Columbia University Medical Center Consent Form

Attached to Protocol: IRB-AAAB9658
Principal Investigator: Robert Taub (rnt1)
IRB Protocol Title: A Randomized, Phase II, Lung-Sparing Combined Modality Protocol for the Treatment of Malignant Pleural Mesothelioma: The Columbia Protocol.

Consent Number: CF-AAAC6294
Participation Duration: 5 years
Anticipated Number of Subjects: 48

Contact

Contact	Title	Contact Type	Numbers
Robert Taub	Professor of Clinical Medicine	Principal Investigator	Telephone: 2123054076
LILIAN BATISTA	PROJECT COORDINATOR	Study Coordinator	Telephone: 212-305-6837
Elethea Hare	Physician Assistant	Co-Investigator	Telephone: 212-305-4076

Research Purpose

This is a randomized, Phase II study whose primary goal is to determine if a combination of three types of therapy (surgery, pleural chemotherapy and pleural radiation), called trimodal therapy, can improve the survival time of patients with pleural mesothelioma in addition to lengthening the time a patient's disease does not progress or grow. The second goal of this study is to determine how well this treatment regimen is tolerated and what side-effects, if any, patients may experience while receiving trimodal therapy in comparison to those who receive trimodal therapy in combination with three additional chemotherapy treatments during weeks 3, 6, and 9.

Information on Research

Introduction

You are invited to take part in a research study because you have been diagnosed with pleural mesothelioma for which your doctors feel will continue to grow without effective treatment. The goal of this study is to determine the overall effectiveness of chemotherapy combined with P32 radiation when administered into the chest cavity in the treatment of pleural mesothelioma. Since this

particular combination of treatments has not been used extensively, we cannot be certain of its effectiveness and risks.

Currently, treatments utilized at this and other institutions have not been satisfactory at arresting tumor growth or recurrence without undue toxicity. Therefore, we wish to evaluate an intensive combination of limited lung-sparing surgery, pleural chemotherapy and radioactive treatment directed at the pleural surfaces surrounding your lung in an attempt to kill tumor cells while simultaneously preserving lung function. This study is primarily designed to scientifically investigate whether such combined treatment (called "trimodal" therapy) may be of benefit to patients like you. Specifically, whether it can reduce or eliminate your mesothelioma tumor so that you will not need to undergo radical surgery to remove your entire lung. This study is randomized. What this means is that you have a 1 in 2 chance of being randomized to receive either trimodal therapy alone or trimodal therapy in combination with an additional three intraveous chemotherapy treatments during weeks 3, 6, and 9.

Before you agree to participate in this research study, it is important that you be told the purpose, procedures, risks, discomforts and precautions of the research. You may take this consent form home with you so that you will have time to read it carefully and discuss it with your family members or friends before making a decision. If there are any words or information that you do not understand, please feel free to make markings or notations on this document so that you will be able to have a meaningful discussion with your doctor. Reading this informed consent form and discussing any questions you might have about the nature and risks of this treatment with your doctor and the study staff are all part of an important process called informed consent.

In addition to discussing this study with you, your doctor will provide you with information concerning what alternative treatments and/or procedures may also be available to you. If you decide to take part in this research study, you must sign this consent form.

Expected Subject Participation
This research study will involve approximately 48 subjects.

Study Procedures
Because pleural mesothelioma is an aggressive disease, we intend to administer an intensive treatment regimen which will include surgery, intrapleural chemotherapy, and intrapleural radiation which may kill your cancer cells while, at the same time, minimize the exposure to your lungs and surrounding tissues.

During your initial visit you will have the opportunity to discuss this study with your doctor and the study staff and to review the necessary procedures and treatments you will need to undergo prior to and during your participation.

