UNIVERSITY OF PENNSYLVANIA RESEARCH SUBJECT COMBINED INFORMED CONSENT FORM AND HIPPA AUTHORIZATION

Protocol Title:	A Phase II, Single-Arm Study Of Carboplatin, Weekly Taxane, And Ramucirumab In Advanced Non-Squamous Non-Small Cell Lung Cancer (NSCLC) After Progressive Disease On Maintenance Pemetrexed And/Or Pembrolizumab
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Study Summary

You are being invited to participate in a research study. Your participation is voluntary. Before agreeing to join the study, you should completely understand the requirements and risks of the study. Feel free to ask the study team any questions you have about the study. If, at any time, you have questions about your rights as a research participant, or simply want to speak to someone not on the study team, please contact the University of Pennsylvania Institutional Review Board at (215) 898-2614.

You are being invited to participate because you have non-small cell lung cancer (NSCLC) which came back after you were first treated. The purpose of this study is to determine if the combination of three anti-cancer drugs carboplatin, paclitaxel, and ramucirumab, is helpful in shrinking tumors or delaying tumor growth in participants like you. This study will also assess whether it is safe to combine these drugs. Your participation in this study may or may not benefit you, however, it may help other patients with this disease in the future.

Your participation in this study will be up to about 3 years, including around 1 year of treatment depending on how well you tolerate the treatment and how your cancer responds to the study therapy.

Most of the required tests and procedures are part of the normal medical care that you would receive even if you were not in the Study. Tests and procedures needed before you begin

treatment that are specific to the study include: electrocardiograms (also known as ECG or EKG), pregnancy testing, and urine samples.

All three study drugs are approved by the Food and Drug Administration (FDA) for treatment of cancer, but using them together to treat NSCLC after the disease has progressed has not been tested before. This is a brief list of the most common side effects seen in another research study using the same combination of drugs: fatigue, numbness and tingling in the hands or feet, and low platelet count which can increase your risk of bleeding and bruising. Rare, yet serious and possibly fatal side effects have also been recorded in subjects taking these drugs.

Other treatment options may be available to you. These could include treatment of your symptoms, without any effect on your disease and/or treatment with currently approved drugs such as ramucirumab with docetaxel. Ask your study doctor or regular doctor about alternate treatments available for your condition, and any known risks related to these treatments.

Please note that there are other factors to consider before agreeing to participate, such as additional procedures, use of your personal information, costs, and other possible risks not discussed here. If you do decide to participate, you are free to stop participating at any time for any reason.

Main Consent

Why am I being asked to volunteer?

You are being asked to participate in this research study because you have non-small cell lung cancer (NSCLC) that has come back after initial chemotherapy. Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, your clinical care will not be affected.

Before agreeing to participate in this research study, it is important that you read the following explanation of the proposed procedures and how long you will be in the study. This document describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time.

Your doctor may be an investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

Please take time to read the following information carefully. You may wish to discuss it with your family, friends, and your personal doctor (family doctor or primary care doctor). If you have any questions, you may ask your study doctor and/or the research team for more information. Take time to decide whether or not you wish to take part. If you decide to participate, you will be asked to sign this form.

If you decide to participate, you can change your mind at any time and withdraw from the study without giving a reason and without any impact to your subsequent care.

What is the purpose of this research study?

This research study involves treatment with carboplatin, paclitaxel, and ramucirumab. All of these drugs are approved for use in humans by the Food and Drug Administration (FDA) and have been given as treatment for NSCLC. Carboplatin and paclitaxel are chemotherapeutic IV agents that directly stop the growth of cancer cells. Ramucirumab blocks the growth of blood vessels that feed cancer cells. carboplatin and paclitaxel are commonly given as initial treatment for NSCLC that has spread beyond the lungs into other areas of the body, but are not used as often for treatment after disease has gotten worse (progressed) out of concern for more side effects such as low white blood cell counts which may increase your risk of infection, fatigue, numbness and tingling in the hands or feet from damage to the nerves, low platelet count which may increase your risk of bleeding and bruising, decreased appetite, constipation and high blood pressure.. Because of this we are using lower doses of these three drugs than those given as initial (first line) therapy. Ramucirumab plus docetaxel is FDA approved in the treatment of patients with advanced NSCLC that has progressed after patients received treatment with a platinum anti-cancer-drug (cisplatin, carboplatin, oxaliplatin), but this study does not include docetaxel. The combination of carboplatin, taxane (drugs such as paclitaxel and docetaxel) and ramucirumab has been given safely in the first line treatment of advanced NSCLC, but not tested as part of treatment after disease has progressed, which is one of the reasons for this study. The most common side effects observed in the study of this combination as first line therapy at a higher dose were fatigue, peripheral nerve damage, nausea, nose bleeds and muscle pain.

