

Subject Information and Consent Form

A Phase 3, Double-Blind, Placebo-Controlled Study of Maintenance Pemetrexed plus Best Supportive Care versus Best Supportive Care Immediately Following Induction Treatment with Pemetrexed + Cisplatin for Advanced Non-Squamous Non-Small Cell Lung Cancer

Qualified Investigator: [Insert name and contact information]
Sub-Investigator(s): [Insert name(s) and contact information, if required]
Sponsor: Eli Lilly Canada Inc.

Introduction

You are being invited to take part in a research study (*also called a clinical trial*). This research will study a drug known as pemetrexed (Alimta®). It is your choice if you want to be in this study or not. Research studies are different from regular care. Research studies are ways of finding out new information that might help other people with similar conditions or illnesses to yours. This form explains why we are doing the study, and how the treatment that is being offered to you is different from regular care. It tells you what will happen during the study. It also tells you about any inconvenience, discomfort or risk with this study. It also gives you a complete description of the treatment offered. This information will help you decide whether you wish to be part of the study.

What Is The Purpose of The Study?

The main reason for doing this study is to help answer the following research question:

- Whether the administration of pemetrexed as a maintenance treatment will improve upon therapy you initially received (pemetrexed in combination with cisplatin) and will prevent your cancer from growing or recurring.

Who Can Take Part In The Study?

To take part in this study you must have the diagnosis of unresectable, locally advanced, stage IIIB or stage IV, non-squamous non-small cell lung cancer. The study doctor or study staff has discussed with you the requirements for being in this study. It is important that you are completely honest with the doctor and staff about your health history. You should not take part in this study if you do not meet all requirements.

You cannot participate in this study if:

- You have an active infection or other serious condition such as cardiac disease
- You have had another malignant cancer less than five years ago
- You take aspirin or aspirin like medication that you are unable to stop taking for a few days during each cycle of therapy
- You are unable or unwilling to take folic acid, vitamin B12 and dexamethasone or other corticosteroids medication.
- You have had a yellow fever vaccination within the last 30 days or plan to have it.

- You have excess fluid around your lungs or in your abdomen that cannot be removed prior to study entry

If you are a woman and could become pregnant, you must talk to the study doctor about birth control. You must avoid getting pregnant during the study and for 6 months after the study is completed. If you are planning to get pregnant during the study, you should not take part.

If you are a man, you must avoid the chance of your female partner becoming pregnant during the study and for 6 months after the study is completed. The study doctor will discuss birth control with you.

What Does The Study Involve?

About 900 study subjects will be taking part in this study.

Your participation in this study is expected to last until you or your physician decides that there is no clear benefit for you to continue treatment. However, your physician will ask you afterwards to visit him on regular basis to follow-up on your health status. The expected minimal trial duration would be approximately 16 weeks (if only part 1).

If you decide to take part in this study, the procedures and visits you can expect are explained in the attachment called Study Procedures - Attachment 1. This will give you information about what taking part in the study will mean to you, for example, how often you have to come to see the study doctor, how long each visit might take, when blood samples will be taken and when tests and procedures will be performed.

Treatment Assignment

This trial consists of **2** parts.

During the **first part** you will be administered 4 intravenous infusions of pemetrexed in combination with cisplatin (approximately 3 weeks apart).

If you have benefited from this therapy, you will then enter the **second part** of the trial. You'll be assigned to receive either pemetrexed or placebo (a saline solution that has similar appearance to the study drug but has no medicine). Each pemetrexed or placebo (normal saline) intravenous infusion will be repeated approximately every 3 weeks. Whatever treatment you're assigned to, you will also receive Best Supportive Care (BSC) which is defined as treatment given to maximize quality of life without the intention of stopping your cancer to grow.

The treatment you will receive will be determined by chance (like flipping a coin). Neither you nor your doctor will be able to choose which treatment you will receive. You will have twice the likelihood of receiving pemetrexed than placebo. Once you are assigned to a treatment neither you nor the study doctor will know what medication you are receiving.

You will continue to receive this treatment, BSC + pemetrexed or BSC + placebo, until the status of disease worsens, you have significant side effects or your doctor believes that it is in

your best interest to stop taking the drug. Afterwards, your doctor will ask you to visit him on regular basis to follow-up on your health status.

