APPENDIX E: SAMPLE INFORMED CONSENT

PROTOCOL M18-007: A 3-Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

Principal Investigator: _____

Before you decide whether or not to take part in this research study, it is important for you to understand the purpose of the study, what risks may be involved, and what is expected of you during the study. If you have any questions that are not answered or if there are words that you do not understand in this consent form, a member of the research team will give you further information. Once you understand the purpose of this study, and if you decide to volunteer to participate in the study, you will be asked to sign this consent form.

You are being asked to participate in this research study because you have been diagnosed with advanced non-squamous non-small cell lung cancer that is no longer operable.

PURPOSE AND BACKGROUND

Current cancer therapies often produce an initial reduction in tumor size but may not have long-term benefits. One possible explanation for this is the presence of a specific type of cancer cell known as a cancer stem cell. Cancer stem cells represent a small part of the tumor but are believed to be responsible for much of the growth and spread of the cancer. Cancer stem cells may also be more resistant to traditional types of therapy, such as chemotherapy and radiation therapy.

The purpose of this study is to test the efficacy and safety of a new experimental drug, demcizumab, when given in combination with carboplatin and pemetrexed. To evaluate the efficacy of demcizumab, demcizumab will be compared to placebo (looks like demcizumab, but does not contain any medication). The administration of carboplatin and pemetrexed is a standard treatment for patients with non-squamous non-small cell lung cancer. You will also be given 2 vitamins (folic acid and vitamin B12) and 1 corticosteroid (dexamethasone) to reduce the adverse effects of pemetrexed.

Demcizumab is a humanized monoclonal antibody and was developed to target cancer stem cells. Demcizumab may block the growth of cancer stem cells and the remaining cancer cells, and it may also prevent the growth of new blood vessels that tumors need to grow and spread. Demcizumab, used in this study, is experimental. That means that the United States Food and Drug Admininstration (FDA) has not approved it for use by the general public. This study is sponsored by OncoMed Pharmaceuticals, which is referred to as OncoMed or the Sponsor in this consent form.

WHAT IS EXPECTED FROM YOU?

When deciding whether to participate, consider whether you are able and willing:

- To follow the study rules
- To commit the time required to keep appointments
- To tell the study doctor truthfully about your complete medical history
- To report any new problems, illnesses, or changes in medication during the study

PROCEDURES

At least 201 patients will be enrolled at up to approximately 60 to 90 centers in North America, Western Europe and Australia. Up to 28 days (4 weeks) prior to treatment you will undergo testing to determine your eligibility to take part in this study, and then, if enrolled in the study, you will receive intravenous (in the vein) infusions of demcizumab (or placebo), carboplatin, and pemetrexed administered on the same day, every 21 days for 4 cycles, or until it has been shown that your cancer has gotten worse. If your physician decides to delay treatment with one of the agents due to side effects, the other agents may still be administered as scheduled. After 4 cycles, if you have stable or improved disease, you will continue to receive pemetrexed once every 21 days as maintenance therapy. After 8 cycles, if you have stable or improved disease, you will receive demcizumab (or placebo), every 21 days for 4 more cycles. You will undergo assessments every 6 weeks to determine the status of your disease.

In addition to routine testing of blood and urine (for complete blood counts with differential and platelets; coagulation studies to determine how quickly your blood is clotting; serum chemistries; B-type natriuretic peptide [BNP], which indicate how well your heart is working; creatinine clearance to measure your kidney function; and urinalysis), special tests will be performed during the study at specific time points listed below. The special tests include the following:

- Tumor markers: These are substances that can be detected in higher than normal amounts in blood, urine, or body tissues for certain types of cancer. The tumor marker level may indicate the extent of the cancer in your body and may show how you are responding to treatment. For this study, only blood samples will be taken to check for tumor markers. The tumor marker for non-small cell lung cancer is CEA. If your baseline CEA tumor marker is not elevated, the test will not be repeated during the study. If your baseline CEA is elevated at baseline, the test will be repeated every 6 weeks.

- Antibodies to demcizumab: Antibodies are proteins produced by your body's immune system in response to a foreign substance. In some cases, the development of antibodies to a treatment will not have any impact on the effectiveness of the treatment. In other cases, the development of antibodies to a treatment can cause the treatment to be ineffective. Blood will be drawn every 6 weeks while you are receiving study drugs (demcizumab or placebo, or carboplatin or pemetrexed) and at the termination visit to determine if you are developing antibodies to demcizumab. Additional testing may also

be done to provide information on the response seen in the demcizumab test. Various experiments would be performed on the samples taken from you for antibodies to demcizumab testing. These experiments will determine the identity and obtain more detailed information on the anti-drug antibody response.

- Pharmacokinetic Analysis: Blood samples will be obtained prior to your demcizumab (or placebo) infusion on Study Days 0, 42, 84, 126, 168, 210, 252, 294 and 336, and at the end of infusion on Study Days 0, 42, 168 and 210, and at your termination visit, to determine how the demcizumab is distributed and eliminated from your body.

- Biomarkers: On Study Days 0 and 28, and at your termination visit, blood samples will be obtained to assess whether the demcizumab is producing desired changes to the genes and proteins related to your cancer. In addition, archival tumor tissue sections (formalin-fixed paraffin-embedded, FFPE) will be collected any time after enrollment, if available, for gene and protein testing of biomarkers related to your cancer. No additional procedures or surgery will be performed to obtain these archival tumor tissue sections. If you agree to have DNA testing on your FFPE tissue, you will sign a separate consent. DNA testing of your tumor may help to identify biomarkers that could be used in the future to predict which patients are more likely to respond to demcizumab, carboplatin and pemetrexed treatment.

