ID: UMCC 2017.057	Pembrolizumab in Combination With Platinum-Based Chemotherapy in Non-Small Cell Lung Cancer (NSCLC) Patients With Targetable Genetic Alterations, Previously Treated With Appropriate Targeted Agents, With Progressive Disease	NCT03242915

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

Study title: Phase II multi-center study of pembrolizumab in combination with platinum-based doublet chemotherapy in NSCLC (non-small cell lung cancer) patients with targetable genetic alterations in their tumor previously treated with appropriate targeted agents with progressive disease (UMCC 2017.057)

Company or agency sponsoring the study: The University of Michigan along with support from MERCK

Name, degree, and affiliation of the principal investigator conducting the study:

Gregory Kalemkerian, MD Department of Internal Medicine, Hematology/Oncology, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying a new drug, pembrolizumab, in small numbers of people to learn about its safety and its effect on your body at certain doses as a treatment for lung cancer. The purpose of this study is to test the effectiveness (how well the drug combination works), safety, and tolerability of the drug combination of carboplatin, pemetrexed and pembrolizumab in NSCLC patients with EGFR mutations and with other genetic alterations following appropriate targeted therapy. Your health-related information along with blood and tissue will be collected for this research study.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include serious health complications that may be life threatening, requiring hospitalization, or prolonging hospitalization, no improvement of your cancer, or new symptoms for the use of the study drugs. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but information gained in this study may help future patients who are diagnosed with non-small cell lung cancer. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be approximately 2 years.

You can decide not to be in this study. Alternatives to joining this study include standard of care treatment, other clinical trials, treatment for your cancer symptoms, or no treatment at all.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
Tyrosine kinase inhibitors are the standard first line therapy for advanced NSCLC patients with tumors that have epidermal growth factor receptor gene (EGFR) mutations, or are positive for the anaplastic lymphoma kinase (ALK). However, many patients develop tumor progression because the disease becomes resistant to the TKI therapy. After progression, patients are often started on a platinum-based doublet chemotherapy such as carboplatin and pemetrexed in combination.

In May 2017, pembrolizumab was approved by the Food and Drug Administration (FDA) in combination with pemetrexed and carboplatin for patients with metastatic non-squamous NSCLC who have not received any prior treatment. For this study you need to have received prior TKI treatment to be eligible.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?
Adult men or women who have NSCLC that is EGFR mutation positive with measurable and progressive disease following prior appropriate targeted therapy or other genetically altered NSCLC previously treated with appropriate targeted therapy with measurable and progressive disease. Patients taken off an appropriate targeted therapy due to intolerance are eligible.

There are many other inclusion and exclusion criteria which the doctors will use to determine if you can participate in this study. It is important that you discuss your full medical history and all of your medications with your doctor.

3.2 How many people (subjects) are expected to take part in this study?
A total of approximately 62 subjects at several institutions will take part in this study, including approximately 20 from the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?
The study team will explain the research study and answer any questions you have about the study. If you want to participate in the study, the study team will request you sign the consent form prior to any activities occurring that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Many of the procedures that will be performed during the study, including routine blood tests, tumor evaluations (radiology scans), physical examinations, vital signs (blood pressure, heart rate, breathing rate, and temperature)

and measurement of height and weight, would normally be done as part of your standard of care regardless of study participation. However, some of these may be done more frequently as a result of your participation in this study. Administration of the study drug combination, tissue/blood collection and analysis are solely for research purposes. Tests and procedures that are done more often than your regular medical care because of your study participation and that are solely for research purposes will be identified below. The study staff will inform you of the types of tests and procedures you have to undergo during the study.

During the study you must:

- Follow the instructions you are given.
- Come to the study center for your visits with the study doctor.
- Tell the study doctor or study staff about any changes in your health and/or medications you are taking.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

Before starting the study:

If you have not stopped taking your oral TKI for the treatment of your cancer, the research staff will instruct you on when to stop. It must be stopped prior to receiving treatment on this study. If it is not stopped, this will delay you being treated on this study.

You will need to have the following exams, tests or procedures to find out if you can be in this study. If you have had some of them recently, they may not need to be repeated. The screening tests and procedures do not have to be completed in one day and you are allowed to take breaks if you have multiple procedures in one day.

