Study Title: A randomized Pilot Study of Evolocumab plus Nivolumab/ipilimumab in Treatment-Naïve Patients with metastatic NSCLC

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DUKE UNIVERSITY HEALTH SYSTEM

Consent To Participate In A Research Study

A Randomized Pilot Study to Investigate the Safety and Immunologic Impact of Evolocumab when Given in Combination with Ipilimumab and Nivolumab in Treatment-Naïve Patients with Metastatic Non-Small Cell Lung Cancer

CONCISE SUMMARY
This is a research study to find out the safety and tolerability of combining the drug evolo cumab with standard immunotherapy in people with advanced lung cancer (a type called non-small cell lung cancer).

Nivolumab (Opdivo™) and ipilimumab (Yervoy™) are immunotherapy-type drugs which are approved for the treatment of advanced lung cancer that has expression of PD-L1 greater than or equal to 1%. Evolocumab is being combined with nivolumab and ipilimumab to see if it will improve the anti-tumor capabilities of the immunotherapy. Adding evolocumab to the combination of nivolumab and ipilimumab has not been tested in people before and is considered investigational.

To objectively assess the effects of adding evolocumab, the study is randomized. This means that half of the subjects will receive evolocumab plus nivolumab and ipilimumab and half will receive only nivolumab and ipilimumab as determined by chance. After six weeks, there will be an option to add evolocumab for subjects who did not initially receive it and whose disease did not worsen.

Nivolumab and ipilimumab are given by injection into a vein (intravenous) and evolocumab is given by injection under the skin. You will need to come to Duke every 2 weeks to receive study drugs and continue to take study drugs as long as you are benefitting to a maximum of 2 years. The study will also require a sample of your tumor tissue before you receive study drugs and this may require a new research tumor biopsy. A second research tumor biopsy would be done while you are receiving study drugs.

There are risks to this study that are described in this document. Some risks include diarrhea, fatigue, itching, and rash. If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you have or are suspected to have advanced non-small cell lung cancer and have not received treatment. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

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Dr. Scott Antonia will conduct the study and it is funded by the Department of Defense (DOD). The DOD will pay Duke University to perform this research, and these funds may reimburse part of Dr. Antonia's salary.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Scott Antonia or a member of his study team will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this research study is to investigate the safety and the anti-tumor effects of adding the drug evolocumab to the approved immunotherapy regimen of nivolumab and ipilimumab. It will also investigate in the laboratory how the body's immune system is affected by this approach.

Researchers have found that sometimes the body's own immune system may slow down or control cancer growth. Sometimes though, this natural immune system response stops, and the cancer is not killed by your own immune system. In some patients, cancer cells and immune cells start to give off signals that stop the body's immune system from killing the cancer. Drugs such as nivolumab and ipilimumab were developed to block a specific protein (PD-1) that acts as one of these stop signals, but the tumors develop ways to circumvent blockage. Emerging science suggests that drugs such as evolocumab could synergise (work together) with nivolumab and ipilimumab and produce improved tumor shrinkage.

The combination of nivolumab (Opdivo™) and ipilimumab (Yervoy™) has been approved in the U.S. for the treatment of advanced lung cancer with a PD-L1 expression greater than or equal to 1%. Treatment of advanced lung cancer with PD-L1 expression less than 1% with ipilimumab and nivolumab is not FDA approved and is considered investigational. Evolocumab (Repatha™) has been approved in the U.S. for the treatment of people with high cholesterol who have not responded adequately to other cholesterol-lowering drugs and diet changes, and in patients with established cardiovascular disease to reduce the risk of myocardial infarction (heart attack), stroke and coronary revascularization (restoration of blood flow to the heart). The use of evolocumab to treat cancer is considered investigational.

The use of nivolumab and ipilimumab combined with evolocumab in this study is considered investigational. This combination of study drugs has not been tested before in people. The word "investigational" means the study drugs are still being tested in research studies and are not approved by the U.S. Food and Drug Administration (FDA).

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HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 38 people will take part in this research study.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. The study doctor and study staff will explain the study and answer any questions you may have. Nothing related to the study will take place before you have signed and dated the form. You may ask any questions you might have and discuss the study with anyone you would like. You may take as much time as you need to think about your options and decide whether or not you want to be in this study.