As part of the screening process, you will undergo a physical examination and will be interviewed by the study doctor who will record your prior medical history and the medication that you are currently

taking. In addition, you will also be scheduled to undergo the following examinations: (1) routine radiological tests to evaluate your tumor burden (CT scan, chest x-ray); (2) blood tests requiring approximately 5-6 teaspoons of blood; an electrocardiogram (ECG) to measure the electrical activity of your heart; and, (4) a PET scan (optional). For females who could become pregnant, you will be asked to have a pregnancy test. Nursing mothers cannot participate in this study. If any of these tests have been performed recently as part of your care, you will not need to repeat them to assess your eligibility for this study. Once you have completed your screening tests and your doctor says you are eligible to participate, you will be randomized to receive either trimodal therapy alone or trimodal therapy in combination with 3 additional intraveonous chemotherapy treatments during weeks 3, 6, and 9.

Surgical Thoracoscopy and Mediport Placement and Hyperthermic Chemotherapy [Weeks 0-1].

To administer intrapleural chemotherapy and radiotherapy, you will need to have 2 small tubes placed temporarily in your chest cavity into which your treatments will be administered. In order to do this, your surgeon will need to perform a thoracoscopy. During this procedure, your surgeon will insert a tube and camera through three separate small incisions in your chest wall in order to help him place two soft plastic tubes (catheters) into your chest cavity. Then, the surgeon will attach these two tubes to a small hollow button-shaped chamber under your skin called a "mediport" thru which you will receive your subsequent intrapleural treatments. Prior to your leaving the operating room, you will receive a brief infusion of cisplatin chemotherapy.

Outpatient Intrapleural Chemotherapy [weeks 1-9]

Prior to initating your first course of intrapleural treatment, you will need to have a repeat CT scan in order to determine where the chemotherapy drugs will localize in your pleural cavity. During each of your intrapleural chemotherapy treatments, you will receive a combination of cisplatin and doxorubicin. After each treatment, a small amount of saline will be injected in order to flush/wash the mediport and internal surface of the catheter free of chemotherapy. Instillation of chemotherapy into the pleural cavity as proposed here is considered experimental and non-standard treatment.

ARM A

If you are randomized to Arm A of the study, you will receive 3 cycles of intrapleural chemotherapy treatment consisting of 3 weeks each (21 days) for a total of 9 weeks (63 days). Intrapleural chemotherapy with cisplatin and doxorubicin will be administered during weeks 1 and 2 of each cycle of treatment and during week 3, you will receive intravenous chemotherapy with cisplatin and Alimta (pemetrexed). Prior to receiving each chemotherapy treatment you will undergo routine blood work testing, an assessment of your vital signs, and documentation and treatment for any new side effects you may be experiencing. On the days you are receiving intrapleural chemotherapy, a chest x-ray will be performed to allow your doctor to asses your lungs, the volume of pleural fluid present, and your pleural cavity.

At the conclusion of your third cycle of chemotherapy (week 9), you will have a 3 week rest period in

which you will not receive any treatment in preparation for your intrapleural radiation therapy during week 12.

ARM B
If you are randomized to Arm B of the study, you will receive 3 cycles of chemotherapy treatment consisting of 3 weeks each (21 days) for a total of 9 weeks (63 days). Intrapleural chemotherapy treatment with cisplatin and doxorubicin will be administered during weeks 1 and 2 only, followed by a one week rest period in which no treatment will be administered. During your chemotherapy treatment you will have weekly routine blood work testing, an assessment of your vital signs, and documentation and treatment for any new side effects you may be experiencing. On the days you are receiving intrapleural chemotherapy, a chest x-ray will be performed to allow your doctor to asses your lungs, the volume of pleural fluid present, and your pleural cavity.

At the conclusion of your last treatment (week 8), you will have a 3 week rest period in which you will not receive any treatment in preparation for your intrapleural radiation therapy during week 11.

It is important that you tell your doctor if you have experienced or still are experiencing any untoward events since your last visit. In addition, it is also important that you inform your doctor of any new medications you may have recently started taking or discontinued. If, during the course of your treatment, you begin to experience untoward side effects you should call your doctor immediately so that he can provide you with the appropriate information and treatment to alleviate your symptoms.

Intrapleural Radiation Therapy with Radioactive P-32 [week 11 or 12].
Three weeks after your last dose of chemotherapy you will return to the hospital where your pleural space will be imaged in the Nuclear Medicine Department using a nuclear scanner called a gamma camera. This procedure is done in order to determine if it is safe to administer radioactive P-32 into your pleural cavity and where the injection of radioactive P-32 will localize inside your pleaural cavity.

