

MARQUETTE GENERAL HEALTH SYSTEM

Regional Medical Center

CONSENT TO PARTICIPATE IN AN INVESTIGATIONAL STUDY

TITLE: CTSU E1505 - A Phase III Randomized Trial of Adjuvant Chemotherapy With or Without Bevacizumab for Patients With Completely Resected Stage IB (≥ 4 cm) -IIIA Non-Small Cell Lung Cancer (NSCLC) Version Date: September 15, 2010

INVESTIGATORS: Sheetal Acharya, MD
Amy Bolmer, DO
Rifat Elkhatab, MD
Santosh Gowda, MD
Gustavo Morel, MD
Ross Siemers, MD
Amy M. Weise, DO
1414 W. Fair Avenue
Marquette, MI 49855

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have non-small cell lung cancer, which has been removed by a surgeon.

WHY IS THIS STUDY BEING DONE?

This research is being done because even with the most aggressive after-surgery treatment with chemotherapy, many people still have the lung cancer recur (come back).

The purpose of this study is to determine if adding the new drug bevacizumab to chemotherapy improves the chance for cure for patients who have had surgery for the removal of the lung cancer. We will compare the effects (good and bad) of adding bevacizumab to chemotherapy with standard chemotherapy alone on you and your lung cancer to see which is better at preventing the cancer from coming back. Bevacizumab is investigational, which means it has not been approved by the FDA for use in this cancer.

All patients will receive what is felt to be a standard form of chemotherapy to be given as an outpatient. Only the combination of cisplatin and vinorelbine in patients with early stage lung cancer who have had the cancer removed (adjuvant chemotherapy) has been shown to improve survival when given every 28 days. The other 3 chemotherapy regimens in this study (cisplatin and

docetaxel vs. cisplatin and pemetrexed vs. cisplatin and gemcitabine) have not been tested as adjuvant chemotherapy. They are, however, proven to be as active (or perhaps even more active) than the combination of cisplatin and vinorelbine for patients who have metastatic lung cancer (lung cancer that has spread to other parts of the body). It is therefore felt by most doctors that they will work just as well as cisplatin and vinorelbine as adjuvant chemotherapy and that is why they are options in this trial.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 1500 people in North America and Europe will take part in this study.

WHAT IS INVOLVED IN THIS STUDY?

Please see the **Study Plan** on the last page of this form.

You will be "randomized" into one of the study arms described below in the section called "Procedures". Randomization means that you are put into a treatment arm by chance. You will have an equal chance of being placed in either arm. You and your study doctor will NOT be able to choose which arm you will be in. You and your study doctor will, however, choose which particular chemotherapy regimen within either study arm you will receive.

If you take part in this study, you will have the following tests and procedures:

Tests

- History and Physical exam every 3 weeks initially, then every 6 weeks for up to one year.
NOTE: If you are on Arm B, you will have your weight and blood pressure checked every 3 weeks for the first year.
- Blood work (CBC, chemistries, coagulation tests):
 - If you are on Arm A:
 - chemotherapy regimen 1 or regimen 3
twice every 3 weeks for the first 12 weeks, then once at 3 months post-treatment
 - chemotherapy regimen 2 or 4
every 3 weeks for the first 12 weeks, then once at 3 months post-treatment
 - If you are on Arm B:
 - chemotherapy regimen 1 or regimen 3
twice every 3 weeks for the first 12 weeks, then every 6 weeks while on treatment (for up to 1 year) then once at 3 months post-treatment visit
 - chemotherapy regimen 2 or 4
every 3 weeks for the first 12 weeks, then every 6 weeks while on treatment (for up to 1 year) then once at 3 months post-treatment visit
- Blood work (Coagulation Test A + B): Coagulation tests are not expected to be done as frequently as the CBCs and blood chemistries.
- Chest x-rays every 3 months up to 2 years from study entry, then every 6 months during years 3-5 from study entry, then once per year during years 6-10 from study entry.
- Urinalysis every 6 weeks for patients on Arm B for up to one year.
- Pregnancy test (where appropriate) one time only.
- Electrocardiogram (ECG) one time only.

Some of these tests would be done even if you do not take part in the study.

If your disease returns (recurrence), it is strongly encouraged that a biopsy be obtained for the purpose of verifying recurrence of the disease. Additional tests may be required that will document the extent of disease such as a CT scan of your chest and abdomen, a scan of the brain (either CT or magnetic resonance imaging [MRI]) and a scan of your bone (either a radionuclide bone scan or positron emission tomography [PET] scan).