You are being seen at Duke because you have (or are suspected of having) lung cancer and it is felt that immunotherapy may be an effective approach for your cancer. This study will combine a standard approved immunotherapy combination of two drugs (nivolumab and ipilimumab) with the drug evolocumab. One cycle of study drugs is six weeks long. You would continue to receive your study drugs for up to two years as long as you are benefitting.

Nivolumab is given by injection into a vein (intravenously) every 2 weeks. Evolocumab will be given every 2 weeks by injection under the skin (subcutaneously) and this would be done when you are in the treatment room to receive your nivolumab. Ipilimumab is given every six weeks intravenously.

In order to objectively evaluate the effects of adding evolocumab, the study is randomized. You would be assigned by chance to receive either:

1) Nivolumab + ipilimumab + evolocumab
2) Nivolumab + ipilimumab

There is a 50/50 chance that you would be assigned to either group 1 or group 2. After six weeks, subjects in group 2 may receive evolocumab if their disease has not worsened.

A safety evaluation of the combination of the study drugs will be done initially in the first six subjects who enroll in the study in each group. If no safety issues occur, the study will continue to enroll after a 30 day pause.

This research study requires a fresh tumor tissue sample before study drugs are administered for studies in the laboratory. You will be required to undergo a research tumor tissue biopsy in order to be in this study. If you have not yet had a biopsy for diagnosis, when the biopsy is done extra tissue will be removed for the purposes of the research study. A second research tumor biopsy will be done while you are receiving study drugs. The type of biopsy that will be done will depend on where you have accessible tumor located. The types of biopsies and their associated potential risks are described in the

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Risks section of this consent form. A research tumor biopsy would only be done if it medically feasible and safe.

The study is divided into phases: **Screening, Study Drug Administration, End of Study , and Follow-up .** The schedule of visits and tests to be performed are summarized in a table that follows.

Screening Visit:

There are certain tests and procedures that must be done to help determine if you are eligible to take part in this study. These tests / procedures are part of the Screening Visit.

You will have the following done at this visit:

- **Medical History**: You will be asked about your medical and surgical history, including your smoking history. You will be asked about your overall health and well-being and how well you are able to perform normal daily activities
- **Physical exam**: A complete physical exam will be done which will include obtaining your height and weight and your vital signs (blood pressure, temperature and pulse)
- **Performance Status:** Assessment of your overall well-being and how well you are able to perform normal daily activities
- **Routine laboratory blood and urine tests will be done**, including specific blood tests to see how well your thyroid gland and your kidneys are working. About 15 ml blood (about 3 teaspoons) will be collected each time you have routine laboratory blood work.
- **Pregnancy test**: If you are a woman who could possibly become pregnant, a urine pregnancy test will be done no more than 48 hours before any study drugs or procedures
- **Electrocardiogram**: An electrocardiogram (ECG) which records the electrical activity of your heart
- **Tumor Imaging: A** computed tomography (CT) scan of your chest and abdomen will be done to find the location of and to measure the size of your tumor(s). A CT scan or MRI scan of your brain will be done to determine if your disease has spread to your brain. Your study doctor will decide which brain imaging study you will have.

- **Research Tumor biopsy**: As previously described, in order to be in this study, a sample of your tumor tissue collected before you receive study drugs is needed so that the study doctors may study the tumor tissue in the laboratory. This will require a new tumor biopsy. Your study doctor will discuss this with you in detail.

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- If the sample from the fresh tumor biopsy is inadequate for the purposes of the protocol, a stored tumor tissue sample, if available (called an archival sample), may be used.

A biopsy is a procedure performed to **remove tissue or cells from the body for examination under a microscope**. There are several different biopsy procedures which are generally determined by the site of the biopsy where tumor is located. Your doctors will explain the biopsy procedure to you and you should feel free to ask any questions you may have. A portion of this tissue will be used for the study. Regardless of the site of the tumor biopsy, a tumor biopsy would only be done if it is determined to be medically feasible and safe. No biopsies that entail significant risk would be done. The types of biopsies and their potential risks are described in the Risks section of this consent form. Your tissue samples will be tested at Duke for the purposes of the research study (as described above) and any remaining tissue may be stored in a secure facility for up to 15 years.A portion of your tumor tissue biopsies will be sent to Xilis, Inc. Researchers are studying the use of MicroOrganosphere (MOS) tumor organoids as a way of evaluating response to study drugs in the laboratory. A laboratory model of a patient's tumor is created to use as a way of screening drugs for efficacy against a particular tumor. This research study will determine the feasibility of generating MOS from your tumor tissue and then using it as a study drug screen.