Test of localization of radioactivity with radioactive Technetium sulfur colloid (Days -1/-2):
Within 24 to 48 hours of your P-32 treatment, your doctor will ask you to have a very brief CT scan to assess your pleural space. The nuclear radiologist will then inject into each of your mediport catheters a radioactive substance called Technetium sulfur colloid (99m-Tc-colloid. This procedure is done in order to determine if it would be safe for you to receive a subsequent therapeutic dose of radioactive P-32.

Following the injection of radioactive 99m-Tc-colloid, the technician will ask you to lay on your stomach, turn on your side, stand, sit, and flex your body into various positions so as to assure an even distribution of radioactivity. At various intervals, the technician will use a gamma counter to take pictures of your chest cavity. These images will help the doctors determine where the injection of a radioactive substance will localize. If the doctors feel that it will be safe to administer P-32

radiotherapy, you may receive a subsequent injection of P-32 or you will be asked return to the hospital the next day for the P-32 radiation treatment. If, based on the initial distribution of Technetium sulfur colloid, it is determined that is not safe for the nuclear radiologist to administer additional treatment, you will not receive a second injection containing radioactive P-32.

Injection of Radioactive P-32 (Day 1):
Prior to receiving an injection of P-32 radiation, you may undergo repeat imaging with Technetium sulfur colloid (99m-Tc-colloid) to further confirm where the therapeutic dose of radioactivity will localize.

Radioactive P-32 sulfur colloid will be injected into your pleural space utilizing the same ports utilized previously. Following the injection of radioactive P-32, the technician will ask you to reposition your body as you did previously so as to assure an even distribution of radioactive P-32 throughout your pleural cavity.

Although this type of intrapleural irradiation has been used for many years for other diseases or conditions, it is not considered standard-of-care treatment for pleural mesothelioma.

You will be able to continue on study even if you are unable to be treated with P-32 radiotherapy.

Surgical Thoracoscopy, Mediport Removal, Intraoperative Chemotherapy [week 13].
After you have successfully completed your treatment(s), your surgeon will perform a repeat thoracoscopy to remove your catheters and mediport. Prior to your leaving the operating room, you will receive a brief infusion of cisplatin chemotherapy.

Elective Surgery and Radiotherapy
Following completion of the above course of intrapleural chemotherapy with/without P-32 treatment, you may elect to receive additional surgical treatment, conventional external beam IMRT radiotherapy, systemic chemotherapy, or a combination of these as deemed necessary or feasible by your treating oncologist and surgeon.

Additional surgery following completion of this trimodal therapy may consist of a lung sparing pleurectomy and decortication (P/D) or an extrapleural pneumonectomy (in which your disease lung is removed) followed by radiation therapy. A pleurectomy and decortication procedure is one in which the surgeon makes a large incision in your chest and surgically removes any noticeable residual disease whereas an extrapleural pneumonectomy (EPP) is an extensive surgical procedure which not only involves the removal of your lung and the covering around the lung (pleura) but also, the removal of all coverings surrounding the heart and diaphragm.

Only patients undergoing EPP may or may not receive additional high dose radiation therapy post surgical resection of their lung.

If you undergo an EPP your participation in this treatment portion of this study will end but you will continue to be followed by your doctor in the office or periodically by telephone. In this way your doctor will be able to collect important information on your disease status and any other treatment regimens you may have initiated since your participation in this study.

To date, neither of the above surgical procedures (P/D vs. EPP) have been shown to be superior to the other, or better than non-operative treatment, for prolongation of overall survival or time to recurrence.

Cisplatin and Alimta (pemetrexed) Chemotherapy

Whether or not you elect to undergo surgery, you will receive six more courses of outpatient intravenous chemotherapy with cisplatin in combination with Alimta (pemetrexed). This treatment will begin three weeks after you have completed your last intrapleural chemotherapy, surgery, or external bean radiation therapy.