Eligible patients have done well on carboplatin and pemetrexed plus pembrolizumab as first-line therapy, and then had disease progression after receiving pemetrexed with pembrolizumab as maintenance therapy. These patients have not yet received therapy that blocks the growth of blood vessels, like ramucirumab, and since they have already received pembrolizumab, which helps the body's immune system, they may not respond to additional immunotherapy.

Combinations of anti-cancer drugs with platinum-based chemotherapy (carboplatin or cisplatin) are thought to be very effective in lung cancer and it might be helpful to use this type of therapy again for patients who received it initially and did well.

The purpose of the study is to find the answers to these research questions:

- Is carboplatin, paclitaxel and ramucirumab safe to give in combination after initial carboplatin based therapy?
- For subjects who did well initially on platinum-based therapy, is a second course of platinum-based beneficial?

Description of study

There are generally 3 phases in testing of new treatments. During the early phases (phases 1 and 2), researchers figure out whether a new treatment is safe, what its side effects are, and the best dose of the new treatment. They also make sure that the treatment has some benefit, such as slowing tumor growth. In the later phase (phase 3), researchers study whether the treatment works better than the current standard therapy.

This is a phase 2 open-label, multiple-dose, single-arm study.

- "Open-label" means that both you and your study doctor know what test drug you are receiving.

- "Multiple-dose" means that each participant will receive more than one dose of chemotherapy unless there are complications after the first dose.
- "Single-arm" means that all patients will receive the same therapy (carboplatin, paclitaxel, and ramucirumab). There are no placebos.

How many people will be in the study?
Overall, 49 patients will be treated in this study.

Who is sponsoring this study?

Dr. Corey Langer, the Principal Investigator, is also the sponsor (entity responsible for the design, conduct and regulatory oversight of the study). Eli Lilly and Company, the manufacturer of ramucirumab, will be providing the drug during this research study. Your study doctor and the University of Pennsylvania will receive payments to cover some of the research costs such as the collection and reporting of study information. Carboplatin, paclitaxel (sb- and nab-paclitaxel) are FDA approved and part of routine care. The cost for these drugs will be billed to your insurance company.

How long will I be in the study?

The exact length of time you will remain on the study will depend on how you tolerate the treatment and how your cancer responds to the study therapy. You will receive four to six 21-day cycles of carboplatin plus paclitaxel plus ramucirumab, If your cancer does not progress during this part of the treatment and you do not have severe side effects, you will receive additional treatment with 21-day cycles of ramucirumab plus paclitaxel. This treatment will continue until your cancer progresses or you have severe side effect. After you finish treatment, we will follow you for about 2 years.

What am I being asked to do?

If you meet all of the criteria to participate in the study, you will receive four to six 21-day cycles of carboplatin plus paclitaxel plus ramucirumab, depending on what your study doctor recommends. If your cancer does not progress during this part of the treatment (called "re-induction") and you do not have severe side effects, you will receive additional treatment (called "maintenance") with 21-day cycles of ramucirumab plus paclitaxel. Maintenance therapy will continue until your cancer progresses or you have severe side effects. About 30 days after you receive the last dose of study treatment, you will have an End of Treatment visit. After that, we will follow you for about 2 years either during your regular clinic visits, by telephone or by email about every six (6) months or we will check your medical record until the end of the study.

The office visits, tests and procedures are described in more detail below.

Screening Procedures: These procedures are done to evaluate your cancer, overall health, and eligibility. Most of the exams and procedures conducted during screening are part of your routine clinical care and would be done even if you did not choose to participate in the study; however, some are for research purposes only.

If you have had some of these tests/procedures recently, they may not need to be repeated. These tests and procedures need to be done within 4 weeks before you receive your first dose of study drug, unless otherwise indicated.

- Review of your medical history including any medications that you are taking or recently stopped taking, and any medical problems you have;
- Physical exam, including height, weight and vital signs);
- A review of how well you are able to get around and perform everyday activities (performance status);
- Blood sample (about 2 teaspoons) will be drawn to test blood cell counts, blood chemistry to test your kidney and liver function and the minerals in your blood, thyroid function tests to see how your thyroid is working and how fast your blood clots;
- Computed tomography (CT) or magnetic resonance imaging (MRI) scan to measure your cancer;
- MRI scan of your brain if you have had cancer in your brain or spinal cord (central nervous system) or if you have symptoms that suggest that you could have this cancer in your central nervous system.