After the study ends, you may be given the choice to continue to receive pemetrexed. This will happen only if the study doctor and study sponsor believe the drug may be of benefit to you. Pemetrexed may be provided by the study sponsor until your disease worsens OR until pemetrexed is approved for sale in Canada if the study doctor continues to believe it is benefiting you and the study sponsor continues development of pemetrexed.

Study Procedures

Blood samples will be taken at different time points as described in Attachment 1. The purpose of these blood samples is to help your study doctor decide if you can take part in this study and to check your health during the study. The blood samples will be tested to make sure the levels of certain things in your blood are normal (e.g. Liver Function Tests, to make sure your liver is working right). About 2 to 3 teaspoonfuls (up to 15 milliliters) of your blood will be taken each time. A blood sample will also be taken at the beginning of the study if you are a female to see whether you are pregnant or not.

All Blood samples 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.

At every other visit (Visit 2, 4, and so on), or when needed, radiological exams will be completed to take a series of pictures of your body. These will include CT scans, Magnetic Resonance Imaging (MRIs) or chest X-rays, as applicable.

Following your active participation in the study, the study doctor or one of the staff members may contact you to obtain information regarding the status of your health and quality of life. If you have moved or plan to move, please provide your new contact information to the study doctor or his staff.

What Are The Possible Harms and Side Effects?

If you take part in this study, there may be risks to you.

As of 13 March 2008, approximately 15,925 patients had been enrolled in clinical studies around the world to receive pemetrexed (ALIMTA®, LY231514).

Risks and Discomforts Associated with Pemetrexed

Very common (≥10%)

Very common side effects reported by those taking pemetrexed include a decrease in white blood cells and red blood cells, and short-lived increases in some tests that show how the liver is working. A decrease in white blood cells increases the chance of developing an infection, with or without fever. A decrease in red blood cells (anemia) may cause loss of

energy and feelings of being tired. Additional very common side effects include nausea and vomiting, diarrhea, hair loss, loss of appetite, inflamed mucous membranes (especially the lining of the mouth), skin rash (which may be itchy, or may progress to become serious), abdominal pain, edema (swelling, usually of the limbs and face), fever, weakness, fatigue, difficulty breathing, cough, constipation, and headache.

Common ($\geq 1\%$ and $< 10\%$)

Common side effects include decreased platelet counts (which may increase the chance of bruising and bleeding after injury), cellulitis (inflammation of tissues under the skin), decreased kidney function, urinary tract infection and other types of infection, difficulty sleeping, loss of body fluid (dehydration), pneumonia, allergic reactions, neuropathy (tingling and/or weakness of the arms, hands, feet, and legs), increased heart rate, conjunctivitis (pink eye), heartburn, taste disturbances, chest pain, heart attack, irregular heart rate, and renal failure.

Uncommon ($\geq 0.1\%$ and $< 1\%$)

Uncommon side effects reported by those taking pemetrexed include injection site reactions, intestinal obstruction, gastrointestinal bleeding, and formation of blood clots in deep veins.

This information relates to pemetrexed when taken as a single agent. These 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, hair loss, decreased kidney function, injection site reactions, intestinal obstruction, gastrointestinal bleeding, and formation of blood clots in deep veins and serious skin reactions. Other chemotherapy drugs and treatment modalities such as radiation will also have their own, often unique, side effect profile and this should be taken into consideration 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, and possibly death.

There is slight risk of severe allergic reaction to the drug, which may be life threatening. There is always a risk involved in taking a new drug but every precaution will be taken to minimize the risk

Postmarketing Data

Rare ($\geq 0.01\%$ and $< 0.1\%$) cases of colitis (inflammation of the lining of the large bowel) have been reported in patients taking pemetrexed. Rare cases of radiation recall (a severe skin reaction) have been reported in patients who have previously received radiotherapy.

Rare cases of interstitial pneumonitis (pneumonia involving the connective tissue of the lung) have been reported in patients treated with pemetrexed.

Rare cases of edema have been reported in patients treated with pemetrexed.

Side effects can sometimes be serious or life threatening. Your doctor should be informed of all side effects you experience.

