

**Protocol H3E-US-S130: Randomized, Open-Label, Phase
3 Study of Pemetrexed plus Carboplatin Followed by
Maintenance Pemetrexed versus Paclitaxel plus
Carboplatin and Bevacizumab Followed by Maintenance
Bevacizumab in Patients with Advanced Non-Small Cell
Lung Cancer of Nonsquamous Histology**

Protocol No.: H3E-US-S130

Participant Information and Consent Form

Sponsor: Lilly USA, LLC

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Introduction

You are being asked to take part voluntarily in a research study of a study drug known as pemetrexed. Your participation in this study is expected to last up to 3 years. Up to 360 patients will be participating in this study.

Lilly USA, LLC is sponsoring this study. Before agreeing to participate (take part) in this research study, it is important that you read and understand this form. It describes the purpose, procedures, benefits, risks and discomforts and precautions of the study. It also describes the alternative (other) procedures that are available to you and your right to withdraw (leave) from the study at any time. If you participate, you will receive a copy of this signed and dated form to keep for your records.

Purpose of the Study

The main purpose (reason) of your participation in this study is to help answer the following research question:

- How treatment with pemetrexed plus carboplatin followed by more pemetrexed compares to treatment with paclitaxel plus carboplatin plus bevacizumab followed by more bevacizumab

All of these drugs are approved by the US Food and Drug Administration. Although pemetrexed in combination with carboplatin is being tested as a treatment for a condition that you have, there is no guarantee that you will receive any medical benefit.

Requirements to Participate

The Principal Investigator, Dr. Deveras, and/or your study doctor
_____ and/or study coordinator have discussed with
you the requirements for participation in this study.

You cannot participate in this study if:

- You have a central nervous system (CNS) disease other than stable, treated brain metastases
- You have another serious disorder or illness

- You have had a serious heart condition within the last 6 months
- You have a history of high blood pressure crisis or brain problems caused by high blood pressure
- You have a history of spitting up blood or bloody mucous that totals a half a teaspoonful or more within the last 3 months
- You are allergic to paclitaxel, bevacizumab, carboplatin, or pemetrexed
- You have had serious inflammatory problems with your stomach, or intestines, especially if you needed antibiotics or were put in the hospital
- You have history of a stroke within the last 6 months
- You have a medical need to take full-dose warfarin or equivalent (similar)
- You are unable to stop treatment with aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) for a 5 to 8 day period during the administration of chemotherapy. (Patients are allowed to be on aspirin during the administration of chemotherapy if the dosage is 1.3g/day or less)
- You have clinically significant third-space fluid collections, which is an abnormal collection of fluid resulting from excess fluid production or decreased absorption of fluid.
- You have had recent surgery (7 days for minor, 1 month for major, and 6 months for neurosurgery)
- You have non-healing ulcers
- You are pregnant or breast-feeding
- You are unable to take a corticosteroid
- You have a history of a bleeding or clotting condition
- You have a history of another cancer other than superficial basal cell and superficial squamous skin cell or superficial carcinoma of the cervix within the last 5 years
- You have a history of being unable to take vitamins
- You have previously received treatment with paclitaxel, carboplatin, pemetrexed, or bevacizumab
- You have received treatment with an experimental drug in the last 30 days

- You have serious peripheral vascular disease or an episode of arterial thrombosis in the last 6 months
- You have uncontrolled high blood pressure

Birth Control

You cannot be in this study if you are a woman and you are not willing to avoid or do not commit to avoid becoming pregnant during this study.

If you are a woman of childbearing potential and have begun experiencing menses (period), a blood pregnancy test will be done to determine if you are pregnant before any study medication can be administered (given). You must have a negative blood pregnancy test at the Baseline Visit. You cannot take part in this study if you are pregnant or become pregnant. You cannot breast feed while participating in this study. If you become pregnant or suspect you are pregnant during this study, you must tell your study doctor immediately.

Females who are sexually active and/or are capable of becoming pregnant are asked to follow an acceptable method of birth control such as: abstinence (not having sex), birth control pills, Norplant System, Depo-Provera, IUD or double barrier method (such as a condom and foam) throughout the study and for 3 months after the study is completed.

If you are a man and you have a partner of childbearing potential, you should inform her of your participation in this clinical study and commit to reducing the risk of your female partner becoming pregnant during the study. You must agree to use highly effective methods of birth control during treatment with the study drugs and for an additional 3 months after stopping the study. Some methods of birth control might be less effective due to a possible interaction with pemetrexed, carboplatin, bevacizumab, and/or paclitaxel. Highly effective methods of birth control include abstinence (not having sex), vasectomy, or a condom in combination with hormonal birth control or barrier methods used by the woman. Men should not donate sperm while they are in this study.