The following procedures would not typically be done as a part of your standard of care treatment:

- Electrocardiogram (ECG) tests your heart rhythm;
- Pregnancy blood test for women of childbearing potential;
- A urine sample will be collected for urinalysis in order to check for infection or kidney problems.

Procedures associated with the administration of the study drug(s)

When you have been found eligible to enter this study, and you agree to participate, you will be scheduled to receive study drugs. You will see the study team and have exams, tests, and procedures to evaluate your health and to have a baseline before you receive study treatment. At each study visit, you will be asked how you are feeling, if you have had any side effects, if you have had any medical procedures, and about any medications you are taking. It is important that you check with your study doctor before starting any new medications. Taking other drugs (including alcohol, over-the-counter medications, herbal preparations, illegal drugs, or nutritional supplements) may cause additional side effects or even life-threatening reactions when combined with the drugs being used in this study. If you experience side effects, changes in your health and/or changes in medications, please contact your study doctor or a study team member.

Study treatment is given in 3-week (21 day) cycles, however, it could take longer if any of the planned study drugs are delayed. If the study drug is delayed, certain procedures may also be delayed since they are scheduled according to when you receive the drug.

Part 1: Re-induction

In the first part of the study, called re-induction, you will receive four to six 21-day cycles of ramucirumab plus paclitaxel plus carboplatin, depending on what your study doctor recommends. On Day 1, you will receive premedication to prevent or reduce side effects related to the chemotherapy drugs, followed by treatment with carboplatin plus paclitaxel plus ramucirumab. This clinic visit will last about 6 hours. On Day 8, you will receive

premedication followed by paclitaxel only. You will have labs drawn on Day 15, but you will not have an office visit on that day.

The premedication drugs are given by mouth or through a needle into a vein in your arm (IV) approximately 30 to 60 minutes before the study drugs. The premedication drugs would be used even if you were not participating in a research study. Your study doctor and team will tell which premedications will be used.

Re-Induction Procedures				
Tests/Procedures:	Day 1	Day 8	Day 15	Every 6 weeks
Physical exam	X			
Vital signs, weight	X	X		
MD or NP study visit	X	X		
Review of medications and side effects	X	X		
Blood tests	X	X	X	
Urine sample	X			
CT or MRI scan				X
Protocol Treatment:				
Premedications	X	X		
Ramucirumab infusion	X			
Paclitaxel infusion	X	X		
Carboplatin infusion	X			

Day 1 of each cycle:

- Physical exam, vital signs, and weight
- Review of any medications that you are taking or recently stopped taking, and any side effects
- A review of how well you are able to get around and perform everyday activities (performance status)
- A blood sample (about 2 teaspoons) will be drawn to test blood cell counts, blood chemistry, thyroid function tests to see how your thyroid is working and how fast your blood clots
- A urine sample (about ½ cup) will be analyzed for protein in the urine
- Premedications, by mouth or IV, about 30 to 60 minutes prior to chemotherapy infusion
- Ramucirumab infusion over 60 minutes
- Paclitaxel infusion over 30 or 60 minutes depending on the formulation chosen by your doctor
- Carboplatin infusion over 30 minutes

Day 8 of each cycle:

- Vital signs and weight
- Review of any medications that you are taking or recently stopped taking, and any side effects

- A blood sample (about 1 teaspoon) will be drawn to test blood cell counts, and blood chemistry
- Premedications, by mouth or IV, about 30 to 60 minutes prior to paclitaxel infusion
- Paclitaxel infusion over 30 or 60 minutes

Day 15 of each cycle:

- A blood sample (about 1 teaspoon) will be drawn to test blood cell counts, and blood chemistry (no office visit is needed)

Every 6 weeks you will have a computed tomography (CT) or magnetic resonance imaging (MRI) scan to measure your cancer

If your cancer does not progress and you do not have severe side effects, you will continue to the second part of the study, called maintenance, and you will receive 21-day cycles of ramucirumab plus paclitaxel until your cancer progresses or you have severe side effects.