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 Associated with Other Drugs

Cisplatin

Like any other medication, cisplatin may cause side-effects. Nausea and vomiting, loss of appetite and a general feeling of sickness are the most common. Other reported adverse events are listed below:

- **Gastro-intestinal:** Most patients have a loss of taste, stomach-aches and diarrhea. In rare cases inflammation of the mouth and a greyish discoloration of the gums have been reported.
- **Blood production:** The number of blood cells (white blood cells, red blood cells and platelets) you have may decrease. As a consequence, this may increase your risk of infection, fatigue, abnormal bleeding and bruising.
- **Hearing:** patients might experience tinnitus (ringing in the ears), vertigo (dizziness) or a loss of hearing.
- **Heart:** Rarely, cisplatin affects the heart causing a change in heart rate. In very rare cases cardiac arrest has been reported when cisplatin was taken with other chemotherapy drugs.
- **Nervous system:** In rare cases a numb feeling, tingling and a feeling of weakness in the limbs, tremor and partial loss of the sense of taste and sight, confusion, indistinct speech or amnesia may be experienced.
- **Urinary tract:** Treatment with cisplatin may cause damage to the kidneys (decrease in normal function or kidney failure). In order to reduce the risk of serious kidney damage, plenty of intravenous fluids will be given before and after the administration of cisplatin.
- **Serious Allergic Reactions:** including a rash, itching, redness and swelling of the face, trouble swallowing, wheezing, rapid heartbeat and a drop in blood pressure have been rarely reported. These effects may occur within a few minutes after infusion and are treated with appropriate medications.
- Treatment with cisplatin may also cause symptoms of gout (sensitive, painful, swollen joints).
- **Laboratory Results:** Treatment with cisplatin may influence the concentrations of the different substances found in your blood and/or urine.
- **Other:** The area where cisplatin is injected may become temporarily swollen and sore. Other rare effects are a loss of hair, sensitive, swollen breasts, problems with fertility and problems with blood circulation.

Dexamethasone or other corticosteroids

The side effects reported by patients taking dexamethasone include edema (fluid retention), high blood pressure, sodium retention and/or potassium loss, increased appetite and weight gain, extreme mood swings, tiredness, depression, inability to sleep, nausea, vomiting. Patients may also experience increased sweating, increase blood sugar, irregularities in the menstrual cycle (periods), excess hair, thinning of bone, increased risk of picking up infections or mild infections get worse, hiccups, abdominal pain, stomach ulcers and skin disorders. Additionally some patients reported allergic reactions, blood clots, eye disorders including increased eye pressure. Patients with pre-existing schizophrenia, epilepsy may experience worsening of their disease; patients with heart disease may experience heart

failure. The longer a patient takes these drugs and the larger the dose may increase the incidence of the side effects listed above.

Folic acid

An allergic reaction including a rash, swelling or, in severe cases, difficulty in breathing has been reported in patients taking folic acid. Rarely, patients may suffer from mild stomach upsets.

Vitamin B12

Patients may experience some discomfort from the intramuscular injection. Fever, chills, hot flushes, dizziness, feeling sick, an acne-like rash and blisters have also been reported. Hypersensitivity reactions including skin reactions (e.g. rash, itching), and occasionally anaphylaxis (which may include collapse and difficulty breathing) may occur. Irregular heartbeat has been reported during early stages of treatment.

Risks and Discomforts Associated with Study Procedures

Blood Tests

You might experience some temporary discomfort when the blood sample is taken. There is a small risk of bruising, infection or swelling at the site where the needle is inserted and you might feel faint and dizzy.

Magnetic Resonance Imaging (MRI)

Generally there are no bad effects of an MRI scan. But you should not have the scan if you have any metal objects in your body. For example you might have metal in your body if you have a metal plate in your leg after a break. You may also have metal in your body if you have been exposed to metal fragments during welding. You should tell the study doctor, or MRI staff if you have any tattoos since some older tattoo ink may contain metal. Some people who do not like to be in small spaces might feel bothered by an MRI. You may also be bothered by the noise the scanner makes. You will be given ear plugs to reduce the noise of the scanner.

Computed Tomography Scan (CT Scan)

The x-rays are painless. Some people may have discomfort from lying on the hard table. Contrast (or dye) given through an 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. 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 are done.

X-rays

You may have chest 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

about what you would get in 12 days normally from all sources (natural and man-made). You may feel slightly uncomfortable as you stand for the chest x-ray.

