Research Study Informed Consent Document

Study Title for Participants: Targeted Treatment (ramucirumab plus pembrolizumab) for Advanced Non-Small Cell Lung Cancer

LUNGMAP, "A Master Protocol to Evaluate Biomarker-Driven Therapies and Immunotherapies in Previously-Treated Non-Small Cell Lung Cancer (Lung-MAP Screening Study)"

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

S1800A, "A Phase II Randomized Study of Ramucirumab Plus MK3475 (Pembrolizumab) versus Standard of Care for Patients Previously Treated with Immunotherapy for Stage IV or Recurrent Non-Small Cell Lung Cancer (Lung-MAP Non-Matched Sub-Study)"
(NCT 03971474)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have non-small cell lung cancer that has spread outside your lungs, and your tumor sample did not have a biomarker that matches one of the treatment studies that are open or because you were not a candidate for a biomarker-matched treatment study.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can we lower the chance of your lung cancer growing or spreading by combining two drugs that work with your immune system to fight your cancer?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your lung cancer. The usual approach is defined as care most people get for their lung cancer.

What is the usual approach to my lung cancer?

The usual approach for patients who are not in a study is treatment with chemotherapy or immunotherapy drugs. If you have already received chemotherapy, other chemotherapy drugs or immunotherapy may be an option. If you have already received immunotherapy, chemotherapy may be an option. In addition, immunotherapy has been Food and Drug Administration (FDA) approved for patients whose disease has gotten worse. The approval was based on results of clinical trials where patients had improved overall survival with immunotherapy compared to standard chemotherapy.

- For patients whose disease has gotten worse while receiving platinum-based chemotherapy (like cisplatin or carboplatin), immunotherapy options include pembrolizumab alone for tumors with a low tumor expression of PD-L1.
- Other available immunotherapy options are nivolumab and atezolizumab, which do not need PD-L1 expression testing.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.
- There are many other options that your physician can talk to you about.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get the current standard of care drug (docetaxel, gemcitabine, pemetrexed, or ramucirumab combined with docetaxel) or you will get

the study drugs (ramucirumab combined with pembrolizumab), until your disease gets worse or the side effects become too severe.

After you finish your study treatment, your doctor will continue to follow your condition for up to three years from the time you went on study and watch you for side effects. If your disease has not gotten worse, follow up visits will occur every 3 months for the first year, then every 6 months up to 3 years from the time you go on study. If your disease has gotten worse, follow up visits will occur every 6 months for 2 years, then at the end of the 3 years from the time you go on study. Your doctor may give you other tests or procedures if they think they are needed for the regular care of your disease.

Should your disease worsen, you have the option to participate in a different sub-study. As before, the new sub-study that you will be offered will depend on a combination of the results of the previous testing done on your tumor sample and the sub-studies available. If the tests show that your tumor has more than one biomarker that qualifies you for a different sub-study, you will be assigned to one of these sub-studies randomly (by chance). A sub-study may be available if your tumor does not have any additional biomarkers being tested or you were not eligible to participate in other sub-studies.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Vomiting, diarrhea, nausea, constipation
- Anemia which may require blood transfusions
- Infection, especially when white blood cell count is low
- Tiredness
- Rash, itching

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that the combination of ramucirumab plus pembrolizumab could shrink your type of cancer or prevent it from returning. It is unlikely that it will work in everyone with your cancer or help you live longer. This study will help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. Contact information for your study doctor is listed on the consent cover page. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor SWOG Cancer Research Network (SWOG). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

End of Overview and Key Information

What is the purpose of this study?

There are several investigational treatments that are being tested in various sub-studies as part of this study. You will have already received the information on your biomarker testing. You have been assigned to this treatment study because your tumor sample did not have a biomarker that matches one of the treatment studies that are open or because you were not a candidate for a

biomarker-matched treatment study. For this sub-study, you will be assigned to treatment with either the usual treatment, which is the current standard of care drug (docetaxel, gemcitabine, pemetrexed [for non-squamous cell NSCLC only], or ramucirumab combined with docetaxel) or to the investigational therapy (ramucirumab combined with pembrolizumab).

The purpose of this study is to compare the usual treatment to using ramucirumab plus pembrolizumab. The combination of ramucirumab plus pembrolizumab, drugs that work with your immune system to fight your cancer, could shrink your cancer, but it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better, the same, or worse than the usual approach. The study doctors hope to learn if the study drug combination will enable patients to live longer compared to the usual approach.