Part 2: Maintenance

You will receive additional treatment (called "maintenance") with 21-day cycles of ramucirumab plus paclitaxel. On Day 1 you will receive premedication to prevent or reduce side effects related to the chemotherapy drugs, followed by treatment with ramucirumab plus paclitaxel. On Day 8 you will receive premedication followed by paclitaxel only.

The premedication drugs are given by mouth or through a needle into a vein in your arm (IV) approximately 30 to 60 minutes before the study drugs. The premedication drugs would be used even if you were not participating in a research study. Your study doctor and team will tell which premedications will be used.

Maintenance therapy will continue until your cancer progresses or you have severe side effects.

Maintenance Procedures				
Tests/Procedures:	Day 1	Day 8	Day 15	Every 9 weeks
Physical Exam, Performance Status	X			
Vital signs, weight	X	X		
MD or NP study visit	X	X		
Review of medications and side effects	X	X		
Blood tests	X	X	X	
Urine sample	X			
CT or MRI scan	X			X
Protocol Treatment:				
Premedications	X	X		
Ramucirumab infusion	X			
Paclitaxel infusion	X	X		

Day 1 of each cycle:

- Physical exam
- Vital signs and weight
- Review of any medications that you are taking or recently stopped taking, and any side effects
- A review of how well you are able to get around and perform everyday activities (performance status)
- A blood sample (about 2 teaspoons) will be drawn to test blood cell counts, blood chemistry, thyroid function tests to see how your thyroid is working and how fast your blood clots
- A urine sample (about ½ cup) will be analyzed for protein in the urine
- Premedications, by mouth or IV, about 30 to 60 minutes prior to chemotherapy infusion
- Ramucirumab infusion over 60 minutes
- Paclitaxel infusion over 30 or 60 minutes

Day 8 of each cycle:

- MD or NP study visit
- Vital signs and weight
- Review of any medications that you are taking or recently stopped taking, and any side effects
- A blood sample (about 1 teaspoon) will be drawn to test blood cell counts, and blood chemistry
- Premedications by mouth or IV about 30 to 60 minutes prior to paclitaxel infusion
- Paclitaxel infusion over 30 or 60 minutes

Day 15 of each cycle:

- A blood sample (about 1 teaspoon) will be drawn to test blood cell counts, and blood chemistry (no office visit is needed)

Every 9 weeks you will have a computed tomography (CT) or magnetic resonance imaging (MRI) scan to measure your cancer

End of Study Visit

Approximately 30 days after your last dose of study drug, you will come in for an end of study visit. The following tests and procedures will be performed:

- Physical exam
- Vital signs and weight
- Review of any medications that you are taking or recently stopped taking, and any side effects
- A review of how well you are able to get around and perform everyday activities (performance status)
- A blood sample (about 1 teaspoon) will be drawn to test blood cell counts, and blood chemistry

- Computed tomography (CT) or magnetic resonance imaging (MRI) scan to measure your cancer (this would not be done as part of your standard of care treatment)

Follow-up Contact

We will follow you for about 2 years either during your regular clinic visits, by telephone or by email about every six (6) months, or we will check your medical record until the end of the study.

What are the possible risks or discomforts?

Carboplatin:

The most common side effects of carboplatin are:

- Low red blood cell counts (anemia), which may cause tiredness, or may require blood transfusions.
- Low white blood cell counts may increase your risk of infection. This sometimes requires a medication to increase the number of white blood cells.
- Low platelet count may increase your risk of bleeding and bruising. This sometimes requires a platelet transfusion.
- Allergic reaction during the infusion. This can happen at any time during the treatment course.
- Damage to the nerves in your hands and feet sometimes causing numbness, tingling and pain.
- Nausea, diarrhea and weight loss

Serious side effects of carboplatin include:

- An allergic reaction during the infusion of carboplatin resulting in difficulty breathing.
- A higher risk of infection if white blood cells decrease severely.
- Rare risk of kidney damage

Paclitaxel (sb-paclitaxel or nab-paclitaxel):

The most common side effects of paclitaxel are:

- Low red blood cell counts (anemia), which may cause tiredness, or may require blood transfusions.
- Low white blood cell counts may increase your risk of infection. This sometimes requires a medication to increase the number of white blood cells.
- Low platelet count may increase your risk of bleeding and bruising. This sometimes requires a platelet transfusion.
- Change in heart rhythm that can be dangerous (nab-paclitaxel).
- High blood pressure.
- Damage to the nerves in your hands and feet sometimes causing numbness, tingling and pain.
- Nausea, vomiting, diarrhea, abdominal pain.
- Hair loss.