Follow-up Assessments.

After you have completed your participation in this study, you will be asked to return to your doctor's office once a month for the next six months in order to assess your disease. After your six-month follow-up visit, your doctor may extend your follow-up visits to once every 2-3 months through your second year and then once every 6 months for an additional 3 years. Therefore, the total length of time you will be participating in this protocol is 5 years.

Risks

It is important to note that the preoperative instillation of intrapleural chemotherapy can be expected to delay conventional thoracotomy based treatment by 2-1/2 months possibly increasing your risk and/or reducing the effectiveness of such surgery.

Risks Associated with Cisplatin

Common side effects associated with cisplatin include: nausea and vomiting, diarrhea, changes in taste, loss of appetite or weight, generalized fatigue, thinning of hair or brittleness, numbness or tingling of the fingertips and toes (neuropathy).

Risks Associated with Doxorubicin

Nausea and vomiting occurs frequently and may be severe but can be alleviated by using anti-nausea therapy prior to and following your chemotherapy treatment. Mucositis (ulcerations in the mouth) may develop 5 to 10 days after your first dose of doxorubicin. You should speak to your doctor if these sores are painful as he will be able to give you medication(s) to lessen the discomfort associated with this side-effect.

Hypersensitivity reactions which include fever, chills and urticaria (hives) have occasionally been reported. In very rare instances, leaking of doxorubicin out of your vein into the surrounding tissue

may cause severe cellulitis (skin infection) and, in rarer instances, tissue death.

Hair loss usually occurs rapidly (within weeks) and is complete. Your doctor will advise you on where to obtain hair prosthesis (wig) should you wish to do so. Our experience is that your hair will begin to come back approximately 2 months after discontinuation of chemotherapy.

In very rare instances, patients who have been exposed much higher doses of doxorubicin, or have received doxorubicin in combination with radiotherapy to the mediastinum, have developed heart failure due to damage to their heart muscle caused by doxorubicin. Effects on the heart due to this therapy is unlikely to occur as the total cumulative dose of doxorubicin you will receive on this study (120 mg) is significantly less than that received by patients who developed heart failure.

The occurrence of secondary acute myeloid leukemia with or without a preleukemic phase has been reported in patients concurrently treated with doxorubicin in combination with DNA-damaging chemotherapy agents. Such cases could have a short (1-3 years) latency period. An analysis of 1474 breast cancer patients who received adjuvant doxorubicin treatment in clinical trials, showed a 10-year estimated risk of developing treatment-related leukemia at 2.5%.

Risks Associated with P-32 Radiation Therapy to the Lungs
Side effects of intrapleural radiotherapy are extremly rare but may include mild nausea, low-grade fever, or generalized fatigue. Many of these symptoms are transient and resolve within hours of treatment without medical intervention.

Risks Associated with High Dose Radiation
This research study involves exposure to radiation from chest x-rays, CT scans of the chest, intrapleural Tc-99m sulfur colloid, and therapeutic P-32 intrapleural radiotherapy. Although the majority of the radiation exposure you will receive while participating in this study is thought to be necessary for your medical care, exposure to ionizing radiation is linked with cancer induction and a potential for development of hereditary defects.

You should understand that your exposure high doses of radiation is considered medically justifiable and its risks do not outweigh the overall clinical benefit you may experience. However, you should also understand thata positive result from this therapy cannot be guaranteed.

Occasionally hypersensitivity reactions (including very rare life-threatening anaphylaxis) may occur following the injection of any radioactive pharmaceutical (Tc-99m Sulfur Colloid or P-32).

Risks Associated with Alimta (pemetrexed) when Administered In Combination with Cisplatin.
The combination of pemetrexed and cisplatin is currently approved for the treatment of malignant mesothelioma. The side effects associated with this combination of chemotherapy drugs are known to be: nausea and vomiting, lowered white blood cell counts which can put you at risk for infection, low red blood cell counts (anemia) which can cause you to feel tired or short of breath, decreased

kidney function, ulcerations in the mouth, loss of appetite (anorexia), diarrhea, tingling in your hands and feet (peripheral neuropathy), fatigue, development of skin rashes which may become itchy, ringing in your ears, and alterations in your taste. In rare instances, patients receiving cisplatin may experience high frequency hearing loss; occasionally, deafness may occur.