Before you begin the study, you will need to have the following screening procedures:

- **Medical history**: including any past treatments, surgeries, infection and autoimmune diseases.
- **Medications**: It is important that you tell your doctor about all of the medications that you have been taking, including over the counter medicines, vitamins or herbal treatments.
- **Physical exam**: including measurement of your height, weight, blood pressure, heart rate, respiratory rate and temperature.
- **Performance status**: Your ability to perform day to day activities and care for yourself.
- **Routine blood tests (approximately 2 teaspoons)**: will be drawn for tests to check blood counts and chemistry.
- **Blood tests** to check the health of your thyroid (within 2 weeks of your first dose).
- **Pregnancy test**: (urine or blood – approximately 1 teaspoon): if you are a woman able to have children
- **Urinalysis**: A urine sample for standard laboratory tests to check your general health.
- **Scans of your cancer**: these could include Computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, brain and upper and lower belly.
    - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a “contrast material” (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.
    - A MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a “contrast material” (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie down on a narrow bed which will slide into a tunnel that is 6 feet long by 22 inches across and is open at each end. You will be asked to lie quietly for about one hour, during which time you will hear a loud machine-like noise. A MRI scan takes about an hour and a half to complete.

- **The following will be done for research purposes:**
  If the exams, tests and procedures show that you can take part in the study, and you choose to take part, then you will have the following procedures:
    - Circulating tumor cells (CTCs) analysis: CTCs are cancer cells that are in the blood stream. It is thought this is how cancer spreads from one area off the body to another. Your blood samples will be analyzed to see if CTCs can predict if the drugs given in this study are effective in shrinking your cancer. Approximately 3 teaspoons of blood that will be required to be collected and banked for future analysis.
    - PD-L1 testing: If your PD-L1 status is not known, your doctor will order the test as part of standard of care. The test will be run on a piece of stored tumor sample from a previous biopsy or surgery. If your PD-L1 status is not known and no stored tumor tissue is available, you will need to have a tissue biopsy. The biopsy will be paid by the study.
    - Mutational Load: This genetic testing will determine if you have any other mutations related to your lung cancer. This analysis will help researchers better understand the reasons for cancer development, growth, spread and its response to the study regimen. In order to complete this testing, we will need tumor tissue and blood (approximately 5 teaspoons). The tissue can come from a previous biopsy or surgery, or from the biopsy you are planning to have in order to get tested for PD-L1.

Loss of Confidentiality
Your samples will be coded however there is a risk of loss of confidentiality of your information. If your samples are provided to research collaborators the following information may be made available: your diagnosis and treatments, the time the samples were collected in relation to your study regimen, your disease status, and demographic data (for example gender, race, age, etc.). Please ask the Study Doctor or Study Nurse if you would like to know more about how your information will be protected.

Study Intervention (for Research):

If you qualify to participate in the study based on the results of the screening tests and procedures, you will return to the study doctor's clinic.

You will receive the combination of pembrolizumab, carboplatin and pemetrexed given through your vein (IV) every three weeks for a maximum of 4 cycles. A cycle is defined as 21 days.

After you receive 4 cycles of the combination of pembrolizumab, carboplatin and pemetrexed, you will receive the combination of pemetrexed and pembrolizumab given through your vein as long as you are benefiting from the therapy and not experiencing adverse events. You will receive the combination of pemetrexed and pembrolizumab for up to 24 months from when you first started therapy on this study.

If you experience adverse events, you might have to stop taking all of some of the study drugs and if you recover from your adverse events, you may be able to restart the study drugs.

<u>Day 1 of each Cycle</u>

- Physical exam. After Cycle 6, you will have a physical exam every other cycle as often as your treating physician thinks is necessary.
- Performance Status. After Cycle 6, your performance status will be obtained only as often as your treating physician thinks is necessary
- Medication review
- Routine blood tests (approximately 2 teaspoons)
- Blood tests to check the health of your thyroid (only every 4 cycles)

- Toxicity evaluation: You will be asked about any side effects or illnesses you experience.
- Scans. After every 2 cycles for the first 6 cycles you will have scans. After the first 6 cycles, you will have scans as often as your treating physician thinks is necessary, but no fewer than at least every 4 cycles.