Other Risks

In addition to the risks named above, pemetrexed, the other drugs required by the protocol, the combination of these drugs, and the study procedures might have other unknown risks.

Some methods of birth control might be less effective due to a possible interaction with pemetrexed.

It is possible that if a woman who is pregnant or breastfeeding takes pemetrexed it will harm her embryo, fetus, or breastfeeding infant.

At any time during this study, you may experience a return or worsening of your disease. It may be more likely that you will experience such return or worsening of your disease if you receive placebo in the second part of the trial (a saline solution that has a similar appearance to the study drug but has no medicine) as your study drug.

There might be unknown risks of the study drug interfering with other medications, both prescribed and over the counter. You must tell your study doctor about any medications you are currently taking. You should also consult with your study doctor before taking any new medications.

What If New Information Becomes Available?

You will be told about any important new information that is found during this study that might affect your health, well-being or willingness to stay in the study.

Will This Study Help Me?

Although the combination of pemetrexed plus cisplatin followed by pemetrexed is being tested as a possible treatment for your illness, you may not receive any health benefit from taking part in this study. You might feel better. On the other hand, it might not help you at all. It might even make you feel worse.

You might receive information about your health from any study procedures that are done during this study.

Information obtained from this study will benefit the sponsor of the study, Eli Lilly Canada Inc, and might help patients in the future.

You do not have to take part in this study to be treated for your lung cancer. There are other treatments and therapies available to you. These might include cisplatin and another chemotherapy drug. Your study doctor can discuss these treatments and therapies with you.

Do I Have To Take Part In This Study?

Your taking part in this study is entirely voluntary. Whether or not you take part is completely up to you to decide. You will continue to receive the best possible care no matter what you decide.

If you choose to take part and later change your mind, you can stop participating at any time. A decision to stop being in the study will not affect how your health care is provided to you. If you decide to stop the treatment, please talk to the study doctor or one of the staff members. They can tell you about any other treatments, and arrange to continue your usual care.

Your study doctor or the sponsor might decide, at any time and for any reason, to stop your taking part in the study, even though you might want to continue. This might happen if you have a bad reaction to pemetrexed or if there is new information about the safety or effectiveness of pemetrexed. The study doctor or one of the staff members will explain the reasons why you must stop and arrange for your health care to continue.

Treatment and Compensation for Injury

In Canada, health care is provided through a system of provincial insurance. This insurance may or may not provide coverage for certain types of injuries that might result from your taking part in this study. To the extent that provincial insurance does not cover physical injury caused by any substance or procedure properly given under the plan for this study, Eli Lilly and Company will pay the medical expenses for the treatment of that injury so long as you have followed the direction of the doctors in charge of the study. Signing this form does not mean you give up any of your legal rights. The study doctor, sponsor or hospital would still have legal and professional responsibilities to you.

What Will The Study Cost Me?

Study drug and study procedures will be provided at no cost to you. However, you might have to pay for some expenses related to your taking part in this study, such as *[transportation, parking, meals or others]*.

You will be paid *[insert amount per study visit]* to reimburse you for *[transportation, parking, meals or other]* expenses related to your taking part in this study. If you withdraw from the study early you will be paid for these expenses for the portion of the study that you completed.

Who Is Paying For The Research Study?

The sponsor is paying the study doctor and/or *[name of Institution or site]* for their work in this study.

Who Do I Contact If I Want To Report Health Problems Or Have Questions?

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the study doctor or other study staff. You can call at any time, day or night, to report such health experiences. *[insert contact details]*

If you have any questions about this study or your rights, please contact Dr. [insert study physicians name] at [insert address and phone #].

If you have any questions about your rights as a research subject, please contact [insert ethics contact or other neutral or disinterested party] at [insert address and phone number].

Will My Taking Part In This Study Be Kept Confidential?

The study doctor and staff will handle your personal health information in a confidential manner. Your health information will be used and disclosed as explained in the following Data Privacy Statements.

In this section, “personal health information” means information about a person that relates to things like the person’s physical or family health history, health care, health care provider or substitute decision-maker and that directly identifies the person, and ”study data” means study-related health information that does not directly identify a person (that is, it does not contain the person’s name, address, health number or other identifying information) but that does contain an assigned code number for the person and/or the person’s initials.