In addition, you will have an electrocardiogram (ECG) and Doppler echocardiogram performed during screening, then every 28 days on study (up to Study Day 336, assuming you receive all doses of demcizumab/placebo) and at your termination visit. Your Doppler echocardiograms may be sent to a cardiologist at another hospital who may perform a central read on some of the Doppler echocardiograms in this study. Finally, you will have imaging of your brain (magnetic resonance imaging [MRI] or computerized tomography [CT]) at baseline, and CT scans and/or other radiographs performed at baseline, then every 6 weeks, and at your termination visit, to assess the status of your tumor. A CT pulmonary angiogram (CTPA; or MR angiogram or VQ scan) may be performed if you are diagnosed with pulmonary hypertension to see if you have a pulmonary embolism.

SCREENING

If you volunteer to be in this study and you sign this informed consent form, you will be screened within 28 days before study entry to make sure that you are a suitable candidate. No study-related tests will be performed prior to signing this informed consent form. Your doctor will conduct a review of your physical health and medical history, including other cancer treatments that you have had and a review of any medications you are or have been taking. In addition, a physical examination including height and weight will be performed, and vital signs including your pulse, blood pressure, breathing rate and temperature will be measured. Blood and urine samples will be collected for routine testing, including BNP. Blood will also be drawn for testing of the tumor marker CEA. Approximately 3 tablespoons of blood will be taken at this

visit. You will also have an ECG, Doppler echocardiogram, and either a CT scan or MRI of your chest, abdomen, pelvis, and head. Finally, if your tumor involves your esophagus, stomach, or intestinal tract or if you have symptoms that suggest that your tumor may involve these areas, you will also have a colonoscopy and/or upper gastrointestinal endoscopy to ensure that your tumor does not currently involve your gastrointestinal tract. If you are a female of childbearing potential, you will have a serum pregnancy test within 7 days prior to randomization (time when you are assigned a treatment arm), to ensure that you are not pregnant at the start of the study.

TREATMENT PHASE

Demcizumab (or Placebo)

Once your doctor has evaluated the results of your screening tests to ensure that you meet the criteria for the study and are eligible to participate, you will be randomized in the study and assigned to a treatment arm.

You will receive 5 mg/kg demcizumab or placebo as shown in the treatment arms, below. A placebo looks like the demcizumab, but does not contain any medication. The demcizumab or placebo will be administered intravenously (in the vein) over 30 minutes, every 3 weeks for 63 days, starting on Day 0 and again starting on Day 168. With each infusion, your vital signs will be obtained at least four times: before the infusion; 15 minutes after the start of the infusion, at the end of the infusion, and 15 minutes after the end of the infusion.

You will be randomly (by chance) assigned to one of the three treatment arms:

Arm 1:

- to receive carboplatin, pemetrexed plus **placebo** every 3 weeks for 4 cycles (last dose on Day 63)
- then, starting on Day 84, to receive pemetrexed alone every 3 weeks for 4 cycles (last dose on Day 147)
- then, starting on Day 168, to receive pemetrexed plus **placebo** every 3 weeks for 4 cycles (last dose on Day 231)
- then, continue to receive pemetrexed every 3 weeks

Arm 2:

- to receive carboplatin, pemetrexed plus demcizumab every 3 weeks for 4 cycles (last dose on Day 63)
- then, starting on Day 84, to receive pemetrexed alone every 3 weeks for 4 cycles (last dose on Day 147)
- then, starting on Day 168, to receive pemetrexed plus placebo every 3 weeks for 4 cycles (last dose on Day 231)
- then, continue to receive pemetrexed every 3 weeks

Arm 3:

- to receive carboplatin, pemetrexed plus demcizumab every 3 weeks for 4 cycles (last dose on Day 63)
- then, starting on Day 84, to receive pemetrexed alone every 3 weeks for 4 cycles (last dose on Day 147)
- then, starting on Day 168, to receive pemetrexed plus demcizumab every 3 weeks for 4 cycles (last dose on Day 231)
- then, continue to receive pemetrexed every 3 weeks

You will have an equal chance of being assigned to Arm 1, Arm 2 or Arm 3. Neither you nor your doctor will know which treatment arm you have been assigned to or whether you are receiving demcizumab or placebo.

Pemetrexed

Pemetrexed will be administered at a dose of 500 mg/m^2 as an intravenous infusion over ≥10 minutes on the first day of every 21-day cycle for 4 cycles, after the administration of demcizumab or placebo. Pemetrexed may be given for 4 cycles unless you have side effects or disease progression that necessitates stopping the drug. After 4 cycles, if you have stable or improved disease, you will continue to receive pemetrexed once every 21 days as maintenance therapy until your tumor progresses.

In order to reduce gastrointestinal and hematologic side effects, you will take folic acid of ≥400 µg daily for at least 5 of the 7 days before the first dose of pemetrexed is administered and you will continue to take ≥400 µg of daily folic acid throughout the treatment period and for the first 21 days after the last dose of pemetrexed. You will also receive an intramuscular injection of vitamin B12 at a dose of 1000 µg during the week before the first dose of pemetrexed and every 63 days while you are being treated with pemetrexed (on Days 63, 126, 189, etc.).

In order to reduce the occurrence of skin rashes, you will receive dexamethasone, 4 mg orally twice a day on the day before, the day of, and the day after pemetrexed administration, unless your physician determines that this is not right for you.

Carboplatin

Carboplatin will be administered as an intravenous infusion over 15–60 minutes on Day 1 of every 21-day cycle for 4 cycles, after the administration of demcizumab and pemetrexed. The dose will depend on several factors including your kidney function as determined by the creatinine clearance test and your serum creatinine level. Carboplatin may be given for 4 cycles unless you have side effects or disease progression that necessitates stopping the drug. Your physician may prescribe medication to prevent nausea and vomiting from the administration of pemetrexed and carboplatin therapy.