Procedures

If you are on Arm A:

Treatment will be with one of four chemotherapy regimens (please see the Study Plan at the end of this form), which will be chosen by you and your study doctor. The four options are:

- Regimen 1: Cisplatin and Vinorelbine will each be given on day one and repeated every three weeks for up to four treatment cycles. The vinorelbine only will be repeated on day 8 of the treatment cycle (i.e. one week after the two chemotherapy drugs are given together, the vinorelbine alone will be given). The study drugs will be administered through a vein in your arm. The vinorelbine will be administered over about 5 to 10 minutes, the cisplatin over 60 minutes. On chemotherapy days that include cisplatin (day 1 of each cycle) you will also receive fluids by vein that will take up to 8 hours. These fluids will be to keep you well hydrated and will consist of sterile salt water (saline solution) with extra minerals (potassium and magnesium) to help protect your kidneys from the chemotherapy. You may also receive a diuretic, a medication to help the kidneys remove this fluid from your body and protect the kidneys from damage. You will not need these on day 8 (vinorelbine alone).
- Regimen 2: Cisplatin and Docetaxel will each be given on day one and repeated every three weeks for up to four treatment cycles. The study drugs will be administered through a vein in your arm. The docetaxel will be administered over 60 minutes, the cisplatin over 60 minutes. On chemotherapy days you will also receive fluids by vein that will take up to 8 hours. These fluids will be to keep you well hydrated and will consist of sterile salt water (saline solution) with extra minerals (potassium and magnesium) to help protect your kidneys from the chemotherapy. You may also receive a diuretic, a medication to help the kidneys remove this fluid from your body and protect the kidneys from damage.
- Regimen 3: Cisplatin and Gemcitabine will each be given on day one and repeated every three weeks for up to four treatment cycles. The gemcitabine only will be repeated on day 8 of the treatment cycle (i.e. one week after the two chemotherapy drugs are given together, the gemcitabine alone will be given). The study drugs will be administered through a vein in your arm. The gemcitabine will be administered over 30 minutes, the cisplatin over 60 minutes. On chemotherapy days that include cisplatin (day 1 of each cycle) you will also receive fluids by vein that will take up to 8 hours. These fluids will be to keep you well hydrated and will consist of sterile salt water (saline solution) with extra minerals (potassium and magnesium) to help protect your kidneys from the chemotherapy. You may also receive a diuretic, a medication to help the kidneys remove this fluid from your body and protect the kidneys from damage. You will not need these on day 8 (gemcitabine alone).

Regimen 4: Cisplatin and Pemetrexed will each be given on day one and repeated every three weeks for up to four treatment cycles. The study drugs will be administered through a vein in your arm. The pemetrexed will be administered over 10 minutes, the cisplatin over 60 minutes. On chemotherapy days you will also receive fluids by vein that will take up to 8 hours. These fluids will be to keep you well hydrated and will consist of sterile salt water (saline solution) with extra minerals (potassium and magnesium) to help protect your kidneys from the chemotherapy. You may also receive a diuretic, a medication to help the kidneys remove this fluid from your body and protect the kidneys from damage. If you are on this regimen you will also received a shot in your arm or buttock of vitamin B12 every 9 weeks, starting on the first day of chemotherapy or a week or two earlier until 3 weeks after the last dose of pemetrexed. You will also have to take a vitamin, folate (folic acid) daily starting about a week before your first dose of chemotherapy and continuing every day for at least 3 weeks after your last dose of chemotherapy. You may also have to stop taking medications commonly used for pain such as ibuprofen (motrin) for a few days before and after the chemotherapy to help protect your kidneys. You will also have to take a steroid medication for the day before, day of and day after chemotherapy to reduce the risk of rash.

If you are on Arm B:

You will receive the same chemotherapy as those on Arm A (i.e. one of the 4 regimens listed above) PLUS the addition of the drug bevacizumab (also given on the same day as day 1 of chemotherapy). Bevacizumab works by preventing the formation of new blood vessels, including those that surround and supply cancer cells, with the oxygen and nutrients they need to survive and grow. By taking away the blood supply, drugs like bevacizumab (also called angiogenesis inhibitors) may reduce tumor cell growth and cause cancerous tumors to grow more slowly or to become smaller. The bevacizumab will be infused over 30-90 minutes and repeated every three weeks. The bevacizumab will continue beyond the chemotherapy for up to one year (measured from the first dose of chemotherapy and bevacizumab), or until evidence of tumor growth, or if the side effects from treatment are too severe to continue treatment.

