsible for all charges relating to standard of care which includes laboratory charges, radiological studies, cystoscopy procedure, and hospitalization charges (if necessary). The study doctor will provide you with an estimate of the cost of participation in the research.

Payments to You for Participating

Study participants will not be paid for participating in this study.

Compensation in Case of Injury

We will make every effort to prevent study-related injuries and illnesses. If you are injured or become ill while you are in the study and the illness or injury is due to your participation in this study, you will receive emergency medical care. The costs of this care will be charged to you or to your health insurer. No funds are available from Scottsdale Healthcare or the federal government to compensate you for a study-related injury or illness. This does not mean that you are giving up any of your legal rights.

Your Rights as a Participant in The Study

Participation in this study is entirely voluntary. You have the right to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Should you decide to leave the study, please call Dr. Lamm at 602-493-6626. Should you decide not to participate or to withdraw, your medical care will not be affected nor will your relations with your physicians, other personnel, and the hospital. Your care, however, may be managed by different researchers or physicians.

Problems and Questions

Call Dr. Lamm at 602-493-6626 day or night if you have questions about the study, any problems, unexpected physical or psychological discomforts, any injuries, or think that something unusual or unexpected is happening.

The Scottsdale Healthcare Institutional Review Board (IRB) has reviewed this document for compliance with federal guidelines, and ethics. If you have questions about your rights as a research participant, you may call or write: Amy Wood, IRB coordinator or Robert Marlow, MD, Chair, IRB, 9003 E. Shea Blvd., Scottsdale, AZ 85260, 480-323-3071.

Withdrawal by Investigator, Physician, or Sponsor

The investigator (doctor involved with the study) may withdraw you from participating in this research study if circumstances arise which warrant doing so. Your participation in this study will continue as long as the following conditions are met:

1. You agree to take part in the study.
2. Your disease does not return. If this occurs, your treatment will be stopped and alternative care will be offered. You will continue to be followed by the investigator.
3. You follow the instructions for participation in this study.
4. The principal investigator (doctor in charge of the study) and sponsor agree to continue to conduct the study.

5. You do not experience side effects or are able to tolerate the side effects you do experience.

Investigator's Statement

I have fully explained this study to the participant. I have discussed the procedures and treatments, the possible risks and benefits, the standard and research aspects of the study, and have answered all of the questions that the participant and the participant's family members have asked.

Signature of Investigator
or Investigator's Designee _____ Date_____

Participant's Consent

I have read the information provided in this Informed Consent Form (or it was read to me by _____). All my questions were answered to my satisfaction. I voluntarily agree to participate in this study.

[Upon signing, you will receive a copy of this form, and the original will become part of your medical record.]

Your signature _____ Date _____

INFORMATION ABOUT YOUR GENETIC SAMPLE

Please indicate by checking and initialing the category below whether or not you want to receive genetic information we learn about you. It is your responsibility to let the investigator know if your address and/or telephone number changes. Dr. Lamm's address is on the first page of this consent.

I want to receive: ρ Genetic information about myself.
ρ No genetic information about myself.

The risks associated with genetic testing occur only if the information is provided to you or others. Genetic information can be associated with the risk of developing cancer. Knowing such information can cause worry and increased medical testing. The information will be closely guarded so the risk of being denied medical insurance or being subjected to discrimination based on this information should be negligible.

The specific genetic information to be searched for will be genes that are associated with the development and progress of bladder and other cancers as well as genes that regulate hormones or other molecules that cancer cells use to their advantage. Such molecules may tell us which patient is likely to respond to drug treatment or be targets for future drug development.