You will not receive any payment or have any ownership or rights from any discoveries or commercial development that may result from research done on your samples. The results of research, including your donated materials, may be patentable or have commercial value. There are no plans to provide financial compensation to you should this occur.

Study Drug Administration Phase

The following tests and procedures will be done on day 1 of each cycle while you are receiving study drugs.

- **Physical exam**: A complete physical exam will be done which will include obtaining your height and weight and your vital signs (blood pressure, temperature and pulse)
- **Performance Status:** Assessment of your overall well-being and how well you are able to perform normal daily activities
- **Review of side effects:** You will be asked about how you are feeling and if you are experiencing any symptoms or side effects
- **Routine laboratory blood and urine tests will be done**, including specific blood tests to see how well your thyroid gland and your kidneys are working. About 15 ml blood (about 3 teaspoons) will be collected each time you have routine laboratory blood work.
- **Research blood test collection**. Blood will be collected for research blood tests on Cycle 1, days 1 and 15, and the first tumor imaging after study drugs started. A sample would also be collected

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at the time of disease progression. Approximately 34 ml or slightly less than 3 tablespoons will be collected each time.

- **Pregnancy test**: If you are a woman of child-bearing potential, a urine pregnancy test will be done within 72 hours of first receiving study drugs.
- **Tumor Imaging:** CT scans will be repeated every six weeks while you are on study drugs for 48 weeks. Thereafter, scans will be done every 12 weeks.
- **Research Tumor biopsy**: A second research tumor biopsy will be done on day 29 of cycle 1.

End of Study (EOS) Visit (Follow-up #1): The End of Study visit will occur approximately 35 days after your last doses of study drugs. If you stop the study drugs because your disease gets worse, you have serious side effects to the study drugs, or you just decide to no longer take part in the study, you will have these tests / procedures done approximately 35 days after your last doses of study drugs.

You will have the following tests / procedures:

- **Physical exam** including your weight and vital signs (blood pressure, temperature and pulse)
- **Performance Status:** Assessment of your overall well-being and how well you are able to perform normal daily activities
- **Side Effect Review:** You will be asked about how you are feeling and if you are experiencing any symptoms or side effects
- **Routine laboratory blood tests:** including specific blood tests to see how well your kidneys are working. About 20 ml blood (about 4 teaspoons) will be collected each time you have routine laboratory blood work.

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	Screen	Day 1 Cycle 1	Day 15 Cycle 1	Day 29 Cycle 1	Day 1 Cycles 2+	Day 15 Cycles 2+	Day 29 Cycles 2+	Tumor Assessment	EOT f/u visit #1	F/U Visit #2	Progression	Long Term f/u
Evaluations												
Informed consent	X											
Medical history	X											
Physical exam	X	X	X	X	X	X			X	X		
Height,weight & vital signs	X	X	X	X	X	X						
Performance status	X	X	X	X	X	X			X	X		
Concomitant medications	X	X	X	X	X	X			X	X		
Side effect review	X	X	X	X	X	X			X	X		
Laboratory Tests												
Routine blood tests for safety	X	X	X	X	X	X	X		X	X		
Thyroid blood test	X	X			X							
Urinalysis	X											
Pregnancy Test		X			X							
ECG	X											
Disease Evaluations												
MRI	X							X				
CT Scan	X							X*				
Survival Status	X								X	X		X
Tumor tissue collection	X			X								
Research Blood Test collection		X	X		X						X	
Treatment												
Nivolumab		X	X	X	X	X	X					
Evolocumab		X	X	X	X	X	X					
Ipillumab		X			X							