Smoking Status Survey:

This study includes a survey asking whether or not you smoke, and if so, how much. The questionnaire regarding your smoking habits is brief. You will take this survey before you begin study treatment, and every 3 months thereafter, for up to a year from study entry. On the same days you fill out your questionnaire, you may also be asked to take a urine dipstick test at your study doctor's office to verify your smoking status.

This survey is being performed to determine what the relation is between smoking status and your disease and overall survival. The effect of gender on smoking status will also be examined.

HOW LONG WILL I BE IN THE STUDY?

If you are randomized to Arm A (chemotherapy treatment) you will likely participate in the trial for about 3 months. If you are randomized to Arm B (chemotherapy and bevacizumab), you will likely participate in the trial for about 1 year.

Information about your health will be collected for approximately 10 years and reported to the sponsors of the clinical trial.

CAN I STOP BEING IN THE STUDY?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the drugs can be evaluated. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Chemotherapy alone has shown to be beneficial to patients who have had surgical removal of non-small cell lung cancer. If you decide to stop treatment with chemotherapy, you may reduce your chances of benefiting from the chemotherapy. Many studies have shown that on average, people who receive chemotherapy after lung cancer surgery have a higher chance of being alive 5 years after than surgery than people who don't get chemotherapy. We do not know if bevacizumab will improve survival rates for early stage lung cancer beyond that with adjuvant chemotherapy alone.

Also, the study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest (e.g. you experience serious side effects); if you do not follow the study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects listed below. The chemotherapy drugs, pemetrexed, cisplatin, vinorelbine, docetaxel, gemcitabine and the antibody bevacizumab may cause some, all, or none of the side effects listed. You should discuss these with your study doctor. There may also be other side effects that we cannot predict. Other drugs will be given to prevent or decrease the severity of side effects. Examples of some of these drugs include dexamethasone, antihistamines (diphenhydramine, ranitidine, cimetidine or others), epinephrine, bronchodilators, Imodium, Lomotil, and anti-nausea drugs (compazine, ondansetron, granisetron or others). Many side effects go away shortly after the treatment drugs are stopped, but in some cases side effects can be serious, long-lasting, permanent, or life-threatening. Death is rare, but possible.

If you are a woman:

If you are able to become pregnant, a blood test will be performed before the study to insure you are not pregnant. Because the drug in this study can possibly affect an unborn baby and infants, you should not become pregnant or breast feed while you are on this study. Also, since bevacizumab remains in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of bevacizumab.

If you are a man:

Because the drug in this study can possibly affect an unborn baby and infants, you should not father a baby while you are on this study. Also, since bevacizumab remains in your body for weeks to months, you should continue to use adequate contraceptive measures for at least 6 months after your last dose of bevacizumab.

Your physician will check you closely to see if any of these side effects are occurring and routine blood tests will be done to monitor the effects of treatment.

Risks and side effects related to the drugs we are studying include:

Arm A:

Regimen 1: Cisplatin and Vinorelbine

More Likely:

- Low white blood cell counts (may make you more likely to get an infection)
- Low red blood cell counts (may make you feel tired or weak)
- Low platelet counts (may make you more likely to bruise or bleed)
- Nausea
- Vomiting
- Loss of appetite
- Fatigue

- Hair Loss
- Constipation
- Blood measurements of kidney function (creatinine) and normal elements in the blood including blood sugar (glucose), potassium, magnesium, calcium and sodium may become abnormal
- Lightheadedness
- Headaches
- Numbness in the hands and feet
- Changes in blood pressure
- Skin irritation at site of drug injection
- Damage to kidneys
- Damage to hearing
- Electrolytes, which are normal elements measured in the blood, including potassium, magnesium and sodium may become low and possibly require replacement

Less Likely:

- Sores in mouth and/or throat
- Alterations in taste
- Allergic reaction (including flushing, skin rash, changes in blood pressure and/or difficulty breathing)
- Stomach cramps
- Loss of blood supply to the intestines that may require surgery
- Inflamed pancreas
- Diarrhea
- Dizziness and shooting back pain when bending your neck forward
- Confusion
- Blurred vision or a sensation of flashing light
- Mood changes
- Liver damage and/or failure
- Seizures
- Fainting
- Irregular heartbeat
- Heart attack

Rare:

- Acute leukemia

Regimen 2: Cisplatin and Docetaxel

More Likely:

- Low white blood cell counts (may make you more likely to get an infection)
- Low red blood cell counts (may make you feel tired or weak)
- Low platelet counts (may make you more likely to bruise or bleed)
- Nausea
- Vomiting
- Loss of appetite
- Diarrhea
- Fatigue
- Muscle weakness
- Joint and muscle aches
- Hair loss
- Blood measurements of kidney function (creatinine) and normal elements in the blood including blood sugar (glucose), potassium, magnesium, calcium and sodium may become abnormal
- Lightheadedness
- Headaches
- Numbness in the hands and feet
- Changes in blood pressure
- Skin irritation at site of drug injection
- Swelling in legs and rest of body
- Damage to kidneys
- Damage to hearing
- Electrolytes, which are normal elements measured in the blood, including potassium, magnesium and sodium may become low and possibly require replacement

Less Likely:

- Sores in mouth and/or throat
- Alterations in taste
- Allergic reaction (including flushing, skin rash, changes in blood pressure and/or difficulty breathing)
- Stomach cramps
- Loss of blood supply to the intestines that may require surgery
- Inflamed pancreas
- Dizziness and shooting back pain when bending your neck forward
- Confusion
- Blurred vision or a sensation of flashing light

- Mood changes
- Liver damage and/or failure
- Seizures
- Fainting
- Irregular heartbeat
- Heart attack

Rare:

- Acute leukemia

Regimen 3: Cisplatin and Gemcitabine

More Likely:

- Low white blood cell counts (may make you more likely to get an infection)
- Low red blood cell counts (may make you feel tired or weak)
- Low platelet counts (may make you more likely to bruise or bleed)
- Nausea
- Vomiting
- Loss of appetite
- Diarrhea
- Fatigue
- Blood measurements of kidney function (creatinine) and normal elements in the blood including blood sugar (glucose), potassium, magnesium, calcium and sodium may become abnormal
- Lightheadedness
- Headaches
- Changes in blood pressure
- Skin irritation at site of drug injection
- Damage to kidneys
- Damage to hearing
- Rash
- Flu-like illness with fever on day of chemotherapy
- Electrolytes, which are normal elements measured in the blood, including potassium, magnesium and sodium may become low and possibly require replacement

Less Likely:

- Sores in mouth and/or throat
- Alterations in taste
- Allergic reaction (including flushing, skin rash, changes in blood pressure and/or difficulty breathing)
- Stomach cramps
- Hair loss
- Numbness in the hands and feet
- Loss of blood supply to the intestines that may require surgery
- Inflamed pancreas
- Dizziness and shooting back pain when bending your neck forward
- Confusion
- Blurred vision or a sensation of flashing light
- Mood changes
- Liver damage and/or failure
- Seizures
- Fainting
- Irregular heartbeat
- Heart attack

Rare:

- Acute leukemia

Regimen 4: Cisplatin and Pemetrexed

More Likely:

- Low white blood cell counts (may make you more likely to get an infection)
- Low red blood cell counts (may make you feel tired or weak)
- Low platelet counts (may make you more likely to bruise or bleed)
- Nausea
- Vomiting
- Loss of appetite
- Fatigue (loss of energy or strength)

- Blood measurements of kidney function (creatinine) and normal elements in the blood including blood sugar (glucose), potassium, magnesium, calcium and sodium, may become abnormal
- Lightheadedness
- Headaches
- Numbness in the hands and feet or tingling or pain
- Changes in blood pressure
- Skin irritation at site of drug injection
- Damage to kidneys (may cause kidney failure)
- Damage to hearing
- Sores in mouth and/or throat
- Rash or skin discoloration
- Diarrhea

Less Likely:

- Alterations in taste
- Blood clots
- Infection
- Hair loss
- Chills
- Swelling in your hands and/or feet
- Mood changes such as depression
- Changes in liver function without symptoms
- Irregular heartbeat
- Chest pain
- Constipation

Rare:

- Acute leukemia
- Allergic reaction (shortness of breath; closing of the throat, difficulty breathing, swelling of the lips, face or tongue; of hives)
- Damage to your lungs
- Bleeding- blood in the urine, coughing up blood

Arm B

Chemotherapy regimen risks are the same as for Arm A (above). In addition, if you are on this arm, you will receive bevacizumab.