It is important that you are completely truthful with the doctor and staff about your past medical history as well as any symptoms experienced during the study. It may be harmful to you or to other people who may take the drug if you are not truthful with the doctor and staff. You should not participate in this study if you do not meet all qualifications.

Study Procedures

Please read the page(s), called Study Procedures (Attachment 1). This will give you information about what taking part in the study will mean to you, such as, how often you have to come to see the doctor, how long each visit may take, how much blood will be taken, and when tests and procedures will be performed.

After determining whether you are eligible to take part in this study and after obtaining your consent to take part, you will be "randomized". Randomized means that the treatment that you receive will be chosen by chance, much like flipping a coin. This study has two treatment groups (or arms). You will either receive pemetrexed plus carboplatin, followed by pemetrexed or you will receive paclitaxel plus carboplatin plus bevacizumab, followed by bevacizumab. The chance of getting into each of the arms is 1 in 2 (50%). You will know which medication you are receiving.

The treatment is made up of two parts: the Induction Phase and the Maintenance Phase. **The Induction Phase** is standard in the chemotherapy regimens (or arms) offered in clinical practice for non-squamous, non-small cell lung cancer (NSCLC). In this phase, the combination of carboplatin, paclitaxel, and bevacizumab is approved. Pemetrexed and cisplatin is another approved combination for NSCLC. In this trial, cisplatin is replaced with carboplatin in Arm A.

In addition, a **Maintenance Phase** has been included for the two arms of the study. The maintenance chemotherapy is pemetrexed in Arm A and bevacizumab in Arm B.

The length of the maintenance phase is dependent on several things. The treatment may last as long as your tumor does not grow or progress, you wish to remain in the trial, and there are no safety concerns or side effects that require you or your doctor to stop the chemotherapy.

Blood and urine tests, MRIs, CT Scans, and/or X-rays will be done if you decide to participate in this study. The schedule of study procedures is outlined in detail in the *Patient Information and Consent form Attachment I* in this consent.

Following the study, your study doctor or study coordinator may contact you to obtain information regarding the status of your health and quality of life.

You are responsible for keeping your appointments and following the instructions given by your study doctor.

Blood Tests

You will have a number of blood tests. A needle will be placed inside a vein in your arm. For most people, needle punctures for blood draws do not cause any bad problems. However, sometimes they may cause bleeding, bruising, discomfort, infections, and/or pain where you had the blood drawn. Having your blood drawn may also cause you to feel nauseated and/or lightheaded. Fainting and infection are rare occurrences.

The sample(s) of blood will be collected by the following tests:

- Chemistry test (to make sure the contents in your blood are within normal range),
- Pregnancy test – females only (to see whether you are pregnant or not),
- Liver function test (to make sure your liver is working right)
- Complete Blood Count (to make sure the levels of the different kinds of blood cells in your blood are normal),
- Clotting test (to test the ability of your blood to clot properly)

You will also be asked to provide urine samples at certain times during the study. These will be used to measure how well your kidneys are working and if there are any side effects.

These tests will help the study doctor decide if you can take part in this study and to watch your health during the study.

All samples of blood collected for specified laboratory tests will be destroyed within 60 days of confirmation of the test results, unless laws, regulations, or international laboratory certification standards require a longer retention period. This confirmation will either occur immediately after initial testing, or may require that samples be held to be retested at a defined later point in time. The samples will not be sold to another company however, and will not be used for research for a different disease.

Collection of Samples for Translational Research

You will have the chance to voluntarily take part in a sub-study that involves genetic research. Your participation in this sub-study is only limited to the requirement that you allow your blood to be collected for research.

The purpose of this sub-study is to conduct research in order to provide information on how patients respond to or tolerate treatment with medications that you are taking during the main study. The research from this sub-study will involve looking at your genetic material (known as DNA).

Pieces of DNA (also known as genes) cause traits, such as eye or hair color, to pass from parents to their children. Genes also direct cells in your body to make proteins, many of which appear in your blood. Genes affect the way our bodies respond to medicines. For example, whether you are likely to benefit from a drug.

If you agree to be part of this research, a sample of your blood will be collected during the Baseline Visit (about 20mL of blood, which is a little more than 1 tablespoon). If the sample cannot be used, you may be asked to provide another sample. The sample will be collected by inserting a needle into your vein. The procedure will take about 5 – 10 minutes and could be taken at the same time you get blood drawn for the previous blood tests.