- Allergic reaction during the infusion. This is more frequent with sb-paclitaxel.
- Irritation at the injection site on the skin.

Serious side effects of paclitaxel include:

- Severe allergic reaction during the time of infusion (more common with sb-paclitaxel).
    - **Nab-paclitaxel (*Abraxane*) contains a protein derived from human blood, which carries a theoretical risk of viral transfer.*

Ramucirumab:

The most common side effects of ramucirumab are:

- Low white blood cell counts may increase your risk of infection. This sometimes requires a medication to increase the number of white blood cells.
- High blood pressure.
- Increased risk of bleeding and nose bleeds.
- Increased risk of clotting
- Fatigue.
- Diarrhea.

Serious, but rare, side effects of ramucirumab include:

- Bleeding in the gastrointestinal tract (stomach or intestine).
- A hole in the gastrointestinal tract.
- Blood clot in the arteries that can cause less blood to reach vital organs. This could result in death.
- High blood pressure, which could lead to symptoms or complications such as stroke or heart attack.

Tell your doctor if you have any side effect that bothers you or that does not go away.

Combination Effects:

What are the side effects of the combination of carboplatin + paclitaxel + ramucirumab:

- Low white blood cell counts may increase your risk of infection (15%*)
- Fatigue (approximately 50%)
- Numbness and tingling in the hands or feet from damage to the nerves (approximately 30%)
- Low platelet count may increase your risk of bleeding and bruising (20%)
- Decreased appetite (approximately 17%)
- Constipation (approximately 12%)
- High blood pressure (approximately 12%)

Percentages are based on a clinical trial using carboplatin, paclitaxel and ramucirumab at higher doses than are being used in this trial. Forty (40) patients were enrolled to this first line treatment study for NSCLC. They were treated with carboplatin (AUC 6), paclitaxel (200 mg/m2 IV), and ramucirumab (10 mg/kg IV) on Day 1 every 21 days (1 cycle). Patients continued this combination for 6 cycles. If they did not experience disease progression or significant toxicity then they continued only ramucirumab every 21 days until disease progression or significant toxicity.

Reproductive Risks

Female Participants

If you are able to have children, you must agree to use a medically accepted form of birth control (such as diaphragm or cervical cap with spermicide, condom, an intra-uterine device (IUD), or surgical sterility [tubal ligation or a partner with a vasectomy]) during the course of this study and for at least 3 months after your final study treatment, OR you must agree to completely abstain from intercourse for two weeks before you begin study treatment, during participation in this study, and for 3 months after your final study treatment. Your study doctor must approve your form of birth control. Ask your study doctor about the contraceptive methods that are available and which might be the best for you.

Even when you use an approved contraceptive method, there is always a small risk that you could still become pregnant. If you do become pregnant during the course of this study, you must discontinue study treatment, tell the investigator immediately, and consult an obstetrician or maternal-fetal specialist.

Male Participants:

If your spouse or partner has the potential to become pregnant, you must agree to a medically accepted form of birth control during the course of this study and for at least 3 months after your final study treatment. While you are taking these drugs, you should not father a child. If your partner does become pregnant, you must inform your study doctor immediately

You and your partner must use medically accepted form of birth control methods including condoms, diaphragms or cervical cap with spermicide, an intra-uterine device (IUD), or surgical sterility [vasectomy or a partner that has undergone a tubal ligation]), OR you must agree to completely abstain from intercourse for two weeks before you begin study treatment, during participation in this study, and for 3 months after your final study treatment. Your study doctor must approve your form of birth control. Ask your study doctor about the contraceptive methods that are available and which might be the best for you.

You should also inform your partner of the potential harm to an unborn child. She should know that if a pregnancy should occur, you will need to report it to the study doctor immediately, and she should promptly notify her doctor.

For more information about risks and side effects, please ask your study doctor.

Other Study Related Risks

Risks of Blood Draws

Blood samples will be taken for tests throughout this study. The amount of blood to be taken by these blood draws is very small, and may be associated with discomfort and/or bruising at the site where the needle is inserted; and less commonly, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding, and infection.

Risk of IV

An IV line will be used to administer study drug through a vein in your arm. The use of an IV line may cause discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely infection, nausea, and lightheadedness.

Risk of Electrocardiogram

The electrocardiogram (ECG or EKG) is a noninvasive test used to measure the electrical activity of the heart. By positioning leads (electrical sensing devices) on the body in set locations, information about many heart conditions can be learned by looking for patterns on the ECG. You may develop a slight rash or skin irritation in the locations where these leads (electrodes) were placed on your skin. There are no other known risks associated with an ECG.