Risks and side effects related to bevacizumab are:

Bevacizumab

Likely:

- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Headache or head pain
- High blood pressure

Less Likely:

- Lack of enough red blood cells (anemia)
- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT)
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver enzyme (AST/SGOT)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Joint pain
- Abnormal changes in the growth plate that may affect the growth of long bones in very young children. This side effect appeared to be reversible after the treatment was stopped but has not been assessed with long-term use of the bevacizumab drug.
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Fainting
- Sudden decrease of kidney function
- Blood in the urine
- More protein leaking into the urine than usual, often a sign of kidney disease
- Bleeding in the vagina
- Cough
- Shortness of breath
- Nose bleed
- Hoarseness

- Stuffy nose
- Itching
- Skin rash
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare but Serious:

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart
- Irregular heartbeat resulting from an abnormality in the one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation : A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- A condition in which the kidneys leak a large amount of protein into the urine that can cause complications including swelling and kidney failure
- Kidney failure
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs

- Hole in the wall that separates the nostrils of the nose
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke

Reproductive Risks for Patients on Arm A

If you are a woman:

You should not become pregnant while on this study, and for at least 3 months after completing protocol treatment, because the drugs in this study can affect a fetus. You should not breastfeed a baby while on this study, and for at least 3 months after completing protocol treatment. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. For more information about risks and side effects, ask your study doctor.

If you are a man:

You should not father a baby while on this study, and for at least 3 months after completing protocol treatment, because the drugs in this study can affect a fetus. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. For more information about risks and side effects, ask your study doctor.

Reproductive Risks for Patients on Arm B

If you are a woman:

You should not become pregnant while on this study, and for at least 6 months after completing protocol treatment, because the drugs in this study can affect a fetus. You should not breastfeed a baby while on this study, and for at least 6 months after completing protocol treatment. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. For more information about risks and side effects, ask your study doctor.

If you are a man:

You should not father a baby while on this study, and for at least 6 months after completing protocol treatment, because the drugs in this study can affect a fetus. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. For more information about risks and side effects, ask your study doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefits to you.

The possible benefits of taking part in the study are the same as receiving adjuvant chemotherapy (chemotherapy after removal of cancer) for early stage lung cancer without being in the study.

We hope the information learned from this study will benefit other patients with early stage non-small cell lung cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study, like standard chemotherapy (such as the regimens described for Arm A of this study, or others). You may receive chemotherapy, including any of the regimens described for Arm A at this medical center and at other medical centers, even if you do not take part in this study.
- Taking part in another study.
- Getting no further treatment (after the surgical removal of your cancer).

Talk to your study doctor about your choices before you decide if you will take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

The Eastern Cooperative Oncology Group (ECOG) is conducting this study. (It is being conducted locally by Marquette General Hospital). ECOG is a cancer research group that conducts studies for the National Cancer Institute. Your study doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your study doctor and ECOG may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group (ECOG)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories, banks and/or reviewers

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

If assigned to Arm B, The Division of Cancer Treatment and Diagnosis, NCI, will provide you with the investigational agent, bevacizumab, free of charge to all participants. Every effort has been made to ensure adequate supplies of the investigational agent, free of charge, for all participants on Arm B. The use of bevacizumab for patients who have had their cancer surgically removed is experimental. Bevacizumab is a commercially available drug, as it is currently FDA-approved for the treatment of metastatic colorectal cancer and lung cancer. Since bevacizumab is commercially available, if it becomes approved for adjuvant (post-surgery) non-small cell lung cancer, Genentech (the maker of bevacizumab) has committed to providing you with bevacizumab for the duration of involvement in the trial (up to one year of bevacizumab).

You or your insurance company will NOT be billed for the research laboratory tests performed by designated central laboratories as a part of this study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at:

<http://cancer.gov/clinicaltrials/understanding/insurance-coverage>

You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Institutional Funding:

Funds are provided from the study sponsor to Marquette General Hospital on a per patient basis to help with the institution's costs of participating in this study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you tell your study doctor, _____ if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ at _____. During the evenings, weekends, or holidays you may phone Marquette General Hospital at (906) 228-9440, and request to speak with the oncology physician on call.

