INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0107 PRINCIPAL INVESTIGATOR: Giuseppe Giaccone, MD, PhD

STUDY TITLE: A Phase II Study of Neo-Adjuvant Gemcitabine, Cisplatin and Bevacizumab in Stage IIIA (N2) Non-Squamous Cell Non-Small Cell Lung Cancer

Initial Review Approved by the IRB on 01/26/09 Date Posted to Web: 03/20/09
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?

The purpose of this study is to determine the effectiveness of the combination of three anti-cancer drugs given before your surgery, and to find out what effects, good and/or bad, these drugs may have on you and your cancer. The three drug combination consists of (1) Gemcitabine (2) Cisplatin and (3) Bevacizumab given prior to surgery (neo-adjuvant setting) in an attempt to shrink the size of your lung tumor so as to allow your surgeon to remove it completely. Gemcitabine, Cisplatin and Bevacizumab are all approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of many cancers including lung cancer. This study will help to determine if the combination of all three drugs given up front prior to surgery is more effective and as safe, safer, or less safe than other drug combinations given in the neo-adjuvant setting (chemotherapy given before surgery).

We will also look at how well this drug combination works against cancer cells in tumors by evaluating the tumor cells in your original biopsy specimen prior to chemotherapy and then in the resected tumor cells after surgery has been

performed (post chemotherapy). This study will also look at how these drugs may affect the cancer by measuring different proteins in your blood and in the tumor.

Using these drugs together is experimental. Although we hope this therapy will decrease the size of your tumor prior to surgery, we cannot promise the benefits of the treatment at this time. The expected benefit with this drug combination is that your tumor will decrease in size allowing your surgeon to perform more extensive and complete surgery. The 3 drugs used in this combination have known side effects that will be reviewed with you by your medical team before you sign the consent form.

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

You have been diagnosed with Stage IIIA (N2) lung cancer. Approximately 15% of people who are diagnosed with Non Small Cell Lung cancer have Stage IIIA (N2) disease. "Staging" your cancer is the process for looking to see how far the cancer has spread into the body, and is important in determining your treatment options. Stage III lung cancer lies between stage II which is considered operable and stage IV which is considered inoperable. Surgical resection is the treatment of choice for patients with lung cancer. Cure after resection depends on whether lymph nodes are involved. Once a patient is shown to have cancer in the lymph nodes involving the center of the chest (mediastinum) they are defined as having stage IIIA (N2) disease. Many hospitals use upfront chemotherapy followed by surgery as treatment for stage IIIA (N2) disease. This schedule is based on data from clinical studies showing that surgery alone is inferior to chemotherapy upfront followed by surgery. It is proposed that giving chemotherapy upfront may prevent spread of the tumor outside of your chest and may shrink your tumor to allow adequate surgery to be performed. It is also thought that chemotherapy is usually better tolerated before major surgery than after, therefore, allowing greater administration of the chemotherapeutic drugs.

How many people will take part in this Study?

Up to 70 patients will take part in this study.

Description of Research Study

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

Before you begin the study

You will need to have the following examinations, tests, or procedures to find out if you can be in the study. These examinations, tests, or procedures are part of your regular lung cancer care and should be done by your health care team even if you do not join the study. If you have had them recently, they may not need to be repeated. This will be up to your study doctor.

If you decide that you would like to participate in this study, you will be asked to sign this consent form. . You will then have the examinations, tests, and procedures listed below to see if you are eligible to participate further in this study (this is called the screening/baseline evaluation). Invasive procedures such as bronchoscopy or mediastinoscopy (see below) will not need to be repeated once adequate tissue is available.

- A complete medical history.
- A physical examination (including height, weight, blood pressure, pulse, temperature).