Radiology Tests

During your participation in this study, you may undergo routine radiology tests to assess your disease. These include Computer Tomography (CT) scans. These types of scans and the frequency at which they are being performed are considered part of your routine cancer care. Each of these procedures has risks associated with it, and you should talk to your study doctor or the person doing these procedures about the risks before they start.

CT scans involve exposure to radiation. The amount of radiation exposure you may receive from these routine tests will not adversely affect the treatment of your disease. At exposure levels much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the exposure level you will receive, it is very likely that you will see no effects at all.

CT Scans: A computed tomography (CT) scan is an imaging method that uses x-rays to create cross sectional pictures of the body. You will be asked to lie on a narrow table that slides into the center of the CT scanner. Depending on the study being done, you may need to lie on your stomach, back, or side. Once you are inside the scanner, the machine's x-ray beam rotates around you. It is important to remain still during the exam, because movement causes blurred images. You may be told to hold your breath for short periods of time. The scans take about 15 minutes or less to complete.

- Pregnant women will be excluded from having a CT exam due to the possibility of unforeseen side effects to the unborn baby. All female subjects that are capable of becoming pregnant must take a pregnancy test within 24 hours of the CT exam to rule out pregnancy. CT scans produce x-rays, if there is a chance of pregnancy you should inform the study staff, the CT exam should be postponed.
- It is important to inform your study doctor if you have had an allergic reaction to IV contrast material in the past, or if you have an allergy to iodine. Most CT contrast reactions (approximately 95%) are mild to moderate in degree and most resolve themselves without treatment. However, life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. People with heart disease, kidney disease or allergies are more likely to have a more severe reaction to contrast agents. If you have a history of kidney disease, allergies or heart disease, please inform the study staff. Likely contrast reactions include feelings of overall warmth (especially in the bladder area after injection), a metallic taste during the injection, and warmth, burning sensation, or momentary pain during the contrast injection at the injection site. Less likely contrast reactions include nausea, vomiting, headache, hives, and itching. Rare but serious contrast reactions include faster than normal heart rate (tachycardia), high blood pressure (hypertension), low blood pressure (hypotension), heart attack, kidney failure, fluid in the lungs (pulmonary edema), serious allergic reaction, and death. There is also a risk that multiple needle sticks will be necessary to ensure proper intravenous line placement. There may be a small amount of pain or bruising with the

placement of the intravenous catheter (IV) and a small risk of infection at the injection site.

Magnetic Resonance Imaging (MRI): You may have an MRI scan performed only if you cannot have a computed tomography scan (for example, you have a documented allergy to IV and oral contrast that is used for CT scan). The known risks associated with an MRI are minimal. The procedure uses radio waves and a magnetic field to take pictures. The greatest risk of having an MRI is the chance of metal objects flying through the air toward the magnet and hitting you. To reduce this risk, all people involved with the study are instructed to remove all metal from their clothing and all metal objects from their pocket. You must tell your study doctor if you have any metal plates or clips in your body. No metal objects are allowed to be brought into the magnet room at any time. Metal objects inside your body can affect the test results and could lead to injury. Because the magnetic field of the MRI scanner attracts metal, these studies will not be performed on anyone with a pacemaker or any nonremovable metallic foreign objects in their body. If you have any such object on your body, you will not receive the scan. You may feel claustrophobic (fear of being closed in) or anxious. You may experience some discomfort and fatigue from lying in a confined space. There are no known effects from exposure to the magnetic fields.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

Taking part in this study may or may not make your health better. However, while you may not benefit personally, the knowledge learned from your participation in this research study may benefit other patients in the future. It is possible that your disease and/or health may worsen as a result of participating in this study.

What other choices do I have if I do not participate?

Your participation in this study is entirely voluntary. Other possible options include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study
- Not receiving treatment at this time.
- Getting comfort care, also called palliative care, only. This type of care aims to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible. Regardless, you will receive ‘standard of care’ or normal treatment of symptoms while you are on this study.
- Talk to your doctor about your choices before you decide if you will take part in this study.

Will I be paid for being in this study?

You will not be paid for taking part in this study. Will I have to pay for anything?

Carboplatin, paclitaxel (sb- and nab-paclitaxel) are FDA approved and part of routine care. The cost for these drugs will be billed to your insurance company. Eli Lilly and Company will supply ramucirumab at no charge while you take part in this study. The cost of administration for all drugs may be the responsibility of you and/or your insurance provider.