Your samples will be analyzed (examined) and stored at a laboratory that is a part of Lilly USA, LLC located in the United States. The researchers will measure the levels of genes and proteins in the sample. They will also look for any differences in the DNA that occur naturally between people that may give clues as to why people respond to drugs differently.

The results of this research will be matched with some of your medical information obtained during the clinical study (for example, how you responded to treatment, or if you had any side effects). By matching these results, doctors will gain a better understanding of which genes and proteins may be important in how patients respond to and tolerate treatment and which patients with your condition may benefit the most from treatments in the future.

Your blood cells will not be made to grow indefinitely. Your entire genetic makeup will not be determined from your sample. The sample will be stored until it is gone or for up to 5 years after the study is done. Any sample left after this time will be destroyed.

Your agreement to have your sample collected and stored for purposes described in this consent form is entirely voluntary. You may refuse to participate without penalty or loss of benefits to which you are otherwise entitled. If you choose to not participate, this will have no effect on your participation in the main study.

If you agree to participate, you will not have access to the results from the research on your sample(s). You will also not receive, either now or in the future, any compensation (payment), royalty, or any other financial benefit which might result from any product, procedure, or other item that may be developed from studying your sample or information, or data that is a result from such research.

Your study doctor will answer any questions that you may have about the procedures described in this sub-study.

(Please check one)

___ I **Agree** to take part in and have additional blood collected for the optional sub-study for genetic research.

___ I **DO NOT** agree to take part in and have additional blood collected for the optional sub-study for genetic research.

Participant's Signature: _____ Date: _____ Time: _____

Risks

There may be risks to you if you participate in this study.

As of August 31, 2009, about 27,342 patients had been enrolled in clinical studies around the world to receive pemetrexed (ALIMTA®, LY231514).

Risks and Discomforts that are part of taking Pemetrexed

Very common (may occur in 10 or more subjects [participants] in 100) side effects reported during clinical trials by patients taking pemetrexed with folic acid and vitamin B₁₂ supplementation, (a standard premedication prior to pemetrexed) include:

- A decrease in white blood cells. A decrease in white blood cells increases the chance of developing an infection.
- A decrease in red blood cells (anemia) can result in a loss of energy and feelings of being tired
- nausea
- vomiting,
- loss of appetite,
- diarrhea,
- inflamed mucous membranes (especially the lining of the mouth),
- skin rash (which may be itchy, or may progress to become serious),
- loss of energy and feelings of being tired.

Common (may occur in 1 to 9 subjects [participants] in 100) side effects include:

- decreased platelet counts (which may increase the chance of bruising and bleeding after injury),
- abdominal (stomach) pain,
- swelling (edema, usually of the limbs and face),
- decreased kidney function,
- increased activity of chemicals in the liver (inflammation),
- infections in general,
- itchiness,
- allergic reactions,
- skin reaction known as 'erythema multiforme' where itchy reddish purple patches may develop in the skin,
- fever including fever caused by a low count in white blood cells,
- tingling and/or weakness of the arms, hands, feet, and legs (neuropathy),
- hard or infrequent stools (constipation),
- pink eye (conjunctivitis),
- watery eyes,
- hair loss.

Uncommon (may occur in 1 of 9 subjects [participants] in 1000) side effects reported by those taking pemetrexed include:

- include irregular heart rate
- renal failure.
- In about 1% of patients a severe infection (sepsis) which in some cases was fatal occurred.

The side effects mentioned above relate to pemetrexed when taken alone with folic acid and vitamin B₁₂ supplementation. These side effects may also be anticipated when pemetrexed is used together with other chemotherapy drugs, but certain side effects may occur more frequently, such as:

- decreased platelet counts,
- constipation,
- hair loss,
- decreased kidney function,
- kidney failure,
- heartburn (dyspepsia),
- taste disturbance,
- dehydration,
- chest pain.

Other chemotherapy drugs and other forms of treatment such as radiation will also have their own, often unique, side effects which should be taken into account when considering the **likely effects** of the treatment as a whole. The **majority of these side effects** may be experienced by patients receiving most other chemotherapy drugs. Complications of some of the above side effects may lead to life-threatening events such as:

- infections,
- kidney failure,
- bleeding,
- possibly death.

Postmarketing Data

Rare (greater than or equal to 0.01% and less than 0.1% or greater than or equal to 1 out of 10,000 people and less than 1 out of 1000) side effects have been reported in patients taking pemetrexed:

- inflammation of the lining of the large bowel (colitis),
- pneumonia involving the connective tissue of the lung (interstitial pneumonitis),
- severe skin reactions reactions (bullous conditions, including Stevens-Johnsons syndrome)
- Toxic Epidermal Necrolysis which in some cases were fatal.