If you develop side effects during this time period, your physician may decide to hold or reduce the carboplatin and/or pemetrexed. If this occurs, the demcizumab or placebo may still be administered as scheduled.

Study Day 0: The following assessments will be done prior to the infusion of demcizumab or placebo, carboplatin, and pemetrexed: abbreviated physical examination including weight; review of medications you are taking, including any changes in medication since the screening visit; changes in your medical status; and vital signs. Approximately 4 tablespoons of blood will be drawn for routine tests, antibody testing, pharmacokinetic testing (before and after your infusion) and biomarkers.

If you agree to the optional pharmacogenomics testing, you will sign the optional Pharmacogenomics Informed Consent, and a blood sample will be collected.

Study drug will be administered and you will be monitored for at least 15 minutes after the demcizumab (or placebo) has been stopped. Pemetrexed will then be administered, followed by carboplatin.

Study Days 7, 14, 21, 28, 35, and 42: Demcizumab or placebo, carboplatin, and pemetrexed will be given on Study Days 21and 42 only. The following assessments will be obtained weekly: weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs. An abbreviated physical examination will be performed on the days that you receive demcizumab or placebo.

Blood will be taken weekly for routine testing (including BNP on Day 21 and Day 42). At Day 42 only, blood will also be obtained to test for pharmacokinetic testing and antibodies to demcizumab, and blood will be taken for testing tumor markers (if your CEA was elevated at your screening visit). On Day 28, blood will also be obtained for biomarkers. Approximately 3 tablespoons of blood will be drawn on Study Days 7, 14, 21, 28, 35, and 42.

On Day 28, an ECG and Doppler echocardiogram will be done.

In addition, on Day 42, you will undergo a CT scan or MRI of the chest, abdomen, and other parts of your body, if your cancer has spread there, to assess whether your cancer has improved, progressed, or is stable. If the CT scan or MRI shows that you have stable or improved disease, you may continue to receive demcizumab/placebo, carboplatin and pemetrexed.

If the CT scan or MRI shows disease progression, you will be taken off the study and will undergo assessments listed under **Termination Visit**.

Study Day 56: The following assessments will be obtained: changes in your medical status or new health problems since the previous study visit.

An ECG and Doppler echocardiogram will be done.

Study Day 63: Demcizumab or placebo, carboplatin, and pemetrexed will be given. The following assessments will be obtained prior to the infusion of drug: weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs. An abbreviated physical examination will be performed.

Blood, approximately 3 tablespoons, will be taken for routine testing (including BNP).

Study Day 84: Pemetrexed will be given. The following assessments will be obtained: weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs. An abbreviated physical examination will be performed on the day that you receive pemetrexed.

Blood will be taken for routine testing (including BNP). Blood will also be obtained for testing for antibody formation to demcizumab and for pharmacokinetic testing, and blood will be taken for testing tumor markers (if your CEA was elevated at your screening visit). Approximately 3 tablespoons of blood will be drawn.

An ECG and Doppler echocardiogram will be done.

You will undergo a CT scan or MRI of the chest, abdomen, and other parts of your body, if your cancer has spread there, to assess whether your cancer has improved, progressed, or is stable. If the CT scan or MRI shows that you have stable or improved disease, you may continue to receive demcizumab/placebo, carboplatin and pemetrexed.

If the CT scan or MRI shows disease progression, you will be taken off the study and will undergo assessments listed under **Termination Visit**.

Study Day 105: The following assessments will be obtained prior to the infusion of pemetrexed: abbreviated physical examination including weight; review of the medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs.

Approximately 3 tablespoons of blood will be taken for routine testing, including BNP.

As long as your disease is stable or shows a response, you may continue to receive pemetrexed every 3 weeks. You will undergo the tests listed for Study Day 105 during each of these 3-week cycles. You will receive intramuscular injection of vitamin B12 at a dose of 1000 μg every 63 days while receiving pemetrexed. In addition, every 6 weeks you will undergo a CT scan or MRI of the chest, abdomen and other parts of your body, if your cancer has spread there, to assess whether your cancer has improved, progressed, or is stable.

Every 6 weeks blood will be taken for antibodies to demcizumab, and blood will be obtained for tumor markers, if applicable. You will also have an ECG and a Doppler echocardiogram every 4 weeks.

Starting on Day 168, you will receive demcizumab or placebo every 3 weeks for four 21-day cycles. On Day 168 (before and after your infusion), Day 210 (before and after your infusion) and Days 252, 294 and 336 (before infusion) only, blood samples will be taken for pharmacokinetic testing.

TERMINATION VISIT

When you have discontinued receiving study drugs (demcizumab or placebo, carboplatin, and pemetrexed, or pemetrexed alone), and you are no longer being followed with study assessments, including CT scans or MRIs every 6 weeks to assess whether your cancer has improved, progressed, or is stable, the following assessments will be performed: abbreviated physical exam with weight; review of medications you are taking and any changes in medication since the previous visit; changes in your medical status or new health problems since the previous study visit; and vital signs.

Blood samples will be obtained for routine testing (including BNP), antibody formation to demcizumab, and pharmacokinetic testing. Blood will also be obtained for biomarkers unless obtained within the previous 14 days. Blood will also be obtained for tumor marker testing if applicable and for BNP unless obtained within the previous 28 days. A urine specimen will be obtained. An ECG and a Doppler echocardiogram will be performed. A repeat CT scan or MRI of the chest, abdomen, and other parts of your body, if your cancer has spread there, will be obtained unless performed within 14 days of Termination visit.

Approximately 3 tablespoons of blood will be drawn during this visit.