You are still responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Website at: http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Website.

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.

What happens if I am injured from being in the study?

If you have a medical emergency during your participation on this study, you should go to the nearest emergency room. You should contact Dr. Corey Langer, the Principal Investigator, or the Emergency Contact listed on page one of this form.

You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

The University of Pennsylvania will offer you the care needed to treat side effects and/or injuries that occur while you are taking part in this research. We will bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of these costs. There are no plans for the University of Pennsylvania to pay you or give you other compensation for any injury. You may receive bills for injuries/illnesses that occur during your participation in this study. If you have questions about these bills and whether or not they are covered by the research study, please bring copies of these bills to a member of the study team and they will be able to answer your questions.

Financial compensation for such things as traveling, parking, lost wages, disability or discomfort due to injury is not available.

You will not lose any of your legal rights when you sign this form.

When is the Study over? Can I leave the Study before it ends?

You may continue to receive study drug indefinitely, or may stop receiving study drug earlier if your cancer gets worse or if you experience unacceptable side effects. You will then move in

to study follow-up, after which your participation will be complete.

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first. You can also choose to leave the study at any time without giving a reason. It is important to tell the doctor if you are thinking about stopping so any risks for the treatments that you received can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

If new information becomes available that might affect your choice to stay in the study, your study doctor will notify you as soon as possible.

This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Principal Investigator feels it is necessary for your health or safety;
- You have not followed study instructions;
- The Principal Investigator, the Institutional Review Board, or other oversight organization has decided to stop the study;
- It is determined that you are no longer benefiting from the study therapy;
- For reasons not known at this time.

If you are removed from the research study, your study doctor will explain to you why you were removed. Leaving or being removed from the study will not affect your future medical care.

Who can see or use my information? How will my personal information be protected?

If you decide to participate in this study, the study doctor and staff will collect medical and personal information about you as part of completing the study. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Please refer to the information below which explains in more detail how your personal information will be protected. If you do not want to allow these uses, you should not participate in this study. Information identifying you will be kept confidential as described below.

<u>What personal health information is collected and used in this study, and might also be disclosed?</u>

The following personal health information will be collected and used for the purposes of this study.

- Name, address, telephone number, gender, date of birth
- The history and diagnosis of your disease
- Specific information about the therapy you received, including previous treatment(s) you may have had

- Information about other medical conditions that may affect your care
- Medical data including laboratory test results, health status, ECGs, CTs, MRIs, pathology results, etc.
- Information on side effects (adverse events) you may experience, and how these were treated
- Long-term information about your general health status and the status of your disease. This may include information from other health care providers.
- Data that may be related to tissue samples that may be collected from you
- Numbers or codes that will identify you, such as your medical record number
- Information related to study visits and other tests/procedures performed while you are participating on this study.

While collected as part of this study by your study doctor and study team, identifying information (including your name, address, telephone number, medical record number, or any number/codes that will directly identify you) will be kept as confidential as possible and will not be routinely disclosed outside of the University of Pennsylvania. Personal health information that could be used to identify you will not be sent to Eli Lilly and Company, and/or their designated representatives.

You will be assigned a unique subject registration number upon enrollment. This number and your initials will be used to identify you throughout the course of this study so that your identity is protected. The key to this code (which links your name back to the personal health information collected during this study) will be stored in a secure area and only the University of Pennsylvania study team will have access to this code.

However, some of the study data (such as your date of birth) could be used in combination with other information, in order to identify you. If you have questions about the specific information that will be released, you should ask your study doctor.

Why is my personal health information being used?

Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study, and will be used to conduct and oversee this research study, and to help guide your medical care.

Which personnel may use or disclose my personal health information?

The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide care as part of this study or as part of your routine care, to manage accounting or billing matters, etc.). This includes members of the Institutional Review Board (IRB), an Ethics Committee at the University of Pennsylvania who are responsible for reviewing and overseeing research studies to ensure that they are safe and being well managed.

- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of UPHS and the School of Medicine, might receive my personal health information?

As part of the study, the Principal Investigator, the study team and others listed above, may disclose your study-related records, including the results of the research study tests and procedures, to those listed below. This study data may be processed and transmitted using secure computer systems. In all disclosures outside of the University of Pennsylvania Health System and School of Medicine, you will not be identified by name, medical record number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. In records and information disclosed outside of the University of Pennsylvania Health System and School of Medicine, you will be assigned a unique code number.