- Rare cases of severe skin reactions (radiation recall) in patients who had previously received radiation therapy have been reported.

Other Data

Studies in mice have shown that pemetrexed is harmful to the unborn fetuses of these mice. This means that pemetrexed may also be dangerous to the fetuses of mothers who are taking pemetrexed.

Risks and Discomforts that are part of taking Carboplatin

- As of February 2007, a few patients reported that carboplatin caused an allergic reaction, such as rash, high temperature or itching, or, more rarely, a more severe allergic reaction. If this happens to you, it is most likely that it will happen within minutes of you receiving carboplatin.
- Treatment with carboplatin may affect your blood cells, kidneys or liver.

You should check with your doctor immediately if you notice any unusual

- bruising,
- black, tarry stools,
- jaundice (condition in which the body fluids and tissues, particularly the skin and eyes, take on a yellowish color as a result of too much bilirubin)
- blood in your urine.

The following other side effects have been experienced by some patients receiving carboplatin:

- ringing in the ears or slight loss of hearing,
- feeling of numbness or tingling in the hands or feet,
- temporary loss or changes to eyesight,
- change in taste,
- tiredness,
- anorexia (loss of appetite),
- hair loss,
- fever and chills without evidence of infection,

- nausea and vomiting.

Complications of some of the above side effects may lead to life-threatening events and possibly death.

Risks and Discomforts that are part of taking Bevacizumab

As of January 2008, **very common side effects (reported in more than 10% {10 out of 100} of patients taking bevacizumab)** have included:

- high blood pressure,
- problems with wounds healing after surgery,
- feeling of numbness or tingling in the hands or feet,
- decreased number of cells in the blood (including white cells that help to fight against infections),
- decreased number of cells that help the blood to clot,
- lack of energy or tiredness,
- nausea and vomiting,
- pain,
- constipation,
- bleeding from the lower part of the large bowel,
- inflammation (redness and soreness) of the mouth,
- loss of appetite,
- nose bleed,
- fever,
- headache.

Common side effects (reported in between 1% and 9% [1 and 9 out of 100] of patients taking bevacizumab) have included:

- decreased number of cells in the blood (these include white cells which may occur with a fever and red cells),
- bleeding from the tumor,

- lack of energy,
- abdominal (stomach) pain,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- diarrhea, pain (including a headache),
- blood clots in the veins of the legs or difficulties in getting the blood to clot with bleeding,
- localized collection of pus,
- infection in the blood or bladder,
- reduced blood supply to the brain or stroke,
- blood clots in the arteries (which can lead to a stroke or heart attack),
- falling asleep or fainting,
- breathing difficulties,
- nose bleed,
- increased heart rate (pulse),
- protein in the urine,
- runny nose,
- dry skin (flaking and inflammation of the skin or change in skin color),
- change in the sense of taste,
- problems with producing tears in the eye.

Rare, (greater than or equal to 0.01% and less than 0.1% or greater than or equal to 1 out of 10,000 people and less than 1 out of 1000) side effects have been reported in patients taking Bevacizumab such side effects as:

- seizures (convulsions or fits),
- headache,
- confusion,
- changes in vision,

- abnormal tube-like connections between the windpipe and the passage to the stomach (esophagus) have occurred.
- Cases of osteonecrosis of the jaw (ONJ) which is damage to areas of the jaw bone due to poor blood supply to the jaw have been reported in cancer patients that have received bevacizumab treatment. Most of these patients had or were getting at the same time a type of drug given by I.V. (in the vein) called bisphosphonates. These drugs are used to treat bone loss.
- Bevacizumab treatment may increase your chances of developing osteonecrosis of the jaw.
- The possible risk should be considered when bevacizumab and bisphosphonates are given at the same time or in a set order. Your study doctor will discuss this with you.
- Your study doctor will also discuss with you if a dental exam or any dental work should be done before starting treatment with bevacizumab.
- If you have ever had or are now taking I. V. bisphosphonates, be sure to talk with your study doctor about the need for any invasive dental procedures. These should be avoided, if possible.

In addition, there have been very rare (**less than 0.01% or less than 1 out of 10,000 subjects (participants)**) reports of patients developing a hole in the septum of the nose (the structure which separates the nostrils).

Complications of some of the above side effects may lead to life-threatening events and possibly death.