*CT scans will be repeated every 6 weeks for 48 weeks and then every 12 weeks

Follow-Up Phase: Once you have completed the study drug administration period, you will begin the Follow Up portion of the study. There will be two follow-up visits. You will be asked to return 35 days after your last dose of study drugs (visit #1). The End of Study visit may coincide with the first follow-up visit. The second follow-up visit will occur at approximately 80 days after the first follow-up visit. The following will be done:

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- **Physical exam**: A complete physical exam will be done which will include obtaining your height and weight and your vital signs (blood pressure, temperature and pulse)
- **Performance Status:** Assessment of your overall well-being and how well you are able to perform normal daily activities
- **Side Effect Review:** You will be asked about how you are feeling and if you are experiencing any symptoms or side effects
- **Routine laboratory blood and urine tests will be done**, including specific blood tests to see how well your kidneys are working. About 20 ml blood (about 4 teaspoons) will be collected each time you have routine laboratory blood work.

Long Term: For up to 2 years or until the study is closed (whichever comes first), we will follow your vital status by reviewing available medical records, public records or phone calls to you about every 12 weeks.

Collection of an Additional Tumor Tissue Sample from a Stored Tumor Specimen (Archival)
If your new biopsy lacks adequate tissue, and you have a stored (archival) tumor tissue sample from a previous biopsy, we would like your permission to collect a tumor tissue sample from the previously stored sample for research laboratory studies at Duke. Please signify your preference below.

_____I agree to the collection and storage at Duke of tumor tissue from a stored tumor specimen for research analysis.

_____I do not agree to the collection and storage at Duke of tumor tissue from a stored tumor specimen for research analysis.

_____
Subject's initials

Treatment Beyond Progression
Accumulating evidence indicates a small number of subjects treated with immunotherapy (drugs such as nivolumab and ipilimumab), may derive clinical benefit from continuing immunotherapy despite initial growth of their tumor(s). Therefore, if you are eligible, you may continue to receive study drugs. Your doctors would discuss this with you in the event that it would arise. The following criteria would be required to continue study drugs beyond progression:

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- Your doctor has assessed the potential clinical benefit of continuing the study drugs and discussed the potential benefits and risks of doing so
- You do not have rapid tumor growth or clinical deterioration
- The symptoms you are having from your disease are stable
- You can tolerate continuing study drugs

HOW LONG WILL I BE IN THIS STUDY?

You may continue to receive study drugs up to two years as long as you are benefitting. After you complete all phases of the study you will be followed for two years.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?

As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provided, if you choose.

During the study, the study drugs may cause you to experience discomforts and risks (side effects). The combination of nivolumab and ipilimumab is an approved standard treatment for lung cancer and the potential side effects of the combination will be reviewed with you by your doctor and the treatment room staff.

Because nivolumab and ipilimumab have never been combined before with evolocumab, and that there may be risks, discomforts, drug interactions or side effects that are not yet known. Side effects from the addition of evolocumab to ipilimumab and nivolumab may prevent you from receiving standard of care therapies for your lung cancer which include ipilimumab and nivolumab without evolocumab. Your study doctor and your study team will be watching you carefully for side effects. The side effects may vary from person to person. You may experience some, none or all of these side effects and they may be mild to severe and, in some cases, life-threatening. Your study doctor may order other medications to treat side effects and to make you feel more comfortable. For more information about risks and side effects, please ask your study doctor.

POTENTIAL RISKS OF EVOLOCUMAB:

Evolocumab is administered as a single injection under the skin (thigh, abdomen or upper arm) at a dose of 140 milligrams. **Evolocumab** may cause some, all or none of the side-effects listed below.

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Common side effects of evolocumab occurring in greater than or equal to 3%-5% of patients treated include: (greater than or equal to 3-5 people out of 100)

- Runny or stuffy nose (nasopharyngitis) (symptoms like a common cold)
- Sore throat
- Upper respiratory tract infection
- Influenza or influenza-like symptoms
- Back pain
- Injection site reactions (redness, pain and bruising)
- Allergic reactions (rash and hives), which can be serious. Symptoms of an allergic reaction include trouble breathing or swallowing, raised bumps (hives), rash or itching, swelling of the face, lip, tongue, throat or arms.
- High blood sugar levels
- Redness, pain or bruising at the injection site. Reactions at or near the area of the injection may occur. In addition to redness, pain and bruising, other symptoms may include tenderness, warmth, swelling, itching and or infection at the injection site(s).