- The following standard blood tests (requiring about 3 teaspoons of blood) - Complete Blood Count (CBC), which includes: white blood cell count, red blood cell count, platelet count, hemoglobin (oxygen-carrying pigment in red blood cells), and hematocrit (measures the amount of space red blood cells take up in the blood); blood chemistry (which measures the levels of a number of chemical substances that are released from various tissues in the body to evaluate the function of the liver and kidneys); coagulation profile (measures how quickly your blood clots); urinalysis.
- A blood test or a urine test to check for pregnancy for women who are able to become pregnant.
- Urine test to check the level of protein excreted by your kidneys
- EKG and ECHO (tests to evaluate your heart)
- Chest x-ray
- Pulmonary function tests (to check your lung function)
- PET/CT scan, CT scan of chest and either MRI or contrast CT of brain
- Bronchoscopy and Mediastinoscopy. These are standard procedures that are used to both diagnose and adequately stage lung cancer. During these procedures the doctor can look directly at your tumor and can also take biopsies (tiny pieces of tissue) to send to the pathology lab for diagnosis. You will be given anesthesia and then a small, flexible tube with a light on the end of it is put into the lungs (bronchoscopy), or through a small incision in your chest (mediastinoscopy).. You will be asked to sign a separate consent for these procedures and the doctor performing this procedure will describe it in more detail.

<u>During the study</u>

After you are accepted for this study and you choose to take part, you will begin taking the study drugs. For some study procedures we will need you to come to the Clinical Center. You will also have tests performed because you are in the study to see how the study drugs are affecting your body. This will include imaging studies (eg CT scans and PET scans) prior to chemotherapy and after chemotherapy to find out if your cancer has responded. The combination of drugs will be given in cycles. All cycles are 21 days long. Now, we will describe what will happen during each cycle.

Cycle 1:

- Gemcitabine will be given on <u>day 1 and day 8</u> through a vein for 1 hour
- Cisplatin will be given on day 1 through a vein for 1 hour with normal saline administered through a vein before and after cisplatin administration
- Bevacizumab will be given on day 1 through a vein for 60-90 minutes

Cycle 2:

- Gemcitabine will be given on <u>day 1 and day 8</u> through a vein for 1 hour
- Cisplatin will be given on day 1 through a vein for 1 hour with normal saline administered through a vein before and after cisplatin administration
- Bevacizumab will be given on day 1 through a vein for 60 minutes

Cycle 3:

- Gemcitabine will be given on <u>day 1 and day 8</u> through a vein for 1 hour
- Cisplatin will be given on day 1 through a vein for 1 hour with normal saline administered through a vein before and after cisplatin administration

Treatment Plan:

Cycle 1 and 2 (each cycle lasts for 21 days)

Cisplatin given on day 1 every 21 days + Gemcitabine for two doses on days 1 and day 8 every 21 days + Bevacizumab on day 1 every 21 days for **first 2 cycles only**

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Cycle 3
Cisplatin on day 1 + Gemcitabine for two doses on days 1 and 8. **No bevacizumab on 3rd cycle**.

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Re-imaging scans following third cycle of chemotherapy

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Surgery: 4-6 weeks post completion of last cycle (cycle 3) of chemotherapy
(If your disease is stable or smaller and heart and lung function is satisfactory)

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Chemotherapy 4-8 weeks post surgery. Cisplatin on day 1, every 21 days x 4 cycles + Etoposide for consecutive 3 days, on days 1 to 3 every 21 days for 4 cycles.

Re-staging and Response Evaluation:

Two to three weeks following the third cycle of chemotherapy and no more than 14 days prior to your planned operation you will undergo repeat evaluation by Medical Oncology/Thoracic Surgery personnel to determine the clinical response of your tumor to the chemotherapy, and to confirm if your tumor is resectable. Repeat imaging studies will consist of a chest x-ray, CT scan of the chest, PET/CT scan and either a brain MRI or CT brain with contrast. If your doctor feels that there are new lymph nodes in your chest or there are new sites of potentially distant disease then you will need to be further evaluated by either repeat biopsy by either a bronchoscopy (as previously outlined), a mediastinoscopy (as previously outlined) or a biopsy performed under CT guidance. These investigations may be required to rule-out inoperable disease prior to surgery. After you have completed the chemotherapy your surgeon will also ask you to undergo repeat pulmonary function tests (to check your lung function) as well as an EKG and an ECHO (to check your heart function). These tests are performed prior to surgery to rule out any potentially significant deterioration of heart and lung function that could affect your ability to survive a large operation.

Surgery:

- If your surgeon feels that your tumor has either stayed the same size or has got smaller and your heart/lung function is satisfactory then you will proceed to surgery. Surgery will take place 4-6 weeks post completion of the last cycle of chemotherapy. If your tumor has increased in size or new sites of disease have appeared then you will not have surgery and you will be taken off study and treated with standard of care medicines. If your cancer can be removed by surgery, and you decide to have surgery, your doctor will discuss the details of the operation with you, including the location of your tumor, the type of surgery to be performed, and the risks of surgery. After

your surgery you may go to the ICU for additional monitoring. You will be given pain medicines after the operation to make you more comfortable. You will be given specific information from the doctor and nurses about what to expect after your operation.