Pregnancy, Contraception, and Breast Feeding

There may be a possibility that the chemotherapy drugs administered as part of this study may cause harm to a fetus. Because it is advisable not to become pregnant while you are receiving chemotherapy treatment, you and your spouse/partner must agree to use an effective method of birth control to prevent pregnancy. In addition, females who are capable of bearing children will be required to take a pregnancy test prior to entry into this study. If you are sexually active and you or your spouse is able to become pregnant, you must practice effective birth control. You should discuss with your doctor what method(s) of birth control [i.e. oral contraceptives, IUD, implant, vaginal ring, diaphragm with condom and contraceptive cream (or foam), or total abstinence] would be considered adequate for you.

Women should not nurse (breast feed) a baby while participating in this study because it is possible that some chemotherapy drugs can enter breast milk and may possibly harm your/a child.

Other Unforseen Risks

Unanticipated side effects may occur which have not been reported and are currently unforeseen. If new significant findings concerning your disease or treatment become available your doctor will discuss them with you.

Benefits

You may or may not benefit from your involvement in this study. It is impossible to predict whether your cancer may improve, remain stable, or worsen during your participation. Although our primary research goal is to provide a form of therapy which may avoid the need for surgical removal of your affected lung. There is no guarantee that this will occur. It is hoped that the information gained from this study will aid doctors in the development of new approaches for the treatment of pleural mesothelioma.

Alternative Procedures

Patients with pleural mesothelioma usually receive some type of therapy to delay disease progression. As noted previously, surgery (either pleurectomy/decortication or extrapleural pneumonectomy) is commonly performed as the initial treatment. Up until this time, neither procedure has been definitively shown to be superior to the other, or better than non-operative treatment, for prolongation of overall survival or time to recurrence.

There may be other treatments for your cancer which may include chemotherapy with other drugs or radiation therapy. Currently, drugs commonly used to treat mesothelioma include: doxorubicin, carboplatin, oxaliplatin, cisplatin, vinoirelbine, gemcitabine, and mitomycin C, among others. These drugs may either be administered intravenously or intrapleurally, singly or in combination. All have

significant side effects. Their relative usefulness in your situation cannot be determined with certainty.

One of the alternatives you have is to not participate in this research study. Your decision whether or not to participate in this study will have no effect on your medical care at this hospital. If you decide not to participate, any of the above mentioned therapies may be available to you. It is possible that you may decide not to have treatment for your cancer at this time. The study doctor will discuss all of the options that may be available to you at this time.

Confidentiality

Although every effort will be made to protect the confidentiality of your records, absolute confidentiality cannot be guaranteed. By signing this document you grant permission for information obtained during the conduct of this study to be made available to:

(a) The investigator, study staff and other health professionals who may be evaluating the study;
(b) Columbia University;
(c) The New York Presbyterian Hospital;
(d) Authorized representatives of the Food and Drug Administration ("FDA") and the Office of Human Research Protections ("OHRP");
(e) The Columbia University Medical Center Institutional Review Board (IRB) who may independently review the study to assure adequate protection of research participants, as required by federal regulations; and,
(f) The Herbert Irving Comprehensive Cancer Center's Protocol Review and Monitoring Committee, an agent for the study doctor.

The results of this research may be presented at meetings or in publications. Your identity will not be disclosed in any presentation(s).

Research Related Injuries

If you are hurt or become ill during the course of this study, you should contact the Principal Investigator of this study, Dr. Robert N. Taub at (212)305-4076. Although compensation for injury that results from participation in this research is not available, Columbia University will assist you in obtaining medical treatment, including emergency treatment, hospital care and follow-up care as needed.

Your insurance carrier will be billed for the cost of such treatment and will be charged in the usual way. If your carrier denies coverage, Columbia University is under no obligation to pay for the treatment but may do so at its sole discretion. By providing financial or other assistance, neither Columbia University nor the researchers are stating that they are legally responsible for the injury. Further information regarding compensation for injured research subjects may be obtained from the Columbia University Medical Center's IRB office by calling (212)305-5883.