This immunotherapy drug combination, ramucirumab plus pembrolizumab, is not approved by the FDA for use in advanced lung cancer. There will be up to 144 people taking part in this study.

What are the study groups?

This study has 2 study groups.

- **Group 1 – Standard of Care**

  If you are in this group, you will get the usual drugs used to treat this type of cancer based on your previous treatment (docetaxel, gemcitabine, pemetrexed, or ramucirumab combined with docetaxel). Treatment will be given in cycles. Each cycle lasts 21 days. You will receive treatment until your disease gets worse or the side effects become too severe.

  Docetaxel:
  If you receive docetaxel, you will get docetaxel through a vein in the arm over 10 to 30 minutes on the first day of each cycle. You will also receive dexamethasone tablets, an approved medication to help prevent allergic reactions to docetaxel. You will begin taking dexamethasone, twice a day, the day before you receive docetaxel and for two days after.

  Gemcitabine:
  If you receive gemcitabine, you will get gemcitabine through a vein in the arm over 30 minutes on days 1 and 8 of each cycle.

  Pemetrexed:
  Pemetrexed is not FDA-approved for squamous cell NSCLC. You will not receive pemetrexed if you have squamous cell NSCLC.

If you receive pemetrexed, you will be given pemetrexed through a vein in the arm over 10 minutes on day 1 of each cycle. You will also receive dexamethasone tablets, an approved medication, Vitamin B_{12} injections to help reduce side effects of pemetrexed, and folic acid. Folic acid will be given 7 days before you receive pemetrexed on cycle 1 and will continue every day until 4 weeks after the last dose of pemetrexed. Vitamin B_{12} will be given 7 days before you receive pemetrexed every 3rd cycle. You will begin taking dexamethasone, twice a day, the day before you receive pemetrexed and for two days after.

Ramucirumab in combination with Docetaxel:
If you receive ramucirumab in combination with docetaxel, you will be given ramucirumab through your vein in the arm over 60 minutes before you are given docetaxel through a vein over 10 to 30 minutes on the first day of each cycle. You will also receive dexamethasone tablets, an approved medication to help prevent allergic reactions to docetaxel. You will begin taking dexamethasone, twice a day, the day before you receive docetaxel and for two days after.

There will be up to 72 people in this group.