Chemotherapy after surgery:

- 4-8 weeks post surgery patients will receive chemotherapy which is a standard treatment approach.
- Cisplatin will be given on day 1 through a vein for 1 hour with normal saline administered through a vein before and after cisplatin administration. Cisplatin is given on Day 1 every 21 days for 4 cycles.
- Etoposide will be given through a vein for 1 hour for 3 consecutive days, on days 1 to 3 every 21 days for 4 cycles.

Study Chart

Parameter	Prestudy	Before Each Upfront Cycle of Chemo	Prior to Surgery	Before Each Cycle of Chemo after surgery	Follow-Up
History (Dr will ask you questions)	X	X	X	X	X
Physical examination	X	X	X	X	X
Weight	X	X	X	X	X
Measurement of tumor	X		X		X
Performance status (Your ability to perform normal daily activities)	X	X	X	X	X
Complete blood count	X	X	X	X	X
Blood test assessing kidney and liver function	X	X	X	X	X
Urine analysis and assessment of protein level in urine	X	X	X		X
Pregnancy test	X				
Tumor Imaging (CT and PET/CT)	X		X		
Brain CT or MRI	X		X		
Assessment of heart and lung function via EKG, breathing tests and Echo	X		X		

When you are finished taking the drugs (treatment)
You will be seen in the clinic with repeat imaging every 3 months for 2 years then every 6 months for 3 years and then yearly for 3 years.

What does this study involve?

Treatments covered under this study include a combination of medications (chemotherapy) given before surgery, surgery, and then a combination of medicines (chemotherapy) after surgery. The treatment drugs individually are not experimental and all are approved by the United States Food and Drug Administration (FDA) but the combination of the three drugs given before surgery is experimental. Your doctors will describe your treatment plan to you in detail before asking you to sign this consent form. You may be asked to sign a separate consent form for any treatment procedures not outlined in this consent. This study will also look at how well this drug combination works against cancer cells in tumors by evaluating the tumor cells in your original biopsy specimen prior to chemotherapy and then in the resected tumor cells after surgery has been performed (post chemotherapy). This study will also look at how these drugs may affect the cancer by measuring different proteins in your blood and in the tumor. Research blood samples are required at baseline (cycle 1 day 1), cycle 1 day 8, cycle 1 day 22, on the day of surgery and approximately 72 hours post surgery.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how the combination of these medicines would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 3 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.
Effective forms of birth control include:

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

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

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

Risks and side effects related to **Gemcitabine:**

Likely	Less likely	Rare but serious
Swelling, pain, fever, sleepiness, rash, hair loss, severe itching, nausea/vomiting, constipation, diarrhea; anemia (decreased number of red blood cells), inflammation of the mouth, leukopenia/neutropenia (decreased number of white blood cells, decreased number of platelets (cell fragments in your blood), bleeding,; increased liver enzymes, proteins and blood in the urine, difficulty breathing, increased nitrogen in the blood (sign of kidney infection), flu-like syndrome, infection, absence of menstrual periods or abnormal/irregular menstrual periods	Injection site reactions, abnormal sensation/itching, increased creatinine (metabolic waste), bronchospasm (contraction of the air passage of the lung)	Adult respiratory distress syndrome (inflammation of the lungs), severe allergic reaction, eating disorder, abnormal heart rhythm, skin infection, inflammation (redness/swelling) of body tissue, stroke (sudden loss of brain function), heart disease, chills, cough, shedding of skin, increased sweating, decay of body tissue, headache, hemolytic uremic syndrome (decrease in blood cells and kidney disease), hepatotoxic reaction (liver damage from chemicals), increase blood tension, problems sleeping, lung disease, liver failure, feeling faint, heart attack, inflammation (redness/swelling) of blood vessels, petechiae (small purplish spots), swelling in the lungs, water in the lungs, scarring of the lungs, severe skin reaction, kidney failure, inability to breath, inflammation of the nose blood infection, weakness