For questions about your rights while taking part in this study, call the Patient Advocate at Marquette General Hospital at 906-225-3183.

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

ABOUT USING SPECIMENS FOR RESEARCH

If you participate in the clinical trial, we would also like samples of your blood and tissue to be used for research studies. These samples are referred to as "specimens". These specimens and the health information collected during your participation in the clinical trial can be used to help doctors and scientists learn more about caring for and treating people with cancer and other diseases.

Below is some general information you should know before agreeing to allow the use of your specimens for research. After the general information there are descriptions of the research projects. Each project is described separately, including the types of specimens requested and how they are collected. Each description is followed by questions concerning your participation in the project. Your specimens will be used only for the projects in which you agree to participate.

You will not receive any payments for allowing your specimens to be used for these research studies, even if your specimens are used to help develop commercial products or tests someday. You or your insurance company will not be billed for these tests.

How Will My Specimens Be Used Be For Research?

Researchers will study the different types of cells in the specimens such as tumor cells and normal cells. Some of the projects may study characteristics that may be passed on in families (inheritable). The study of inheritable traits is a type of genetic research. To better understand the results, the researcher may compare the test results to the information collected from your participation in the clinical trial (such as your age, side effects you experience, and your cancer's response to treatment).

Additional information on the importance of donating your specimens for research and how specimens are used for research can be found on the patient advocacy website (www.researchadvocacy.org) and on the NCI website at www.cancer.gov/clinicaltrials/.

Where will my specimens be stored and who has access to them?

If you agree to allow your specimens to be used for the research projects, your specimens will be sent to research laboratories for testing. After these tests are completed, the researchers will send any left over specimens to a repository (bank) where, if you agree, they will be stored for use by other researchers. The stored specimens will be kept indefinitely or until they are used up.

Because your specimens are valuable, researchers must present their projects for review and approval to scientific reviewers appointed by the Eastern Cooperative Oncology Group. Any research done on the specimens must also be reviewed by the researcher's Institutional Review Board (a group of people who review the research to protect patient rights). Some projects may also require approval by the National Cancer Institute (NCI).

Will personal information be associated with the specimens?

The specimens sent to research laboratories and repositories will have some identifying information, such as initials and where the specimens were collected. To protect your identity, your specimens and any related information will receive a unique identification code. Researchers approved to use the specimens for future research will only receive the code that is attached to your specimen. Any information from your research records that is approved to go to a researcher will also receive a code.

Any research or information that is published, presented at scientific meetings or made public in any other way will use only coded information.

What are the risks?

There are very few risks in having your specimens and data used for this type of research. The greatest risk, although rare, is the loss of confidentiality caused by unauthorized release or misuse of information from your research records.

We will do everything possible to make sure that the information in your research records are kept private.

Risk from participating in genetic research: Your genetic information is unique to you, you do share some genetic information with your family members. Although rare, there are examples where health insurers or employers have denied insurance or employment based on results from genetic testing. Many states currently have laws to protect against genetic discrimination by employers or insurance companies. Currently there is no federal law that prohibits such misuse or discrimination.

How we will address these risks: We have several safeguards in place to prevent misuse of research results by any third party including insurers or employers: your research results will not be sent to you or your doctor and will not be placed in your medical record; insurers or employers will not be authorized to view any research records; and all information will be coded. As stated before, we also have a Certificate of Confidentiality from the US government, which protects your information from forced disclosure by civil, criminal, administrative, legislative or other proceeding. We believe that the risks to you and your family are very low.

Benefits

The research that may be done with your specimens will probably not benefit you directly. It may help researchers learn more about what causes cancer and other diseases, how to prevent them, and how to select the most appropriate treatment for future patients who have these diseases.

Changing your mind about letting us use your specimens

If at any time you decide you no longer want your specimens used for research, please give your doctor or study nurse a signed note stating your decision. They will contact ECOG and tell us about your decision.

If your specimens were already sent from the repository and are being used for a project when you withdraw your consent, your specimens and accompanying data will still be used for that approved project. Once you choose to end your participation, no further specimens or related information will be sent to researchers from the repository for any new research projects.

Specimens will NOT be returned to you.