Risks and Discomforts that are part of taking Paclitaxel

As of August 2005, the **most common side effects** (may occur in 10 or more subjects [participants] in 100) that are part of paclitaxel have included:

- temporary hair loss,
- nausea, vomiting,
- diarrhea,
- allergic reactions (such as skin rash, flushing, itching and other general infections),
- changes in heart beat rate or rhythm,

- high or low blood pressure,
- bleeding and blood disorders (which may make you slightly anemic or increase your risk of infection or make you bruise more easily).
- In addition, numbness and/or tingling in hands and/or feet,
- muscle and joint pain,
- soreness of the mouth and tongue,
- temporary changes to the nails and skin have occurred.
- Sometimes there has been pain, swelling and possibly skin peeling at the site of the injection and other skin disorders.
- Inflammation of a vein has occurred less commonly.
- Chest pain and/or shortness of breath may occur if you are also receiving other chemotherapy agents and/or radiotherapy.
- Bowel disorders, abdominal (stomach) pain,
- increased sweating and pain in the limbs have also been reported.

Rare, (greater than or equal to 0.01% and less than 0.1% or greater than or equal to 1 out of 10,000 people and less than 1 out of 1000) **side effects** that are part of taking paclitaxel have included:

- raised temperature,
- dehydration
- and swelling of the face/throat,
- wheezing,
- feeling faint and shortness of breath,
- chills and back pain associated with allergic reaction,
- pneumonia and other lung disorders,
- swelling and/or weakness in the hands and/or feet,
- serious abdominal pain,
- heart disorders have also been reported.

Very rare (less than 0.01% or less than 1 out of 10,000 subjects (participants) side effects that are part of taking paclitaxel have included:

- severe infections,
- disturbances to your sight and hearing,
- vertigo, dizziness,
- cough,
- severe allergic reactions (such as a rash that may affect limbs, hands, feet, and mouth),
- seizures (convulsions or fits),
- confusion and other effects on the brain,
- liver disorders,
- loss of appetite,
- constipation,
- headache,
- difficulty coordinating movement,
- hearing and/or balance effects,
- fast heart beat,
- weight loss (anorexia).

Complications of some of the above side effects may lead to life-threatening events and possibly death.

Risks and Discomforts that are part of taking Dexamethasone

As of September 2005, **common bad experiences** reported by those taking dexamethasone have included:

- edema (fluid retention),
- imbalances in the body's electrolytes (especially sodium and potassium),
- increased appetite,
- weight gain,

- nausea,
- flushing,
- bloating of the abdomen.

Less common bad experiences reported by those taking dexamethasone have included:

- mood changes (depression or abnormal feelings of well-being),
- muscle weakness,
- increased sweating,
- difficulty sleeping,
- increased blood sugar,
- other allergic reactions.
- Subjects (participants) who have heart disease may experience heart failure.
- Subjects (participants) with glaucoma (eye disease) may experience increased inner eye pressure.

Risks and Discomforts that are part of taking Folic Acid

As of August 2007, **very serious but rare allergic reactions** have been a result of taking folic acid. These reactions may include:

- a skin rash,
- swelling of the face, lips, tongue or throat,
- difficulty breathing or swallowing.

The following stomach problems have been **rarely reported**:

- nausea,
- loss of appetite,
- feeling of fullness and gas.

Risks and Discomforts that are part of taking Vitamin B-12

As of May 2008, **very serious but rare allergic reactions** have been a part of Vitamin B-12. You may experience some local discomfort from the injection.

Risks and Discomforts that are part of taking Diphenhydramine

As of October 2007, **serious but rare allergic reactions** that have been associated with diphenhydramine are::

- difficulty in breathing
- swelling of the face, neck, tongue, or throat.

Other **less serious side effects** have included:

- drowsiness,
- tiredness,
- dizziness,
- muscle weakness,
- feeling sick, being sick,
- diarrhea,
- constipation,
- stomach pain,
- headache,
- blurred vision,
- ringing in the ears,
- loss of appetite,
- irritability,
- nightmares,
- hallucinations,
- difficulty in passing urine,
- dry mouth,
- fast heart rate,
- tremors,
- skin rashes,

- unusual bruising,
- infections such as sore throats (which may be a sign of very rare changes in the blood).

**Risks and Discomforts that are part of taking H-2 Blockers
(cimetidine/ranitidine/ famotidine)**

As of October 2006, **common side effects** reported by those taking H-2 blockers include:

- abdominal pain (or stomach pain),
- breast enlargement in men (gynecomastia, especially with cimetidine),
- constipation,
- diarrhea,
- dizziness,
- drowsiness,
- headache,
- nausea and vomiting,
- pain,
- rash,
- sore throat,
- itching or hives on the skin,
- swelling,
- shortness of breath, wheezing or trouble breathing,
- weakness.

Risks that are part of Blood Tests and Intravenous Injection

For most people, needle punctures for blood draws do not cause any serious problems. However, they may cause:

- bleeding,
- bruising,
- discomfort,

- infections,
- dizziness,
- pain at the needle site.