FOLLOW-UP AFTER TERMINATION VISIT

If your blood pressure was too high at the Terminiation visit (greater than 150/90 mmHg), your blood pressure will be determined every 2 weeks until your blood pressure is less or equal to 150/90 mmHg for a 4-week period.

You will be contacted every 3 months for up to 5 years by the clinic study staff to check on your condition. This contact may be by telephone or medical record review. Information regarding any anti-cancer therapies that you receive will also be collected through telephone calls, review of medical records, and/or clinic visits.

In addition, if your tumor has not progressed at the time of your Termination visit, your tumor response outcome will continue to be followed until you begin receiving alternative anti-cancer treatment or your tumor progresses, whichever occurs first, and a copy of the corresponding radiographs (e.g., CT scans and/or MRIs) may be provided to OncoMed, the Sponsor of the trial. If you have a BNP ≥400 pg/mL and/or a diagnosis of pulmonary hypertension or heart failure at

the time of termination, all subsequent standard of care BNP data will be collected until the value is <200 pg/mL and all subsequent standard of care left ventricular ejection fraction (LVEF) and peak tricuspid velocity (PTV) values will be collected until they normalize. LVEF and PTV are tests that provide information on how your heart is functioning.

POSSIBLE RISKS AND DISCOMFORTS

Demcizumab

The following are the side effects that were observed in >10% (common) and 5-10% (less common) of the 55 patients treated in the initial **single-agent study** of demcizumab and were considered to be possibly related to demcizumab.

Common (occurred in >10% of patients who received demcizumab)

Hypertension, fatigue, anemia, diarrhea, headache, nausea, decreased protein in the blood and shortness of breath

Less Common (occurred in 5-10% of patients who received demcizumab)

Low sodium in blood, dizziness, weight loss, heart failure, shortness of breath with activity, laboratory values indicating a decrease in liver or kidney function, decreased white blood count in the blood, abdominal pain, chills, fever, insomnia and cough

The following are the side effects that were observed in >10% (common) and 5-10% (less common) of the 99 patients treated in the 4 studies of **demcizumab plus chemotherapy** and were considered to be possibly related to demcizumab.

Common (occurred in >10% of patients who received demcizumab and chemotherapy)

Fatigue, nausea, hypertension, swelling of tissue due to increased fluid, diarrhea, appetite decreased, increased BNP (suggesting possible early damage to the heart), anemia, decreased platelet count in the blood, decreased white blood count in the blood, shortness of breath, headache, increased pressure in the lungs, constipation and rash.

Less Common (occurred in 5-10% of patients who received demcizumab and chemotherapy)

Change in taste, hair loss and laboratory values indicating a decrease in liver function

The majority of the side effects observed in these studies were mild to moderate. The most common adverse event across these studies that was clearly related to demcizumab was hypertension which occurred in 14-60% of the patients. Thus, if you participate in this study, your blood pressure will be checked frequently and, if necessary, you will be treated with medication(s) to lower your blood pressure. If your increased blood pressure is not controlled by medications, administration of demcizumab will be discontinued.

In addition, in these studies, 7 patients developed serious bleeding in the gastrointestinal tract. Two patients died as a result of this bleeding. Because of that, you will not be treated in this study if you have tumor in one or more locations that carries an increased risk for bleeding. If you participate in the study, your hemoglobin (a measurement of the amount of red blood cells) will be tested regularly. If your hemoglobin decreases, your physician will look carefully for the reason. If you develop active significant bleeding, administration of demcizumab will be discontinued.

One patient in the single-agent study died as a result of complications relating to a tumor within the brain. As a result, if you choose to participate in this study, prior to treatment you will have a scan of the brain to ensure that there is no tumor within the brain. Patients who have a tumor within the brain will not be able to participate in the study.

Finally, approximately 40% of patients treated in these trials developed rises in a laboratory test (BNP) suggesting possible early damage to their heart. In addition, approximately 5-10% of the patients had symptoms of heart failure (such as shortness of breath and/or extra fluid in their legs). These patients typically improved after discontinuation of demcizumab and treatment with medications to reduce their symptoms. In addtition, the heart failure typically developed in patients who received demcizumab for at least 3 months. Also, an increase in the blood pressure in the lungs which can also result in heart failure has been observed in some patients that were typically treated for more than than 3 months. As a result, demcizumab will not be given on an ongoing basis in this study. Instead, a shortened regimen of 4 doses over 63 days will be administered either once or twice during your time on study. Approximately 50 patients have received this type of shortened treatment schedule, and none have developed serious heart failure or increased blood pressure in the lungs. However, it is anticipated that heart failure and /or increased blood pressure in the lungs will likely still occur in some patients receiving this shortened duration of treatment with demcizumab. Finally, no patients have been previously treated with a 2nd 63-day course of demcizumab that some patients will be receiving in this study, so the risks of this approach are unknown.

You will not be treated in this study if you have an elevated BNP value, evidence of heart failure or evidence of disease in the vessels in your heart, or have a significant decrease in the amount of blood your heart is pumping on Doppler echocardiogram. Your heart and lung function will be watched closely while you are on study using blood tests and echocardiograms. If these side effects are noted, you will be referred to a heart specialist who may be able to treat the side effects with drugs. If further increases in your BNP occur or the amount of blood your heart is pumping declines further, your demcizumab therapy will be discontinued.

As with all antibody treatments, there is the possibility of an allergic reaction, such as fever, chills, rash, and/or hives associated with the infusion of demcizumab. Rarely, a severe or serious allergic reaction can occur during or following the administration of an antibody.

Not enough patients have yet been treated with demcizumab to fully understand the side effects that may be associated with this antibody.