It is possible that evolocumab could decrease your cholesterol to very low levels in your blood. It is unknown if very low levels of cholesterol are safe. There are people with a very rare inherited condition who lack the PCSK9 protein (the protein that the study drug blocks) and have very low cholesterol levels in their blood. These people appear to be healthy.

Tumor Biopsy:
The biopsy site will depend on where you have accessible tumor located. Your study doctor will discuss this and the specific risks of the biopsy with you at the time of the procedure.

If you have tumor located in the skin or in a superficial lymph node, the sample is obtained by inserting a needle through a small incision in the skin and extracting tissue into a long hollow tube to extract a sample of tissue under local anesthetic (a **core needle biopsy**). Risks of a tumor core needle biopsy are localized bleeding at the needle injection site or from the surgical incision, pain, bruising, inflammation, swelling, and infection. The bleeding may cause discomfort and bruising. In rare circumstances (less than 1%), this bleeding may be severe enough to require further care. If you have a history of excessive bleeding, or if you are receiving medication that might increase your risk of bleeding (such as aspirin or blood thinners), you must notify the physician before the procedure. Infection of the surgical site may require treatment with antibiotics.

A **lung biopsy** may be either a needle biopsy (directly inserted into the lung using CT scan guidance) or involve a procedure called a bronchoscopy. These procedures are described below in detail. Risks of a

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lung biopsy include bleeding, infection, coughing up blood and collapsed lung (called a pneumothorax). A collapsed lung can be life-threatening or fatal.

Depending on the site, the biopsy procedure may use local anesthetics (numbing medicine) or sedatives to reduce the discomfort or pain. All medicines have the possible risk of allergic reaction. Please advise your study doctor if you have ever had an allergic reaction to latex, numbing medicines, or any other anesthetic.

Any complications arising from the biopsy may be treated with observation, additional medications, or in some cases, additional surgery. The study doctor will discuss the specific risks of the biopsy with you at the time of the procedure.

During the healing process, you will be asked to keep the biopsy site clean and dry, and to apply antibiotic ointment. Infection rarely occurs and is largely prevented by the use of an aseptic (or sterile) biopsy technique and proper wound care. If infection does occur, you will be instructed to keep the wound clean and to apply warm, wet compresses for 15 minutes, three times a day, until the infection subsides. If the infection persists, antibiotics may be prescribed.

Bronchoscopy with tumor tissue biopsy

A bronchoscopy is done as an outpatient by a doctor who specializes in these procedures and usually involves moderate sedation and numbing of the area around the nose or throat. You will be awake the whole time. In order to perform a bronchoscopy with a tumor tissue biopsy, the doctor feeds the biopsy instruments (a thin tube) into the lungs through the bronchoscope. This way, the doctor can obtain a piece of tissue for biopsy immediately upon seeing a suspicious area, without having to perform another procedure.

Bronchoscopies are done routinely and are safe for most people. However, like all medical procedures, there are some risks involved. You may have sensations of pressure or mild tugging as the tube moves through the airway. Many patients experience a feeling of suffocation when the tube is in the throat, but there is no risk of suffocation. After a bronchoscopy with biopsy, you may have a sore throat and/or nose and minimal discomfort that should clear up within a few days.

Risks may include bleeding from the site of the biopsy, but this occurs in less than 1% of patients. Other rare complications include lung collapse (less than 2%), lung infection (less than 1%), and temporary hoarseness. You will be monitored closely for several hours after the procedure to make sure no complications arise. There is also a very small risk of abnormal heart rhythm (arrhythmia) and low blood oxygen (hypoxemia).

Percutaneous CT guided lung biopsy:

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This procedure is most commonly done by a radiologist who specializes in these procedures. Using the CT scanner, a needle will be inserted through the chest wall skin and into the lung to the appropriate area. After the procedure, you will be observed for a period of time for complications.

While a CT scan-guided lung biopsy is less invasive than other procedures used to obtain tissue from the lungs, it is not without some risk. Very few patients may experience an air leak due to the needle causing a hole in the lung. This usually heals on its own and will not require further procedures. But if the air leak is big enough, or you experience symptoms due to the air leak, a tube may need to be inserted through the skin and chest wall to drain the air from your chest cavity. And because the procedure involves a needle going through the skin, there is a chance that infection can be introduced to the body, which could require treatment with antibiotics. There is a small chance for bleeding to occur during the procedure.