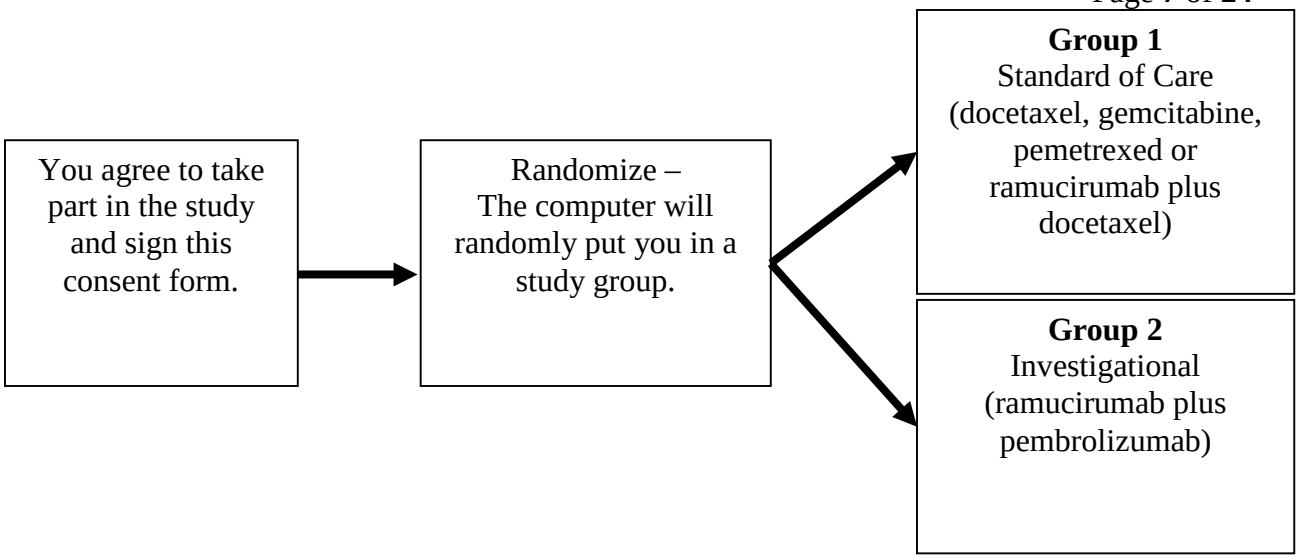
- **Group 2 – Investigational**

  If you are in this group, you will get the study drugs called ramucirumab and pembrolizumab. Ramucirumab will be given through your vein over 60 minutes followed by a 60-minute observation time before you are given pembrolizumab through your vein over 30 minutes. You will receive ramucirumab and pembrolizumab for up to 35 cycles (about two years) and then you will receive ramucirumab alone. If the infusion is well tolerated, the observation period may be reduced at the study doctor's discretion. Each cycle lasts 21 days. Ramucirumab and pembrolizumab will be given on the first day of each cycle. You will receive treatment until your disease gets worse or the side effects become too severe.

  There will be up to 72 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- A blood test to check thyroid function will be done every 3 cycles if you are receiving ramucirumab and/or pembrolizumab

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

- Blood Test (circulating tumor DNA) before you begin the study and if your disease becomes worse

  You will be required to have about 2.5 tablespoons of your blood collected for the circulating tumor DNA testing. An attempt will be made to do this blood draw at the same time as other blood draws. There is a chance that you will have another stick to

obtain the blood. This blood will be tested for DNA not normally found in cells but that is present in your blood because it has been released from the tumors in your body. The information collected will help the study doctors learn about tumor abnormalities that may play a role in tumor evolution. The results of this blood test are not part of normal clinical decision making. You and your doctor will not receive the results of this blood test.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 4 months after you have completed the study.

Blood Draw Risks

Common side effects of a blood draw are a small amount of bleeding at the time of the blood draw, brief pain, and maybe a bruise.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.

4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Contact information for your study doctor is listed on the consent cover page.

Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Docetaxel
(Table Version Date: July 21, 2015)

COMMON, SOME MAY BE SERIOUS In 100 people receiving DOCETAXEL, more than 20 and up to 100 may have:
• **Swelling of the body** • **Hair loss** • **Change in nails** • **Rash, itching** • **Vomiting, diarrhea, nausea, constipation** • **Sores in mouth which may cause difficulty swallowing** • **Infection, especially when white blood cell count is low** • **Anemia which may require blood transfusions** • **Bruising, bleeding** • **Tiredness** • **Numbness and tingling of the arms and legs** • **Fever** • **Absence of menstrual period** • **Swelling and redness of the arms, leg or face** • **Pain** • **Watering, itchy eyes**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving DOCETAXEL, from 4 to 20 may have:
• **Severe skin rash with blisters and peeling which can involve inside of the mouth and other parts of the body.** • **Belly pain** • **Kidney damage which may require dialysis** • **Blood clot which may cause swelling, pain, shortness of breath** • **Abnormal heart rate** • **Shortness of breath, wheezing** • **Chest pain**

RARE, AND SERIOUS In 100 people receiving DOCETAXEL, 3 or fewer may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Cancer of bone marrow (leukemia) caused by chemotherapy**

Possible Side Effects of Gemcitabine
(Table Version Date: January 19, 2016)

COMMON, SOME MAY BE SERIOUS In 100 people receiving GEMCITABINE, more than 20 and up to 100 may have:
• **Flu-like symptoms of muscle pain, fever, headache, chills and fatigue** • **Nausea, vomiting** • **Rash** • **Hair loss** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **Anemia which may require a blood transfusion** • **Muscle weakness** • **Blood in urine** • **Feeling of "pins and needles" in arms and legs** • **Numbness and tingling of the arms and legs** • **Tiredness** • **Difficulty sleeping** • **Swelling of arms, legs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving GEMCITABINE, from 4 to 20 may have:
• **Swelling and redness of the area of radiation** • **Blisters on the skin** • **Diarrhea, constipation**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving GEMCITABINE, from 4 to 20 may have:
• **Sores in mouth which may cause difficulty swallowing** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Scarring of the lungs** • **Shortness of breath** • **Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles** • **Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness**

RARE, AND SERIOUS In 100 people receiving GEMCITABINE, 3 or fewer may have:
• **Severe blood Infection** • **Anemia, kidney problems which may require dialysis** • **Blood clot** • **Blockage of the airway which may cause cough**

Possible Side Effects of Pemetrexed
(Table Version Date: August 4, 2016)