Risks and side effects related to **Cisplatin:**

Likely	Less Likely	Rare but serious
Peripheral neuropathy (disease of the nerve cells leading to pain and numbness), mild hair loss, nausea and vomiting, myelosuppression (decrease in the number of blood cells made), increased liver enzymes, nephrotoxicity (kidney toxicity), ototoxicity (ear toxicity), absence of menstrual periods or abnormal/irregular menstrual periods	Diarrhea, local tissue irritation	Severe allergic reaction, abnormal heart rhythm, blurred vision, slow heart rate, blindness, hemolytic anemia (destruction of red blood cells), increased liver enzymes, , mouth sores, optic neuritis (inflammation of the nerve cells connected to the eye), papilledema (swelling of the area near the nerve cells connected to the eye), low concentration of potassium in the blood, low concentration of magnesium in the blood, kidney failure, increased creatinine (metabolic waste), azotemia (large amounts of nitrogen waste in the blood), temporary pain at tumor, temporary autoimmune disorders (conditions in which the immune system attacks healthy body tissues)

Risk and side effects related to **Bevacizumab:**

Likely	Less Likely	Rare but serious
High blood pressure Tiredness Loss of appetite Constipation Diarrhea Heartburn Nose bleed Bleeding from gut Pain in abdomen Headache Runny nose Voice changes	Low white blood cells, low blood pressure, fever, shakes/chills, weight loss, rash, skin ulcers, hives, cough, shortness of breath, pain in chest, pain in joints, pain in muscles Impaired wound healing Inflammation of gut (colitis) or mouth (mucositis), Nausea, Vomiting Blood clots in arteries or veins Liver damage	Severe allergic reaction, abnormal heart rhythm, heart attack, weakened heart muscle, very high blood pressure, confusion or other neurological changes because of high blood pressure, wheezing Formation of an abnormal connection (fistula) between your trachea (wind-pipe) and esophagus (gullet) called a tracheosophageal fistula or between your bowel and another organ or the skin

	Kidney damage Protein spillage from kidney into urine Infection of soft tissue/skin Acute infusion reaction (flushing, low blood pressure, dizziness, shortness of breath, swelling)	Formation of a hole in the intestines that may allow material to spill into the abdomen which can make you very ill (perforation) Bleeding from lung (hemoptysis) Bleeding in head Bleeding from vagina, rectum or from bladder Stroke ReversiblePosterior Leukoencephalopathy Syndrome (RPLS) (described below)

Fistulas/Perforations: Some previous studies of lung cancer patients that have been treated with bevacizumab have shown higher fistula and perforation rates than what would be expected.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS is a medical condition related to the leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening and may have long-term effects on brain function.

Bevacizumab is the common name for the commercial drug Avastin. The bevacizumab used in this trial, however, is for use in research studies only and may be made at locations different from those where Avastin is made. Although some differences may exist, bevacizumab for research use and the commercial drug, Avastin, are manufactured by a similar process, meet similar standards for final product testing, and are expected to be very similar in safety and effectiveness. For more information about risks and side effects, ask your study team.

Risks and side effects related to **Etoposide:**

Likely	Less Likely	Rare but serious
Nausea and vomiting, diarrhea, loss of appetite, hair loss or thinning, dizziness, feeling tired or sleepy, fever, high temperature, stomach pain or discomfort, constipation, myelosuppression (decrease in the number of blood cells made)	Inflammation of the mouth (mucositis), local tissue irritation, rash, ovarian failure, absence of menstrual periods or abnormal/irregular menstrual periods	Severe allergic reaction (flushing, low blood pressure, dizziness, shortness of breath, swelling) Acute Leukemia (cancer of the blood) Low blood pressure, rash, hives, itching, shortness of breath, liver damage, abdominal pain, aftertaste, constipation, difficulty swallowing, transient blindness, optic neuritis (inflammation of the

		nerve cells connected to the eye), fever, seizures, chest pain, heart attack, heart failure

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.

Research Subject's Rights

What are the costs of taking part in this study?

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

- You will receive 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.
- 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 comes back 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.

Optional Studies

We would like to keep some of the tissue and blood 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 and blood 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 or blood. Then any tissue or blood that remains 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 and blood 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_____

OTHER PERTINENT INFORMATION

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

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

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, Giuseppe Giaccone, M.D., Building 10, Room 12N226, Telephone: 301-402-3415. If you have any questions about the use of your tissue for futures research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251

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

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

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 _____

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 _____

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 _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JANUARY 26, 2009 THROUGH JANUARY 25, 2010.

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