No monetary compensation for wages lost as a result of injury will be paid to you by The Presbyterian Hospital or Columbia University Medical Center. You are not giving up any legal rights that you otherwise would have as a subject in a research study by signing this consent form or by participating in this research study.

Compensation

You will not receive any payment or other compensation for participating in this study.

Additional Costs

Your insurance company will be billed for the routine costs associated with this treatment to include: chemotherapy drugs and their adminsitration, pre-medications provided to you as part of your chemotherapy, routine office visits, routine blood or urine testing, radiological tests such as chest x-rays, CT or PET scans, surgical procedures, radiation therapy, imaging performed to assess your tumor, and/or other tests or procedures your doctor may order as part of your routine standard-of-care. Your health insurance may or may not agree to pay for these tests or visits. Charges not covered by other payers will be your responsibility. You should speak to your doctor should you have any concerns related to your insurance coverage prior to initiating treatment so that these issues can be addressed in advance of your initiating treatment.

You will be responsible for your own travel costs.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to participate in this study. If you decide to participate, your are free to withdraw from this study at any time. We would only advise that you inform your doctor if you intend to withdraw so that he can provide you with the appropriate medical care. Your decision will not result in any penalty or loss of benefits to which you are entitled.

At any time during and/or following your course of treatment you are free to seek care from a physician of your choice. In the event you withdraw from participation in this study and seek treatment elsewhere, the study doctor will continue to follow you in order to assess your overall response or to determine if you have recovered from any side-effect(s) you may have experienced while participating in this study. Therefore, your current treating physician may be asked to provide portions of your medical records to the study doctor for research purposes only.

Additional Information

Study Termination

Your participation in the study may be terminated by your doctor at his or her discretion without your consent if you are not benefiting from the treatment or if it is determined that the treatment is not appropriate for your condition. This study may also be terminated by The Presbyterian Hospital or by Columbia University Medical Center for any reason.

Questions
If you have any future questions about this study, you may contact the Principal Investigator, Dr. Robert Taub at (212) 305-4076. Also, if you have any questions about your rights as a research participant, you may contact the Institutional Review Board at (212) 305-5883.

Statement of Consent
I have read this consent form and understand the nature and purpose of the study. I have fully discussed this study with _____ to my satisfaction and have had the opportunity to ask questions and have received satisfactory answers. I have been given as part of my informed consent information concerning the reasonably foreseeable risks and discomforts I may experience by participating in this study and my alternative treatment options.

I understand that I can decide not to participate in this study and can withdraw my participation at any time. My decision to not participate or to withdraw from the study will not affect my future care or stauts with my doctor(s).

I understand that I will receive a copy of this signed and dated informed consent form. By signing and dating this consent form, I have not waived any of the legal rights I would have if I were not a participant in this study.

I agree to cooperate with the study investigator/staff and will report to them in a timely manner any unexpected or unusual symptoms that I may have experienced or are currently experiencing.

I agree to release information concerning my medical condition, and my medical records prior to and following enrollment to assist the staff in assessing my candidacy for this study and to aid the evaluation of my response to the study treatment(s) following completion of therapy.

I have been informed that if I believe that I have sustained injury as a result of participation in a research study, I may contact the Principal Investigator, Dr. Robert Taub at (212) 305-4076, or the Columbia University Medical Center's Institutional Review Board at (212) 305-5883, so that I can review the matter and identify the medical resources which may be available to me.

Additional Information
If you have any questions or concerns about the study, please ask and we will do our best to answer them. If you have additional questions in the future, you can reach the study investigator, Dr. Robert Taub at (212) 305-4076 (24 hours).

If you have any questions on your rights as a research subject, you may contact the Columbia University Institutional Review Board at (212) 305-5883.

Signature

Study Participant
Print Name_____Signature_____Date_____

Principal Investigator
Print Name_____Signature_____Date_____

Additional
Print Name_____Signature_____Date_____