The following side effects have been observed in other drugs that have an anti-angiogenic effect (drugs that prevent the growth of new blood vessels that tumors need to grow and spread) and in other drugs that may inhibit the growth of cancer stem cells. It is not known if the administration of demcizumab will result in any of these findings:

- Gastrointestinal perforation sometimes associated with intra-abdominal abscess
- Diarrhea, weight loss, constipation, vomiting, abdominal pain, nausea, and fever
- Wound healing complications
- Hemorrhage including minor bleeding events such as nose bleeds or more serious, sometimes fatal bleeding events
- Arterial or venous thromboembolic events, including cerebral (brain) infarction, transient ischemic attacks (TIAs), myocardial infarction (MI), angina, and other sometimes fatal events
- Hypertension including episodes of severe increased blood pressure
- Neutropenia and/or infection
- Proteinuria (loss of protein through your kidneys)
- Congestive heart failure
- Diarrhea
- Rashes
- Somnolence (sleepiness)
- Fatigue
- Prolonged QT interval (irregular heart rhythm)

Pemetrexed: The following side effects have been reported in >10% of patients receiving pemetrexed:

- Low blood counts. Your white and red blood cells, neutrophils and platelets may decrease. This may put you at an increased risk for infection, anemia, and/or bleeding
- Decreased kidney function
- Fatigue
- Nausea
- Sensory neuropathy. Neuropathy (nerve damage). You may feel weakness, pain, numbness, and/or a tingling sensation especially in your fingers and toes
- Taste disturbance
- Rash, peeling of the skin, hives
- Increases in liver enzymes

Carboplatin: The following side effects have been reported in >10% of patients receiving carboplatin:

- Low blood counts. Your white and red blood cells, neutrophils, and platelets may decrease. This may put you at an increased risk for infection, anemia, and/or bleeding.
- Infection
- Bleeding
- Nausea
- Vomiting
- Peripheral neuropathy
- Hearing loss
- Central neurologic toxicity
- Decreased kidney function
- Elevation of liver function tests
- Electrolyte imbalances
- Pain
- Weakness
- Cardiovascular abnormalities
- Respiratory problems
- Mouth and lip sores and sore throat
- Allergic reaction such as hives, redness and itching
- Serious allergic reactions such as anaphylaxis
- Hair loss

Other less frequent adverse events occur following the administration of carboplatin and pemetrexed.

Infusions

Demcizumab or placebo, carboplatin and pemetrexed will be given as intravenous infusions. There may be minor discomfort from the needle in your arm. Bruising, swelling and, in rare instances, infection and blood clot may occur at the infusion site.

Blood Draws

During the course of this study, your blood will be drawn for laboratory tests (3-4 tablespoons will be collected at each blood draw). The risks of drawing blood include some discomfort from

the needle in your arm, bruising, swelling at the needle site and, in rare instances, infection or fainting.

You will also be informed of any new significant side effects that develop during the course of this research study, or others regarding the use of demcizumab.

Radiation exposure

Risk relevant to the radiation exposure due to the following procedures: Radiographic evaluation: Conventional CT, Spiral CT, or MRI of the chest, abdomen, and pelvis performed in screening, the same radiographic technique of each region must be used consistently throughout the study. Radiographic evaluation: Conventional CT, Spiral CT, or MRI of the head performed in screening.

PREGNANCY

There is a very high risk that demcizumab may be harmful to an unborn baby (embryo or fetus) or newborn child.

Therefore, women who are pregnant or breastfeeding may not participate in this study. Women must have a negative pregnancy test before beginning the study. It is important that both men and women take steps to prevent pregnancy during this study through the use of adequate contraception (for example, a barrier or hormone method or abstinence) prior to study entry and for the duration of the study until 6 months after the last dose of demcizumab.

If you become pregnant or suspect that you are pregnant, or if your partner becomes pregnant or suspects that she is pregnant during the study or within 6 months after the last dose of demcizumab, you must notify the study investigator immediately. If you become pregnant, you will be taken off of treatment and will undergo assessments listed under the Termination Visit section of this document, except for the radiographic studies, which will not be performed. If your partner becomes pregnant, you will remain on the study. If either you or your partner becomes pregnant during the study or within 3 months after the last dose of demcizumab, you and/or your partner will be followed through the first well-baby visit or longer if any abnormality is present.

POTENTIAL BENEFITS

There is no guarantee that there will be any direct benefit to you if you take part in this research study. The treatments you receive may be harmful. It is possible that the information learned from this study may be helpful in the future to other people with cancer.

SIGNIFICANT NEW FINDINGS

Any significant new findings regarding demcizumab that become known during the course of this research study that might reasonably affect your willingness to participate in this study, will be provided to you in a timely manner.

ALTERNATIVE TREATMENTS AND PROCEDURES

If you decide not to participate in this study, you will continue to receive medical care to which you were entitled prior to your participation in this study. Your doctor will discuss other options available to you. Your choice not to participate in this study will not affect your medical care in any way.

TERMINATION OF PATIENT PARTICIPATION

Your participation in this research study may be terminated at any time for medical reasons or because the sponsor finds it necessary to limit or terminate this clinical trial. Some reasons for termination include progression of your disease, any other illness that prevents further administration of demcizumab, unacceptable adverse events, unacceptable BNP and/or LVEF values, general or specific changes in your condition that make further treatment unacceptable in the opinion of your doctor, and protocol non-compliance.

Your doctor may decide to hold or stop the demcizumab or placebo injections at any time during the study for safety reasons.

If your doctor or the sponsor decides to withdraw you from the study, you will undergo the same assessments listed under **Termination Visit**. In addition, your doctor will discuss with you alternate therapies for your disease.