Risks that are part of having MRI Scan

MRI scans do not usually have bad effects unless:

- you have metal in your body.
- You may not be able to take part in this test if you have any pieces of metal in your brain because of earlier injury or surgery.
- You should tell your doctor if you have any metal in your body (such as, pacemaker, pins).
- Some older tattoo ink may contain metal, so you should also tell the study doctor or MRI staff if you have any tattoos.
- People who do not like to be in small spaces (claustrophobia) might feel confined or bothered by an MRI.
- You may be bothered by the noise the scanner makes. You will be given ear plugs or headphones to reduce the noise of the scanner.
- The contrast (or dye) that will be given to you has a very low rate of allergic reactions but some may be serious.

Risks that are part of CT-Scan

The x-rays are painless. Some people may have discomfort:

- from lying on the hard table.
- Contrasts (or dye) given through as IV may cause a slight burning sensation at the IV site. It can also cause a metallic taste in the mouth.
- Some people complain of a warm flushing of the body. These sensations are all normal and go away within a few seconds.
- **Rarely**, some people may have a life-threatening allergic response to the contrast. If you have any trouble breathing during the test, you should tell the scanner operator right away. Scanners have a 2-way speaker, so the operator can hear you at all times. The contrast has been with a part of renal (kidney) failure in some patients.

- CT-scans and other x-rays are strictly controlled to make sure they use the least amount of radiation. CT scans do create low levels of radiation, which have the potential to cause cancer and other defects. But, the risk with any individual scan is small. The risk increases as the number of x-rays increase.

Risks that are part of Chest X-Ray

You may receive x-rays during the study. You will be exposed to a small amount of radiation during the test. The radiation that you receive from each test is about the same amount that you would normally get in 12 days from natural and man-made sources. The x-ray may be slightly uncomfortable as you may have to lie on your back.

Other Risks

In addition to the risks already described, pemetrexed, carboplatin, bevacizumab, paclitaxel, folic acid, vitamin B12; dexamethasone, diphenhydramine, cimetidine, ranitidine, famotidine or the combination of the study drugs and the study procedures may have other unknown risks or may increase the likelihood that known risks occur.

There may also be unknown risks to your embryo, fetus, or nursing infant.

There may be unknown risks of possible harmful interaction with other medication you may be taking. There is a very rare but possible risk of your genetic information being seen by others which could result in loss of insurance, jobs and privacy.

Reporting Health Experiences

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately call the nurses or Dr. Dr. Deveras, Principal Investigator or your Study Doctor _____ at (386) 254-4212 (24-Hour Number) You can call at any time, day or night, to report such health experiences.

Other Treatments

You do not have to take part in this study to be treated for your illness or condition. Other chemotherapy drugs are approved for treatment of non-small cell lung cancer (NSCLC). Your doctor can talk to you about the other treatments that are available.

Participation in the Study

You may have to pay for some expenses related to this study, such as transportation, parking, meals, or others. The study drug (pemetrexed) and study procedures that are not

standard of care will be provided at no cost to you. Carboplatin, paclitaxel, and bevacizumab are commercially available, and will not be paid by the study sponsor. You may also be responsible for the infusion costs that are part of with the study drug (pemetrexed), carboplatin, paclitaxel, and bevacizumab. Your insurance company may not pay for procedures that are not considered standard for the treatment of your condition.

You or your insurance company will be responsible for paying for procedures, tests and possibly medications that are standard treatment for patients with non-small cell lung cancer. Some examples of standard procedures include routine laboratory blood tests, x-rays, MRIs, scans, surgeries, blood transfusions, physicians' charges and routine medical care. Examples of medications you could possibly require in addition to the study medications include antibiotics or other medications to manage side effects of treatment. Your insurance company may not pay for costs that are part of research studies like this one. You are responsible for any charges your insurance company does not pay.

If any important new information is found during this study that may affect your wanting to continue to be part of this study, you will be told about it right away.

Taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop your participation in the study at any time, without a penalty or loss of benefits to which you are otherwise entitled.

Your participation also may be stopped by the study doctor or sponsor without your consent. If this happens, it might be due to a bad reaction you have to pemetrexed or new information about pemetrexed safety or effectiveness.

If you want to stop being a part of this study contact Dr. Deveras, Principal Investigator or your Study Doctor at (386) 254-4212 (24-Hour Number). The doctor or Study Coordinator will talk to you about any medical issues regarding the stopping of your participation.