For Those of Reproductive Potential:

Reproductive Risks

For women: Pregnancy in women with cancer is associated with an increased risk of complications for mothers and babies, and pregnancy may affect the risk of disease progression. The drugs used in this study may have risks that are not yet known to a developing pregnancy or breastfeeding infant. For these reasons, women who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in this study.

If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a urine pregnancy test will be performed, and it must be negative in order to continue in the study. You will also have urine pregnancy tests at follow-up visits as described above, and these also must be negative.

You and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study and for 7 months after the last dose of study drugs, or two methods of contraception for the same length of time. One of these must be a barrier method (condom, diaphragm, cervical cap) PLUS a spermicide. The other must be one of the following:

- Partner vasectomy
- Bilateral tubal ligation
- Intrauterine device (IUD)
- Hormonal methods (birth control pills, implants, injections, patches, vaginal rings)

If you are not currently using one of these methods, or if you are using a method which needs to be stopped prior to your surgery, Dr. Antonia will discuss options with you, given your medical condition, your personal preferences, and the level of effectiveness required by this study.

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Because no method of birth control is 100% effective, you should notify the study team immediately if you think there is any chance you could be pregnant, even if you have had a recent negative pregnancy test. If pregnancy is confirmed, the study drug(s) will be stopped, but Dr. Antonia will continue to follow you to collect information on your health during the pregnancy, and, if appropriate, the health of the baby.

For men: The effects of the study drugs on developing pregnancies that began while the father was taking the drugs are not known. If you have a partner who could possibly become pregnant (she has not completed menopause, or she has not had a hysterectomy and/or both tubes and/or both ovaries removed), you must agree to either abstain completely from vaginal intercourse for the duration of the study and for 7 months after the last dose of study drug, or use a condom with spermicide for the same length of time. This is true even if you have had a vasectomy, or your partner is using another method of birth control. If your partner is pregnant or breastfeeding, you must use a condom for all types of intercourse.

You should inform your partner about your participation in this study and the potential risks to a pregnancy. If she is not using another method of birth control, she should discuss options with her doctor. If she does become pregnant during the study, you should inform the study doctor immediately. He will ask her permission to collect information on her health during the pregnancy and, if appropriate, the health of the baby.

Risks of Drawing Blood:
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Drug and Food Interactions:
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

Radiation Risks:
You will have a number of CT scans and MRI scans that are part of the regular care for your condition and you would have them whether or not you participate in this research. These studies will not add to the risk due to participating in the research. However, if you have concerns about the total radiation exposure you will get, you should discuss them with your physician. The PET, CT or MRI scans are being done as part of your routine medical care for cancer and will be done whether you choose to participate in this study or not.

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Computed tomography (CT) scan: This is a radiology procedure which use X-rays (CT) to create pictures of the inside of your body. These pictures will allow your doctor to monitor your disease before, during, and after you receive your study drug and to see if the tumors change in size. A brain CT (or MRI) will also be required to check for any areas of disease in your brain.

MRI: Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body including medical implants, devices such as pacemakers and internal defibrillators, or certain dyes found in in tattoos. We will also keep the MR room locked so that no one carrying metal objects enters the room while you are in the MR machine.

If there is any question about potentially hazardous metal within the body, you will not undergo the MRI. This may exclude you from participation in this research study. The MRI involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the study. During the study, you can have voice contact and physical contact with someone in attendance if you desire. Let the study doctor know if you have a fear of enclosed spaces.

A rare but serious adverse reaction has been observed in patients that received a gadolinium-based contrast material during MRI examinations, a reaction called nephrogenic systemic fibrosis (NSF). Patients with kidney disease are at increased risk of developing NSF. NSF may cause skin thickening, joint pain and/or swelling. In rare cases NSF can lead to lung and heart problems and cause death. To minimize the likelihood that you will be affected, you will have a blood test to measure your kidney function. If your blood test is abnormal, you will not be permitted to receive gadolinium.