COSTS AND COMPENSATION

The cost of all "standard of care" assessments related to your participation in this study and your medical care will be billed to you and/or your insurance company. These are tests that would normally be performed in patients to evaluate their cancer. Due to the investigational nature of this research study, insurance companies or government health care programs may limit their obligation to pay for experimental treatments and their consequences. You may want to discuss this with your insurance company before agreeing to participate. The cost of all non-standard of care assessments will be paid for by OncoMed.

You will not be paid for participation in this study.

You may be reimbursed for any reasonable travel expenses (bus/train/taxi fares) incurred as a result of taking part in this study on production of a receipt.

COMPENSATION FOR RESEARCH-RELATED INJURY

If you are physically injured as a direct result of demcizumab or a study procedure properly performed under the plan for this study and it is not due to a pre-existing medical condition or underlying disease, or your failure to follow the instructions provided by your doctor or another member of the study team, OncoMed will reimburse you for the reasonable medical expenses for medically necessary treatment of that injury which are not covered by another payor, your own insurance or health care program. No other compensation is available from OncoMed if any injury occurs.

CONFIDENTIALITY

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

HOW WILL YOUR CONFIDENTIALITY BE RESPECTED AND THE PRIVACY OF YOUR PERSONAL INFORMATION MAINTAINED?

You have the right to control the use and disclosure of your personal information. Basic personal information will be recorded including your name, contact details, gender, height, weight and racial origin, as well as information on your medical history, and clinical data collected about your participation in the study. All this information will be used for research and clinical purposes only, including without limitation the pharmacokinetic and optional DNA research described in this consent form.

The following people may also have access to these records: representatives of the FDA, other regulatory authorities, the Institutional Review Board/Independent Ethics Committee, OncoMed representatives and monitors, and OncoMed collaborators and licensees. All personnel accessing your records are required to respect your confidentiality at all times.

To ensure privacy, your name and other identifying information will not be attached to records or samples released for research purposes. Instead, you will only be identified by a code. Only the study doctor and authorized personnel will be able to connect this code to your name, by a list that will be kept securely by the study site for "[insert retention period]" years. Your date of birth (Amend the sentence to account for any country-specific rules) may also be recorded to help identify your study record. Your coded data will be forwarded to OncoMed and its service providers for activities related to the study e.g., laboratory analysis. It will be transferred into a computer database and processed to allow the results of this study to be analyzed and reported or published. If the results of the study are published, your identity will remain confidential, you will not be identified by name, picture, or by any other personally identifying information. A list of companies to whom your coded information is transferred is available from OncoMed via your study doctor.

EMEA: Under data protection law [identification of national law] your study site and OncoMed Pharmaceuticals shall be jointly responsible as 'controllers' for ensuring that your information is safeguarded. OncoMed has appointed [PPD local company name] as its 'representative' in your country to fulfill its obligations under this law.

The information that we collect from you may be transferred to, and stored at, a destination outside the European Economic Area ("EEA"). It may also be processed by staff operating outside the EEA who work for us or for our representative. By participating in the research study, you agree to this transfer, storing or processing outside of the EEA. When transferring such information to destinations outside of the EEA, we will also make sure that your information will be treated with an adequate level of protection as required under your local data protection laws.

APAC: Under data protection law [identification of national law] your study site shall be responsible for ensuring that your named personal information is safeguarded.

USA: Because of the research goals of this study, however, your study records cannot be kept completely confidential. The sponsor of this study is OncoMed Pharmaceuticals.

The study data may be transferred to other countries for processing, including countries not covered by data protection legislation similar in scope to the data protection legislation of your country, or at all. The laws of your state may provide further protection.

CANADA: Under federal data protection law, The Personal Information Protection and Electronic Documents Act (PIPEDA) and regional specific regulations, your study site shall be responsible for ensuring that your information is safeguarded.

You have the right to access, through your study doctor, all the information collected about you and, if applicable, ask for corrections. But, in order to protect the scientific integrity of the study, the treatment you received in this study needs to remain unknown (i.e., blinded) until the study data is analyzed. Recipients of your information may be in countries that do not have data protection safeguards and rights. In such case, OncoMed and its authorized representatives, and regulatory authorities, shall anyway seek to maintain confidentiality within the limits of local laws in these countries and comply with the data export requirements of your country, including any requirements to ensure an adequate level of protection.

If you should withdraw from the study, data collected prior to your withdrawal may still be processed along with other data collected as part of the study. Normally no new information will be collected for the study database unless you specifically consent to such collection. However, the law does require that any side effects you may suffer are documented and reported. To complete the study findings, your long term health status may also be recorded (unless you object). You have the right to require that any previously retained samples are destroyed.

WHAT WILL HAPPEN TO YOUR DATA?

This clinical study may only be performed by collecting and using your medical information. Data protection laws give you the right to control the use of your personal information. Therefore, by signing this form you specifically authorize your information to be checked, transferred and processed as follows:

- The authorized representatives of Oncomed, the Ethics Committee and regulatory authorities' inspectors may review your medical information by direct access to your medical records.
- Study data, including your coded medical information, may be used and shared for legitimate study and scientific purposes, including if you do not object, for future use in medical or pharmaceutical research.

☐ I agree to the use of my coded medical information for future research purposes.

Signature: _____

☐ I don´t agree to the use of my coded medical information for future research purposes.

Signature: _____

- Study data may be transferred to other countries for processing, including countries not covered by data protection legislation similar in scope to the data protection legislation of your country, or at all.

HAS THE STUDY RECEIVED MEDICAL OR ETHICAL APPROVAL?

The Ethics Committee has given this study a positive opinion.

You will be asked to review and sign a HIPAA (Health Insurance Portability and Accountability Act) Research Authorization Form requesting your authorization to collect, use, and disclose your medical information.