By signing the consent document for this study, you will give permission 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 study, your personal health information and study data will be maintained, used and shared in the following ways:

- The study monitor, the study auditor, the sponsor’s clinical research staff and regulatory authorities might have access to your personal health information. This personal health information may include information from your health records such as your medical history, all lab results, ECG readings, specialist reports, and medications that you have been on in the past or currently. The records will be kept and disposed of in accordance with all applicable laws and regulations.
- The study doctor and staff will send your study data to the study sponsor, its associated companies and its representatives (the “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 Canada. If your study data is sent to other countries, your privacy will remain protected as described in this section.
- Your study data will be used by the sponsor for research purposes to support the scientific objectives of the study. This may include studying how well the drug(s) or treatment(s) associated with the study worked and/or how safe they were; to better understand the conditions or illnesses being studied; and/or to improve the design of future studies.
- Your study data, either alone or combined with data from other studies, might be shared with regulatory authorities in Canada, such as Health Canada, and similar

government agencies from other countries, as well as the ethics review board overseeing this study.

- The sponsor works with business partners in drug development. The sponsor might share your study data with a business partner but only if the business partner signs a contract that requires it to protect your study data in the same way as the sponsor.
- Study data (which does not identify you) might be published in medical journals or shared with others as part of scientific discussions.
- To the extent permitted by applicable laws, the sponsor, the ethics review board, Health Canada and/or regulatory agencies in other countries, might review your original health records, which contain information that directly identifies you, to verify the accuracy and completeness of study data collected during the study.

You will have the right to see and copy your personal health information related to the study for as long as the study doctor or research institution holds this information, subject to applicable laws. However, you will not be able to see or copy this information until after the study has been completed.

You may withdraw your permission at any time by providing notice to the study doctor. The study doctor and staff would then no longer use or share your personal health information in connection with the study, unless it is essential to ensure that the study is scientifically reliable. However, the sponsor would still use your study data that was collected before you withdrew your permission. In addition, you would no longer be able to participate in the study.

Subject Information and Consent Form Signature Page

To take part in this study and to allow the use and disclosure of my personal health information for the purposes of the study, I must sign and date this page.

By signing this page, I confirm the following:

- I give permission for my personal health information and study data to be maintained, used and shared as described in this document
- I have read the Subject Information and Consent Form, and have had time to think about whether or not I want to take part in this study.
- All of my questions about the study or this form were answered to my satisfaction. If I did not understand any of the words in this form, the study doctor or a member of the study staff explained them to me.
- I voluntarily agree to take part in the study, to follow the study procedures, and to provide necessary information to the study doctor or other staff members, as requested.
- I understand that I may freely choose to stop being a part of this study at any time.
- I have received a copy of the Subject Information and Consent Form.

Signature of Subject

Date (*ddMMMyy*) [Subject must personally date]

Subject's Name (Print or Type)

Subject Number

Signature of Individual Conducting Informed Consent Discussion

Date (*ddMMMyy*)
[Individual conducting informed consent discussion must date]

Name of Individual Conducting Informed Consent Discussion (Print or Type)

Study Procedures (Attachment 1)