Voluntary Participation

The choice to participate in the optional laboratory research projects or to allow your specimens to be stored for future research is completely up to you. **No matter what you decide to do, your decision will not affect your medical care.** You can participate in the treatment part of the study without participating in these research projects.

Please read the research study descriptions below, review the questions carefully and circle “Yes” or “No”. If you circle “Yes”, you are indicating you understand:

- Coded information collected from your medical records may be given to researchers to perform these studies.
- The research results from your specimens will not be given to you or your doctor, they will not be placed in your medical record and they will not affect your medical care.
- Your specimens may be used in genetic research.
- The risks associated with allowing your specimens to be used in research, including the possible risks associated with genetic research.
- You will not receive any payment for the use of your specimens for these projects. You or your insurance will not be billed for any of these research tests.
- That at any time, you can end your participation in the projects and any remaining specimens or information will not be used for new research.

If you do not agree with any of the statements above, indicate “No” to ALL the questions below.

If you have any questions, please talk to your doctor or nurse, or call the institution’s Patient Advocate at 906-225-3183.

LABORATORY RESEARCH STUDIES

We would like to have samples of your blood, tumor and, if available, frozen tumor tissue, for additional laboratory research studies. The tissue will have been collected at the time of your original biopsy or surgery. Another procedure will not be done to collect this tissue.

If you agree to provide blood, about 3-4 tablespoons, will be collected before you start treatment, after you finish the chemotherapy part of the study (week 13) and on week 25. If you are on ARM B, another blood sample will be collected 3 months after you finish taking the bevacizumab.

These specimens will be tested to learn more about how your cancer works and how your cells may respond to the therapy. Some of the tests that will be done may include genetic tests to learn about how your body processes the treatment drugs and causes of any side effects that you may experience.

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>

For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Your signature below means that you have freely agreed to participate in this investigational study.

Patient's Signature

Date

Signature of person conducting

Date

Informed consent discussion

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the patient indicated, and that any questions about this information have been answered.

Investigator's Signature

Date

Your signature below means that you do not wish to participate in this investigational study.

Patient's Signature

Date

Signature of person conducting
Informed consent discussion

Date

Investigator's Signature

Date

IRB approved Addendum#8 – 08/11/2010
IRB approved Addendum#9 – 10/13/2010

E1505 Study Plan

Between 6 to 12 weeks after surgery to remove the lung cancer, you and your study doctor will decide on 1 of 4 chemotherapy options. (All are given in a vein, intravenously, commonly referred to as IV.)

1) Cisplatin and Vinorelbine

Vinorelbine 30 mg/m² IV push days 1 and 8

Cisplatin 75 mg/m² IV over 1 hour day 1

2) Cisplatin and Docetaxel

Docetaxel 75 mg/m² IV over 1 hour day 1

Cisplatin 75 mg/m² IV over 1 hour day 1

3) Cisplatin and Gemcitabine

Gemcitabine 1200 mg/m² IV over 30 minutes days 1 and 8

Cisplatin 75 mg/m² IV over 1 hour day 1

4) Cisplatin and Pemetrexed

Pemetrexed 500 mg/m² IV over 10 minutes a day

Cisplatin 75mg/M² IV over 1 hour day 1

In all cases, the chemotherapy regimen (described above) will be repeated every 3 weeks (21 days) for 4 times (that is, you will get chemotherapy 4 times with regimen 2 and 4, but 8 times with regimens 1 and 3, since you will also receive chemotherapy on day 8 with those regimens). In all cases, the cisplatin will be given after the other chemotherapy drug.

RANDOMIZE

You will be assigned to Arm A or Arm B. Neither you nor your doctor will decide which arm you will be assigned. You have an equal chance of being in Arm A or Arm B.

ARM A

Chemotherapy as above for 4 cycles

VS.

ARM B

Chemotherapy as above for 4 cycles

Plus

Bevacizumab 15 mg/kg IV every 3 weeks for 1 year*



Follow for progression and survival



Follow for progression and survival

* Bevacizumab will be given on day 1 of each 3-week cycle of chemotherapy for a total of four cycles, either immediately before or just after the chemotherapy, and will then continue to receive it for up to one year, until disease progression, or complications from treatment. The initial dose will be administered over 90 minutes. If you do not experience any side effects, the next dose will be administered over 60 minutes. Again, if no side effects occur, the third and all remaining doses will be administered over 30 minutes.