OR IF SITE DOES NOT HAVE OWN HIPAA FORM:

AUTHORIZATION TO USE AND DISCLOSE MY HEALTH INFORMATION

I authorize (give permission to) insert name of study site to use and disclose (share) my health information solely for the purposes of this research study and research directly related to the use of demcizumab. I understand that my health information that I am authorizing to be used and disclosed (Authorized Health Information) includes all health information about me that has been

and will be created or received by (SITE) and that is in my medical records maintained by (SITE).

I understand that I am free at any time to restrict the (SITE's) use and disclosure of my Authorized Health Information, without penalty or other consequences. However, I also understand that I may be denied participation in, or continued participation in, this research study if at any time I choose to restrict the (SITE's) use and disclosure of Authorized Health Information that is necessary for the completion of this research study.

AUTHORIZED PERSONS AND RECIPIENTS

I authorize the following person(s) and groups of persons to request, receive, and use my Authorized Health Information: representatives of the FDA, other regulatory authorities, the Institutional Review Board/Independent Ethics Committee, OncoMed representatives and monitors, and OncoMed collaborators and licensees. I authorize (SITE) to disclose my Authorized Health Information to these persons and groups of persons.

RE-DISCLOSURES TO THIRD PARTIES

I understand that once (SITE) discloses my Authorized Health Information to the recipient(s) identified in the previous section Authorized Persons and Recipients, (SITE) cannot guarantee that the recipient(s) will not re-disclose my Authorized Health Information to other persons who may not be bound by this informed consent form.

EXPIRATION DATE

My authorization (permission) to use and disclose my Authorized Health Information will continue indefinitely, but that use and sharing will only be for the purposes described in this informed consent form.

EFFECT OF MY REVOCATION OF AUTHORIZATION TO USE AND DISCLOSE AUTHORIZED HEALTH INFORMATION

I understand that my authorization for (SITE) to use and disclose my Authorized Health Information will remain in effect until I withdraw my permission by sending my written notice of revocation (withdrawal of permission) to the Privacy Office listed in the Questions section. My written revocation will be effective immediately upon (SITE's) receipt of my written notice, except that the revocation will not have any effect on any actions take by (SITE) in relying on this authorization before it received my written notice of withdrawal of permission.

QUESTIONS

If you have any question about the study and/or its procedure or safety, you may contact Dr. (Name of Investigator) at (telephone number). In the event of any injury, you may contact Dr. (name) at (telephone number). You may also call (Name) at (telephone number) for information on experimental patients' rights.

If at any time during this research study you feel that you have not been adequately informed of your rights with respect to the privacy of your health information, or you feel that the privacy of your health information has not been adequately protected, you may contact or visit (Site's) privacy office during normal working hours at (Privacy Office name) at (telephone number and address).

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

PROTOCOL M18-007: A Three Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

Your decision to participate in this study is entirely voluntary. You may refuse to participate in or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. A signed copy of this consent form will be given to you for your records and a copy will be retained by the investigator for his or her files

By signing the form below, you acknowledge that you have read the above information about this research study, and have had a chance to ask questions to help you understand your participation in this study and how your information will be used.

_____ _____

Signature of Patient or Patient's Authorized Representative **Date**

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent **Date**

_____

Printed Name of Witness*

_____ _____ _____

Signature of Witness* **Date**

*If the Principal Investigator or Institutional Review Board deems a witness signature is necessary.

APPENDIX F: PHARMACOGENOMICS INFORMED CONSENT

PROTOCOL M18-007: A Three Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

This Informed Consent Form is linked to the main ICF for the trial Master ICF version 1.0. This Informed Consent Form is only valid in addition to the main ICF described above.

WHAT IS THE PURPOSE OF THIS PART OF THE STUDY?

The cells of your body contain deoxyribonucleic acid, or DNA for short. DNA is passed down from your parents. Genes carry the DNA that determine your physical appearance such as the color of your eyes and hair. Differences in our genes help explain why we all look different. Differences in our genes may also help explain why some drugs work and are safe in some people, but not in others. Differences in our genes also help explain why some people get certain diseases, but others do not.

The sponsor would like to study the differences in people's DNA to learn more about diseases and response to drugs. This information will be used to try to develop safer and better drugs. To do this, the Sponsor would like to do DNA tests related to demcizumab and the diseases for which this drug is developed. The DNA tests are only for research. The tests are not for your medical care. All volunteers taking part in the main study are also being invited to take part in DNA research (where possible).

WHAT AM I BEING ASKED TO DO?

You are being asked to give one small blood sample (10 mL, about 2 teaspoons) at Study Day 0. Blood will be drawn from a vein using a needle. DNA will be extracted from your blood sample.

Your DNA may be tested for specific genes relevant to demcizumab, carboplatin and/or pemetrexed (the study drugs), the Notch/DLL4 pathways (the targets of demcizumab) and/or other genes related to your cancer. Only DNA research related to demcizumab, carboplatin, or pemetrexed or to the diseases for which these drugs are developed will be performed. No blood sample for DNA research will be taken from you unless you sign and date this Informed Consent Form.

In addition, if a piece of your tumor was previously collected as part of your diagnosis, you are being asked to have DNA testing performed on your tumor. DNA will be extracted to help to identify biomarkers that could be used in the future to predict which patients are more likely to respond to demcizumab, carboplatin and pemetrexed treatment. Analysis of candidate genes and/or proteins relevant to the Notch pathway may be performed (e.g., Notch1, Hey L, FBW7, etc.). No DNA research will be performed on your tumor unless you sign and date this Informed Consent Form.

The Sponsor will store the samples until there is no DNA left.