Your original medical records also may be reviewed by the sponsor of this study or its designated representatives, the Institutional Review Board overseeing this study, and any of the regulatory or safety oversight organizations outlined below. They may review these records for the purpose of checking data collected for the study, to make sure the study is being done properly, and to analyze the results of the study.

Individuals or organizations responsible for overseeing and administering the study:

- Eli Lilly and Company (the funding sponsor of this study) and their designated representatives.
- The University of Pennsylvania
- Regulatory and safety oversight organizations
- The U.S. Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives, including international agencies
- Public Health agencies and other government agencies (including non-U.S.) as authorized or required by law

Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by United States federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire. If you sign this form, we will collect your health information until the end of the research study. We may collect some information from your medical records even after you finish taking part in this study or after your death. We will keep all of the information forever in case we need to look at it again. We will protect this information and keep it confidential.

Your information will be held in a research database. However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other

than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

The data from this study may be published or used for teaching purposes; however you will not be personally identified in any publication. Your identity will remain confidential unless disclosure is required by law.
There are no research specimens (e.g. blood, tumor tissue) being collected during this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

Can I change my mind?

You have the right to withdraw your permission for the use of your personal health information, but if you do so, you must stop taking part in this study. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research study and no new information will be collected. However, even if you do withdraw your permission to use the data about you, we are required by the FDA and other national regulatory authorities to record anything that relates to the safety of the investigational drug under study.

Will I be able to access my research records?

You have the right to see and get a copy of your medical records kept by the University of Pennsylvania. However, you will not be able to review or receive some of your records related to the study until after the entire study has been completed. When the study is over, you may write to the study doctor to ask to see or copy all of your medical information that was collected during the study. You also have the right to say how your medical information may be used, and to have any incorrect data about yourself updated or corrected.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

By signing this document you are permitting the UPHS and the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

What may happen to my information collected on this study?

Your identifiable information will be stored for future research purposes. The goal of this data sharing is to make more research possible that may improve people's health. Future researchers may receive information that could identify you. Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.
- Your information may be stored and used for future research purposes for an indefinite amount of time.
- The following identifiers will be retained with your information: your unique subject registration number.
- We may share your identifiable information with other research, academic, and medical institutions, other researchers, drug and device companies, biotechnology companies and others.

There is a risk of breach of confidentiality (unintentional release of your information). We will do our best to make sure that this doesn't happen. However, we cannot guarantee total privacy. We will protect your confidentiality during storage and sharing by keeping only your unique subject registration number with your data.

You will likely not directly benefit from future research with your information. Research with your identifiable information may help others by improving our understanding of health and disease, improving health care and making safer or more effective medical therapies, and developing new scientific knowledge.

If you have questions about the storage of your information, or have changed your mind, you can contact the Principal Investigator at the phone number listed on the first page of this consent form. If you change your mind and let the Principal Investigator know that you have changed your mind, no new research uses of your identifiable information or specimens will occur from that point forward, but your specimens will continue to be used in studies that started before you changed your mind. If your information and specimens have already been given to another researcher, person, institution, or company, it may not be possible to limit their continued and new uses.

What is an Electronic Medical Record and/or a Clinical Trial Management System?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (for example, laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study

team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (such as your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (for example, laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (for example health insurance company, disability provider, etc.).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study, you should speak with Dr. Corey Langer, the Principal Investigator at the numbers listed on the first page of this consent form.

If you have any questions about your rights as a research subject, you may contact the Institutional Review Board at the University of Pennsylvania with any questions, concerns or complaints by calling (215) 898-2614.

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). You may also visit the NCI website 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.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, the study has been explained to you, your questions have been answered, you have had time to make your decision, and you have decided to volunteer to participate. You have been given the names of study staff that you can contact if you need assistance or if you have any additional questions or concerns. You agree to follow all of the instructions of your study doctor to the best of your ability, and report any changes in your health that may occur during the study.

Your signature also means that you are permitting the University of Pennsylvania and the School of Medicine to use your personal health information collected for research purposes within our institution. You are also allowing the University of Pennsylvania and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

You agree that your primary care physician can be informed about your participation in this clinical trial.

A copy of this consent form and HIPAA Authorization will be given to you.

_____	_____	_____
Name of Subject (Please Print)	Signature of Subject	Date

_____	_____	_____
Name of Person Obtaining Consent (Please Print)	Signature	Date