COMMON, SOME MAY BE SERIOUS In 100 people receiving PEMETREXED, more than 20 and up to 100 may have:
• **Anemia which may cause tiredness, or may require blood transfusions** • **Constipation, nausea, vomiting, loss of appetite** • **Sores in mouth which may cause difficulty swallowing** • **Tiredness** • **Bruising, bleeding** • **Infection, especially when white blood cell count is low** • **Peeling of skin**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving PEMETREXED, from 4 to 20 may have:
• **Diarrhea** • **Swelling and redness of the area of radiation** • **Kidney damage which may cause swelling, may require dialysis** • **Liver damage which may cause yellowing of eyes and skin** • **Damage to the lungs which may cause shortness of breath** • **Scarring of the lungs**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving PEMETREXED, from 4 to 20 may have:
• **Itching** • **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body**

RARE, AND SERIOUS In 100 people receiving PEMETREXED, 3 or fewer may have:
• **Blockage of the bowels** • **Numbness and tingling of the arms and legs** • **Hair loss** • **Blood clot which may cause swelling, pain**

Possible Side Effects of Dexamethasone
(Table Version Date: September 22, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving DEXAMETHASONE, more than 20 and up to 100 may have:
• **High blood pressure which may cause headaches, dizziness** • **Pain in belly** • **Infection** • **Diabetes** • **Loss of bone tissue** • **Damage to the bone which may cause joint pain or loss of motion** • **Mood swings** • **In children and adolescents: decreased height** • **Swelling of the body, tiredness, bruising** • **Increased appetite and weight gain in belly, face, back and shoulders** • **Difficulty sleeping** • **Skin changes, rash, acne**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving DEXAMETHASONE, from 4 to 20 may have:
• **Blood clot which may cause swelling, pain, shortness of breath** • **Kidney stones** • **Glaucoma** • **Cloudiness of the eye, visual disturbances, blurred vision** • **A tear or a hole in the bowels which may cause pain or that may require surgery** • **Heartburn** • **Numbness and tingling of the arms, legs and upper body** • **Muscle weakness** • **Non-healing wound**

RARE, AND SERIOUS In 100 people receiving DEXAMETHASONE, 3 or fewer may have:
• **Bleeding from sores in stomach** • **Broken bones**

Possible Side Effects of Ramucirumab

(Table Version Date: August 8, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving RAMUCIRUMAB, more than 20 and up to 100 may have:
• **Pain in belly** • **Loss of appetite**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving RAMUCIRUMAB, from 4 to 20 may have**:**
• **Anemia which may cause tiredness, or may require blood transfusion** • **Infection, especially when white blood cell count is low** • **Bruising, bleeding** • **High blood pressure which may cause headaches, dizziness, or blurred vision** • **Swelling of arms or legs** • **Diarrhea** • **Sores in the mouth** • **Tiredness** • **Reaction during or following infusion of the drug which may cause fever, chills, rash, or low blood pressure** • **Headache** • **Nose bleed** • **Rash** • **Redness, pain or peeling of palms and soles** • **Bleeding** • **Watering eyes** • **Abnormal blood clotting in small blood vessels with damage to blood vessels, most commonly in the kidney**

RARE, AND SERIOUS In 100 people receiving RAMUCIRUMAB, 3 or fewer may have:
• **Heart failure (heart stops beating) which may cause shortness of breath, chest pain, swelling of ankles, and tiredness** • **Stroke which may cause paralysis, weakness or headache** • **Blockage of the bowels which may cause pain, or vomiting**

RARE, AND SERIOUS In 100 people receiving RAMUCIRUMAB, 3 or fewer may have:
• **Internal bleeding which may cause blood in vomit** • **A tear or hole in the stomach and/or bowel which may cause pain and may require surgery** • **Damage to the liver which may cause damage to the kidneys, pain, bleeding, or confusion** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, or swelling of the face or throat** • **Severe blood infection** • **Reversible damage to the brain which may cause tiredness or changes in thinking** • **Blood clot which may cause swelling, pain, shortness of breath** • **Non-cancerous tumor on the skin involving blood vessels**

Possible Side Effects of MK-3475 (pembrolizumab):
(Table Version Date: December 27, 2019)

MK-3475 (pembrolizumab) is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving MK-3475 (pembrolizumab). In clinical trials, most immune-mediated side effects were reversible and managed by stopping MK-3475 (pembrolizumab) temporarily, administration of corticosteroids and supportive care.