The sampes will be retained at OncoMed Pharmaceuticals, 800 Chesapeake Dr., Redwood City, California, U.S.A, 94063.You can also decide not to take part at all in DNA research. No blood sample for DNA research will be taken from you unless you sign and date this Informed Consent Form. Your decision to give, or not to give, a DNA sample will not affect the medical care that you receive from your study doctor or his/her staff. Your participation is voluntary.

HOW WILL MY IDENTITY AND RESULTS BE KEPT CONFIDENTIAL?

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you or your family against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Also, GINA does not prohibit discrimination of individuals with a genetic disorder that has been diagnosed.

The Sponsor has taken several steps to keep your identity and results confidential. These are described below.

a) Coding of your DNA Sample

Your DNA sample will not have your name or address on it. Your DNA sample will be coded with your Patient number from the main study. After the study is officially over, the Patient number will be removed from your DNA sample. Your DNA sample and results will be labeled with a new number.

b) Restricted Access to Your DNA Sample

The Sponsor will control your DNA sample. Your DNA sample will be stored in a secure room at a facility in Redwood City, CA, or other site designated by the sponsor. Only authorized staff are allowed to enter the room. Your DNA sample may be transferred to other research partners working with the Sponsor. DNA samples transferred to research partners will not contain your

Patient number. Your DNA sample will not be sold, loaned, or given to any other independent groups for their own use. Research partners working with the Sponsor are not allowed to share DNA samples with anyone else.

c) Restricted Access to Results

Your DNA results will be stored by the Sponsor both on paper and in computer records. You will not be identified by name in these records. Your results will only be labeled with a code number. This is to protect your privacy. Your results will be kept as long as necessary. The following people may see your test results:

- The Sponsor
- Research partners working with the Sponsor
- Independent Ethics Committees/Institutional Review Boards
- Regulatory authorities, like the Australian Health Authority or EMA

Unless the law requires it, your individual results will not be given to anyone who is not listed above. For example, your results will not be given to employers, insurance companies or family members. Research partners working with the Sponsor may not use or share your results without permission from the Sponsor.

DNA results from the study may be published or added to public databases. They also may be presented in public meetings. No publication or presentation will identify you by your code number or name.

d) Separate Storage of DNA Forms

Your study doctor will keep your signed DNA informed consent form, and any other DNA forms, separate from your other medical files. People who have access to your medical files (such as insurance companies) would not know that you took part in a DNA research study by looking at your medical files. You will be given a copy of your signed DNA consent form.

WHAT IF I CHANGE MY MIND LATER?

If you change your mind and decide later that you no longer want to take part in DNA research, you may ask for your DNA sample to be destroyed as long as the study is not officially over. You can stay in the main study even if you change your mind about taking part in DNA research.

WILL I GET MY DNA TEST RESULTS?

The tests will be performed in a research laboratory. Results from a research laboratory may not always be exact. They cannot be used to make a diagnosis about your health. Also, research laboratories cannot give advice on health or health risks. For these reasons, the results of your DNA tests will not be given to you or your study doctor (or his/her staff).

WHAT ARE THE BENEFITS?

You will not directly benefit from taking part in this DNA research. This research could provide information about demcizumab or the diseases for which this drug is developed. This information could help others in the future.

WHAT ARE THE RISKS?

There may be some pain or bruising from the needle stick used to draw the blood. Some people may faint when their blood is drawn. Very rarely, there may be an infection at the place where the needle went into the skin. Any problem that you have from drawing blood will be handled the same way as in the main study. Your research results cannot be used to make a diagnosis about your health.

WILL I BE PAID FOR TAKING PART OR FOR THE USE OF MY RESULTS?

You will not be paid for taking part in the DNA research part of the study. You will not be paid for any use of your DNA sample or results or for any inventions that are made from them. If you take part, you are providing your DNA sample for use by the Sponsor. The Sponsor intends to own any use of the results, treatments, or inventions that can be made from the research.

QUESTIONS

If you have any question about the study and/or its procedure or safety, you may contact Dr. (Name of Investigator) at (telephone number). In the event of any injury, you may contact Dr. (name) at (telephone number). You may also call (Name) at (telephone number) for information on experimental patients' rights.

If at any time during this research study you feel that you have not been adequately informed of your rights with respect to the privacy of your health information, or you feel that the privacy of your health information has not been adequately protected, you may contact or visit (Site's) privacy office during normal working hours at (Privacy Office name) at (telephone number and address).

VOLUNTARY PARTICIPATION AND DOCUMENTATION OF CONSENT

PROTOCOL M18-007: A Three Arm Phase 2 Double-Blind Randomized Study of Carboplatin, Pemetrexed Plus Placebo versus Carboplatin, Pemetrexed plus 1 or 2 Truncated Courses of Demcizumab in Subjects with Non-Squamous Non-Small Cell Lung Cancer

Your decision to participate in this part of the study is entirely voluntary and you may choose not to participate in this part of the study without prejudice or loss of benefits to which you are otherwise entitled in the remainder of the study. A signed copy of this consent form will be given to you for your records and a copy will be retained by the investigator for his or her files.

By signing the form below, you acknowledge that you have read the above information about this research study, and have had a chance to ask questions to help you understand your participation in this study and how your information will be used.

I consent to the processing of my personal data, including any sensitive personal data, as set out above and to the transfer of such data to countries outside of the European Economic Area

☐ Yes ☐ No

I consent to provide the Optional Pharmacogenomics Specimen

☐ Yes ☐ No

I consent to allow my tumor specimen to be analyzed for DNA

☐ Yes ☐ No

_____

Printed Name of Patient or Patient's Authorized Representative

_____ _____

Signature of Patient or Patient's Authorized Representative Personally **Date**

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent Personally **Date**

_____

Printed Name of Witness*

_____ _____

Signature of Witness* Personally **Date**

*If the Principal Investigator or Institutional Review Board deems a witness signature is necessary.