Treatment and Compensation for Injury

If you follow the directions of the study doctor and staff and you are physically injured due to any substance or procedure properly given under the plan for this study, the sponsor will pay the medical expenses for the treatment of that injury which are not covered by your medical insurance, by a government program, or by any other third party.

Possible Benefits

Although pemetrexed is being tested as a possible treatment for a condition that you may have, you may not receive any medical benefit.

Information obtained from this study will benefit the sponsor of the study, Lilly USA, LLC, and may benefit subjects/patients in the future.

You may receive information about your health from any physical examinations and laboratory tests to be done in this study.

Investigator Payment

The sponsor is paying Halifax Health for their work in this study.

Questions

If you have any questions about this study, please contact the Principal Investigator, Dr. Deveras, or your Study Doctor _____ at:

Halifax Health
Center for Oncology
303 N. Clyde Morris Blvd.
Daytona Beach, Florida 32114
(386) 254-4212 (24-Hour Number)

If you have any questions about your rights as a participant in a research study, you may contact

Liberty IRB, Inc.
2024 Larchmont Drive
DeLand, Florida 32724
(386) 740-9278 (Business Hours)

The Liberty Institutional Review Board (IRB) reviews research done at Halifax Health and is a committee that has reviewed this research study to help ensure that your rights and welfare as a research participant are protected and that the research study is carried out in an ethical manner.

Confidentiality

The study doctor and staff will handle your personal health information in a confidential manner. Your health information will be used and disclosed in accordance with the following U.S. Data Privacy Statement.

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U.S. Data Privacy Statement

A federal government rule has been issued to protect the privacy rights of subjects (participants)/patients. This rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). This rule is designed to protect the confidentiality of your personal health information. Your personal health information is information about you that could be used to find out who you are. For this research study, this includes information in your existing medical records needed for this study and new information created or collected during the study.

This Data Privacy Statement explains how your personal health information will be used and whom it will be given to (“disclosed”) for this research study. It also describes your privacy rights, including your right to see your personal health information.

By signing the consent document for this study, you will give permission (“authorization”) for the uses and disclosures of your personal health information that are described in this Data Privacy Statement. If you do not want to allow these uses, you should not participate in this study.

If you agree to participate in the research study, your personal health information will be used and disclosed in the following ways:

- The study doctor and staff will use your medical records and information created or collected during the study to conduct the study.
- The study doctor and staff will send your study-related health information (“study data”) to the sponsor of the study and its representatives (“sponsor”). Because the sponsor conducts business related to clinical research in many countries around the world, this may involve sending your study data outside of the United States. Other countries may have privacy laws that do not provide the same protections as the laws in this country. However, the sponsor will respect the terms of this Data Privacy Statement in all countries.
- The study data sent by the study doctor to the sponsor does not include your name, address, social security number, or other information that *directly* identifies you. Instead, the study doctor assigns a code number to the study data and may use your initials. Some study data sent to the sponsor may contain information that could be used (perhaps in combination with other information) to identify you (e.g., date of birth). If you have questions about the specific health information that will be sent to the sponsor, you should ask the study doctor.

- The sponsor will use the study data for research purposes to support the scientific objectives of the study described in the consent document, to assess the safety or efficacy of any drug or treatment included in the study, to better understand the disease(s) included in the study, or to improve the design of future studies.
- Your study data, either alone or combined with data from other studies, may be shared with regulatory authorities in the United States and other countries, doctors at other institutions participating in the study, and Liberty IRB, the ethical review board overseeing this study.
- Study data that does not directly identify you may be published in medical journals or shared with others as part of scientific discussions.
- Your original medical records, which may contain information that directly identifies you, may be reviewed by the sponsor, monitors, auditors, Liberty IRB, the ethical review board overseeing this study, and regulatory authorities in the United States and other countries. The purpose of these reviews is to assure the quality of the study conduct and the study data, or for other uses authorized by law.
- The sponsor works with business partners in drug development. The sponsor may share your study data with these business partners, but only if the business partners need the information as a part of this work with the sponsor, and only if the business partners signs a contract that requires it to protect your study data in the same way as the sponsor.
- The sponsor will not disclose personal health information to insurance companies unless required to do so by law, or unless you provide separate written consent to do so.
- Your medical records and study data may be held and processed on computers.

Your personal health information may no longer be protected under the HIPAA privacy rule once it is disclosed by your study doctor to these other parties.

You have the right to see and copy your personal health information related to the research study for as long as this information is held by the study doctor or research institution. However, to ensure the scientific integrity of the study, you will not be able to review some of the study information until after the study has been completed.