Radiation Exposure Risks:

Risks of Radiation from Imaging Tests

If you take part in this research, you may have one or more CT scans of your chest and abdomen (with or without the pelvis) and CT guided biopsies which use radiation (two maximum). To give you an idea about how much radiation you will get each time a CT guided biopsy is done, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year called the 'natural background'. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. The chart below the amount of time in the natural background that gives an amount of radiation that is about equal to the amount of radiation each time you have the test.

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A possible health problem seen with radiation exposure is the development of a second cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is also shown in the chart. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

Test	'Natural Background Time' Equivalent for Each Time This Test is Done	Extra Cancer Risk Each Time This Test is Done
CT Guided Biopsy	2 Years	Very Low
Chest/abdomen/pelvis CT	4 years	Low

You may have a number of CT scans that are part of the regular care for your condition, and you would have them whether or not you participate in this research. These studies will not add to the risk of the research. However, if you have concerns about the overall radiation exposure, you should discuss them with your physician.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, it is possible there may be direct medical benefit to you. However, this approach has not been tested in people with lung cancer before and it is not known if there will be any benefit. There is the possibility the study drugs, nivolumab and ipilimumab combined with evolocumab, may delay the growth of your cancer. However, no benefit to you can be guaranteed. We hope that in the future the information learned from this study will benefit other people with your condition.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?

You do not have to participate in this study to be treated for your cancer. The combination of nivolumab and ipilimumab has been approved by the FDA for advanced lung cancer and you can receive it outside of this research study. There may be other approved immunotherapy drugs as well. Other investigational studies with chemotherapy or new anticancer drugs may be available for your disease. Your study doctor is very willing to discuss the benefits, risks, and side effects of alternative treatments including the option of treating your symptoms only, with no further cancer therapy. If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease.

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Usually this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the Duke University Health System Institutional Review Board, the Duke Cancer Institute, the Duke Office of Audit, Risk and Compliance (OARC), and others as appropriate. Representatives of the U.S. Department of Defense (DOD) are also authorized to review your research record as needed. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests, x-rays, and/or procedures performed. Some of these tests, x-rays and/or procedures would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record. If serious adverse events arise, that data will be collected and reported to Amgen. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record.

The study results will be retained in your research record forever. Any research information in your medical record will also be kept indefinitely.

This information may be further disclosed by the sponsor (PI-Duke Cancer Institute) of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law

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designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS?

You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Dr. Antonia. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

Please talk with the Dr. Antonia and/or the study team about the specific services and procedures that will be covered by the study and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he or she can help find a resolution.

Amgen is the manufacturer of evolocumab and will providing the study drug free of charge. The costs of nivolumab and ipilimumab will be charged to your insurance.

WHAT ABOUT COMPENSATION?

You will not be paid to take part in this research study.

The use of your data and samples may result in commercial profit. You will not be compensated for the use of your data and samples.

WHAT ABOUT RESEARCH RELATED INJURIES?

Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, your Duke physicians, the study funding source, the Department of Defense, or the study drug provider, Amgen, Inc. to provide monetary compensation or free medical care to you in the event of a study-related injury.

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For questions about the study or research-related injury, contact Dr. Scott Antonia at (919) 681-9509 during regular business hours and at (919) 970-7292 after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Antonia in writing and let him know that you are withdrawing from the study. His mailing address is:

Scott Antonia, MD, PhD
Box 3198
Duke University Medical Center
Durham, North Carolina 27710

Dr. Antonia or your study doctor may also ask you to return for a checkup before you stop your study drug and to complete the tests that would ordinarily occur when a person completes the study.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. Regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

For withdrawal of tumor tissue samples: Any left-over tissue (coded) may be stored in a secure location for up to 15 years after the end of the study. If you want to withdraw your samples from storage, you must contact your study doctor, Dr. Scott Antonia, in writing and let him know you are withdrawing your permission for your samples to be stored. His mailing address is stated on the preceding page.

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

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WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Scott Antonia at (919) 681-9509 during regular business hours and at (919) 970-6868 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____
Printed Name of Subject

_____ _____ _____
Signature of Subject Date Time

_____
Printed Name of Person Obtaining Consent

_____ _____ _____
Signature of Person Obtaining Consent Date Time