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-3475 (pembrolizumab): more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-3475 (pembrolizumab): from 4 to 20 may have:
• **Nausea** • **Infection** • **Loss of appetite** • **Pain in back** • **Joint stiffness** • **Cough** • **Swelling and redness of the skin** **MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:** • **Anemia which may require blood transfusion**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab): from 4 to 20 may have:

- **Pain in lymph nodes**
- **Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness**
- **Diarrhea**
- **Sores in the mouth which may cause difficulty swallowing**
- **Pain in belly**
- **Sores in the bowels**
- **Chills, fever**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly**
- **Pain or swelling of the joints**
- **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine**
- **Fluid in the joints**
- **Pain in chest**
- **Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives**

RARE, AND SERIOUS

In 100 people receiving MK-3475 (pembrolizumab): 3 or fewer may have:

- **A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss**
- **Swelling of the spinal cord**
- **Feeling of "pins and needles" in arms and legs**
- **Redness, pain or peeling of palms and soles**

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

RARE, AND SERIOUS In 100 people receiving MK-3475 (pembrolizumab): 3 or fewer may have:
• **Heart problems including swelling (fluid buildup around the heart (pericarditis)) and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.** • **Swelling and redness of the eye** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Reaction during or following a drug infusion which may cause fever, chills, rash** • **Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin** • **Damage to organs in the body when the body produces too many white cells** • **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma** • **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.** • **Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck** • **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.** • **Swelling or tenderness of blood vessels**

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Additional Drug Risks

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
  - all medications and supplements you are taking

- any side effects
- any doctors' visits or hospital stays outside of this study
- and if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** You must continue to use your approved method of birth control during the study and for 4 months after last dose. Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 4 months after your last dose of study treatment.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the standard of care costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the study agents (ramucirumab and pembrolizumab) ready and giving it to you.
- the costs of the standard of care agents (docetaxel, gemcitabine, or pemetrexed) and getting it ready and giving it to you.
- the costs of the supporting medications (dexamethasone, vitamin B_{12}, and/or folic acid), and getting them ready and giving them to you
- your insurance co-pays and deductibles.

Note: You or your insurance provider will not have to pay for the ramucirumab (for Study Group 1 and Study Group 2) and pembrolizumab while you take part in this study.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The blood test for circulating tumor DNA at the beginning of the study and if your disease becomes worse.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

No funds have been set aside to compensate you in the event of injury.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- Montana Cancer Consortium
- The study sponsor, SWOG and any company supporting the study now or in the future.
- The NCI Central Institutional Review Board, (IRB), which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration, (FDA), and the groups it works with to review research.
- The National Cancer Institute, (NCI), and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research.
- Transmission of Imaging and Data (TRIAD) and Imaging and Radiation Oncology Core (IROC) -Your medical images with clinical study data (e.g., the treatment Group you are assigned to, etc.) will be transferred using a computer program called TRIAD to IROC, a central imaging laboratory sponsored by the NCI and located at Ohio State University in Columbus, Ohio. Your medical images will be reviewed by physicians at this organization as part of the study analysis for this trial.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact information for your study doctor is listed on the consent cover page.

For questions about your rights while in this study, call the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or

straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, blood and a sample of tissue from your previous biopsy will be collected and stored along with tissue from an optional biopsy if your cancer gets worse. Storing samples for future studies is called "biobanking." The biobank is being run by SWOG and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood and tissue samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About 2 teaspoons of blood will be collected from a vein in your arm (at the same time as other study blood tests) on Weeks 4, 7, 10, and again if your cancer gets worse.

2. A sample of tissue will be collected from an optional extra biopsy if your cancer gets worse after treatment on this study.
3. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
4. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
5. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

1. The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
2. Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain and bruising at the biopsy site, which can be treated with regular pain medications. Rarely, an infection can occur. Rarely, patients may experience partial lung collapse that may require a chest tube or breathing machine. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place. The samples will be kept until they are used up.
3. Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
4. In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.

4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, who will let the biobank know. Contact information for your study doctor is listed on the consent cover page. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:

1. **If my cancer responds to treatment on this study, and then gets worse, I agree to have an optional biopsy to collect a sample of tissue. I agree to have this tumor tissue and related information kept in a Biobank for use in future health research.**
   YES NO

2. **My samples and related information may be kept in a Biobank for use in future health research.**
   YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.
YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes."

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)

(Required for initial consent only)