You may cancel your authorization at any time by providing written notice to the study doctor. If you cancel your authorization, the study doctor and staff will no longer use or disclose your personal health information in connection with this study, unless the study

doctor or staff needs to use or disclose some of your personal health information to preserve the scientific integrity of the study. The sponsor will still use study data that was collected before you cancelled your authorization. If you cancel your authorization, you will no longer be able to participate in the study. However, if you decide to cancel your authorization and withdraw from the study, you will not be penalized or lose any benefits to which you are otherwise entitled.

Your authorization for the uses and disclosures described in this Data Privacy Statement does not have an expiration date.

Patient Information and Consent Form Attachment 1 Study Procedures

Study code H3E-US-S130

Study Visit	Time Between Visits	Approx Visit Length	Study Procedures/ Activities
Baseline		4 – 6 hours	This visit will decide if you can take part in this study. <ul style="list-style-type: none"> • The doctor will get your consent to take part in the study • Physical exam, information on your health and medical history will be collected • For female patients, a urine or blood pregnancy test will be done • If applicable, an MRI, CT Scan, or a chest X-ray will be done • About 12mL of blood (a little less than 1 tablespoon) and a urine sample will be collected • If you are willing to take part in the translational research sub-study, an additional 20mL of blood (a little more than 1 tablespoon) will also be collected
Induction Therapy: Treatment Visit 1 – Up to	21 days	4 – 8 hours	<ul style="list-style-type: none"> • Physical exam and information regarding how you have been since your last visit will be collected • If applicable, an MRI, CT Scan, or chest X-ray will be done at every other visit (about every 6 weeks) • About 8mL of blood (a little more than 1 teaspoon) and a urine sample will be collected at

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4 Visits			<p>each visit during induction therapy</p> <ul style="list-style-type: none"> • Study drug treatment and pre-medication will be given. If you are randomized to Arm A, pemetrexed and carboplatin will be given, along with folic acid, vitamin B-12, and dexamethasone. If you are randomized to Arm B, carboplatin, bevacizumab, and paclitaxel will be given, along with dexamethasone, diphenhydramine, and cimetidine, ranitidine or famotidine
Maintenance Therapy: Treatment Visit 5 – Visit X (depending on when the patient progresses)	21 days	1 -2 hours	<ul style="list-style-type: none"> • Physical exam and information regarding how you have been since your last visit will be collected • If applicable, an MRI, CT Scan, or chest X-ray will be done at every other visit (about every 6 weeks) • About 8mL of blood (a little more than 1 teaspoon) and a urine sample will be collected at each visit during maintenance therapy • Study drug treatment and pre-medication will be given. If you are randomized to Arm A, pemetrexed will be given, along with folic acid, vitamin B-12, and dexamethasone. If you are randomized to Arm B, bevacizumab will be given
Post Dis-Continuation Visit (30-day follow up)	30 days	6 hours	<p>This visit will occur about 30 days after your last treatment with study drug</p> <ul style="list-style-type: none"> • Physical exam and information regarding how you have been since your last visit will be collected • If applicable, an MRI, CT Scan, or chest X-ray will be done at every other visit (about every 6 weeks) • About 8mL of blood (a little more than 1 teaspoon) will be collected
Post Dis-Continuation	As clinically	1 – 2 hours	<p>How often these visits occur will depend on your health</p> <ul style="list-style-type: none"> • Information on your health and medical history may be collected

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Visit (Long Term Follow-up)	directed		• If applicable, an MRI, CT Scan, or chest X-ray may be done
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Printed Name of Person Conducting Informed Consent Discussion

**Signature of Person
Conducting Informed Consent Discussion**

Date

Time

Physician's Printed Name

Physician's Signature

Date

Time

Signatures (For Optional Translational Research)

By signing the Signature Line below, you are confirming the following:

- You have read all of the information in this Patient Information and Consent Form, and you have had time to think about it.
- Your questions have been answered to your satisfaction.
- You authorize the collection, storage, and testing of your blood sample for translational research purposes
- You have received a copy of this Patient Information and Consent Form to keep

Participant's Printed Name

Participant's Signature

Date

Time

Printed Name of Legal Representative , if applicable

Legal Representative's Signature	Date	Time
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If signed by legal representative, state description of relationship to subject/patient or other basis for legal authority

Printed Name of Person Conducting Informed Consent Discussion

Signature of Person Conducting Informed Consent Discussion	Date	Time
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Physician's Printed Name

Physician's Signature	Date	Time
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Signatures for Patient Impartial Witness

FOR ADDITIONAL SIGNATURES	
Signature of Patient Impartial Witness	Date (Patient Impartial Witness must personally date)
[Patient Impartial Witness Name (print or type)]	Patient Number