Study: H3E-EW-S124

Study Visit	Time Between Visits	Approx Visit Length	Study Procedures/ Activities
Baseline (Visit 0)		3 hours	<p>This visit will determine if you are eligible to participate in this study.</p> <ul style="list-style-type: none"> • Your consent will be requested before you participate in this study • Information on your health, medical and smoking history as well as medications you are taking will be collected. • Physical exam including measurement of weight, height, blood pressure and pulse will be performed. • Radiological exam(s) (CT scan, MRI or chest X-Ray as applicable) will be done. • Blood samples will be taken (Up to 15 ml). • A urine or blood pregnancy test will be done if you're a woman and could become pregnant during this study. • You will also be asked to complete one questionnaire on your health status. <p>As supportive therapy, you will take folic acid tablets by mouth every day for at least five days before the first administration of study treatment (day 1 of cycle 1). In addition you'll be given vitamin B12 as an intramuscular injection within 7 days prior to day 1 of cycle 1. The day before the administration of pemetrexed you will also be given dexamethasone or other equivalent corticosteroids by mouth (2 intakes per day).</p>
Visits 1 to 3	Visit 1 : Up to 4 weeks after baseline visit Visits 2 to 3 : separated by approximately 3 weeks	4 hours	<p>At each visit the following tests will be done :</p> <ul style="list-style-type: none"> • Physical exam will be performed; information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Radiological exam(s) taking a series of pictures of your body (CT scan, MRI or chest X-Ray as applicable) will be done at every other visit (at the end of visit 2). • Blood samples will be taken (Up to 15 ml) for routine laboratory tests. • You will also be asked to complete one questionnaire on your health status before each infusion of study treatment. • Study treatment will be administered <ul style="list-style-type: none"> ○ pemetrexed will be administered as a 10 minute intravenous infusion. Administration will be repeated every 3 weeks, followed approximately 30 minutes later by ○ an intravenous infusion of cisplatin. You will also receive fluid by infusion before and after the administration of cisplatin. • You will continue to take folic acid tablets by mouth daily until 3 weeks after the last dose of pemetrexed. You'll also be given dexamethasone or other corticosteroid twice per day the day before, the day of and the day after each pemetrexed administration. Vitamin B12 injection will be repeated every 3 cycles.

Visit 4	Approximately 3 weeks after visit 3	4 hours	<p>At this visit the following tests will be done :</p> <ul style="list-style-type: none"> • Physical exam will be performed; information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Radiological exam(s) taking a series of pictures of your body (CT scan, MRI or chest X-Ray as applicable) will be done at every other visit (at the end of visit 4). • Blood samples will be taken (Up to 15 ml) for routine laboratory tests. • You will also be asked to complete one questionnaire on your health status before each infusion of study treatment. • Study treatment will be administered <ul style="list-style-type: none"> ○ pemetrexed will be administered as a 10 minute intravenous infusion. Administration will be repeated every 3 weeks, followed approximately 30 minutes later by ○ an intravenous infusion of cisplatin. You will also receive fluid by infusion before and after the administration of cisplatin. • You will continue to take folic acid tablets by mouth daily until 3 weeks after the last dose of pemetrexed. You'll also be given dexamethasone or other corticosteroid twice per day the day before, the day of and the day after each pemetrexed administration. Vitamin B12 injection will be repeated every 3 cycles. • The physical exam and radiological tests performed at the end of visit 4 will determine if you're eligible to receive the second part of the treatment. If you are eligible, you will be assigned to 1 of the 2 treatments: pemetrexed + Best Supportive Care or Placebo + Best Supportive Care. Best Supportive Care is defined as treatment given to maximize quality of life without the intention of curing your cancer or slowing it's growth.
Visits 5 and following ones	separated by approximately 3 weeks	2 hours	<p>At each visit the following tests will be done :</p> <ul style="list-style-type: none"> • Physical exam will be performed; information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Radiological exam(s) (CT scan, MRI or chest X-Ray as applicable) will be done at every other visit. • Blood samples will be taken (Up to 15 ml) for routine laboratory tests. • You will also be asked to complete one questionnaire on your health status before each infusion of study treatment. • Study treatment will be administered <ul style="list-style-type: none"> ○ If you're assigned to the pemetrexed + Best Supportive Care treatment, pemetrexed will be administered as a 10 minute intravenous infusion. Administration will be repeated every 3 weeks. ○ If you're assigned to the Placebo + Best Supportive Care treatment, a salt solution will be administered as a 10 minute Intravenous infusion in place of pemetrexed. • You will continue to take folic acid tablets by mouth daily until 3 weeks after the last dose of study treatment. You'll also be given dexamethasone or other corticosteroid twice per day the day before, the day of and the day after each administration of study treatment. Vitamin B12 injection will be repeated every 3 cycles.

Post-discontinuation visit	Approximately 30 days after you stop receiving study drug	1 Hour	<ul style="list-style-type: none"> • Physical exam will be performed; Information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Radiological exam(s), if applicable, may be performed. • Blood samples will be taken (Up to 15 ml) for routine laboratory tests. • You will also be asked to complete one questionnaire on your health status. • You will continue to take folic acid tablets by mouth daily until 3 weeks after the last dose of study treatment.
Follow Up Visits	Approximately every 3 months	1 Hour	<ul style="list-style-type: none"> • Information on your health will be collected. • Radiological exam(s), if applicable, may be performed.