Day 1 of Cycle 3 only

- Blood samples for circulating tumor cells (CTCs) (approximately 3 teaspoons)

30-day Safety Follow-Up visit

About 30 days after your last dose of the combination therapy and before you start another therapy including the second course phase:

- Physical exam
- Performance Status
- Medication review
- Routine blood tests (approximately 2 teaspoons)
- Toxicity evaluation: You will be asked about any side effects or illnesses you experience.

Follow-Up Phase (for disease status):

If you stopped therapy for reasons other than disease progression you will have scans every 12 weeks to assess for your disease status. You will continue to be followed for your disease status until you start a new cancer therapy, disease progression, death, end of study or you start the second course phase (retreatment period).

Second course phase (Retreatment period)

If you stop therapy with stable disease and then your disease comes back (recurs) you may be eligible to take up to one additional year of pembrolizumab with or without pemetrexed. This retreatment is called the Second Course Phase for this study and is only available as long as this study is still open and if you qualify. As your doctor about what is needed to qualify.

If you meet the requirements, you will receive pembrolizumab with or without pemetrexed given through your vein at the same dose/interval as when you received your previous treatment on this study. You will not receive carboplatin again. You will continue to receive therapy as long as you are benefiting from the therapy and not experiencing adverse events for up to 1 year.

Day 1 of each Cycle of the Second Course Phase

- Physical exam. After Cycle 6, you will have a physical exam every other cycle as often as your treating physician thinks is necessary.
- Performance Status. After Cycle 6, your performance status will be obtained only as often as your treating physician thinks is necessary
- Medication review
- Routine blood tests (approximately 2 teaspoons)
- Blood tests to check the health of your thyroid (only every 4 cycles)
- Toxicity evaluation: You will be asked about any side effects or illnesses you experience.
- Scans. After every 2 cycles for the first 6 cycles you will have scans. After the first 6 cycles, you will have scans as often as your treating physician thinks is necessary, but no fewer than at least every 4 cycles.

30-day Follow-Up visit after the Second Course Phase

If you received the second course phase you will have a follow-up visit about 30 days after your last dose of the therapy and before you start any new therapy:

- Physical exam

- Performance Status
- Medication review
- Routine blood tests (approximately 2 teaspoons)
- Toxicity evaluation: You will be asked about any side effects or illnesses you experience.

Long term Follow Up (every 12 weeks)
After you have completed all study therapy you will be contacted by the study team about every 12 weeks to assess your general health. You will continue to be contacted until death, you withdraw your consent or the end of the study, whichever occurs first.

4.2 How much of my time will be needed to take part in this study?
The study drugs are given in cycles. One cycle is 21 days.

The initial screening visit will take approximately 3-5 hours. Each study visit is expected to take approximately 4-6 hours.

4.3 When will my participation in the study be over?
The maximum amount of time you could be on this study is approximately 3 years. Your participation may end sooner if you decide to no longer participate, your study doctor feels it is in your best interest to stop your study participation, your disease progresses, or the study is ended. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

4.4 What will happen with my information and/or biospecimens used in this study?
Your collected information and biospecimens may be shared with Merck.

Your collected information and biospecimens may also be shared with other researchers, both here or around the world, or with companies. Any sharing is subject to contractual obligations with the Sponsor. Additionally:
• With appropriate permissions, your identifiable collected information and biospecimens may be shared, and/or,
• Without your additional consent, your identifiable private information and identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The drugs used in the study may cause certain side effects and discomforts. You may have all, some, or none of the known side effects. There is also a risk that other rare or unknown side effects may occur. Your doctors and nurses will check you closely for side effects, and may give you medicines or other treatments to stop or reduce some of these effects. Some side effects may go away soon after the study medication is stopped, but in some cases, side effects may be serious, long lasting, and/or permanent. There is even a chance that a side effect may cause death. If you have any side effects, it is important that you report them to your study doctor or research staff.

We will minimize the risks by monitoring you carefully. We will provide the usual supportive care that would be routinely given to someone with your condition. If you have side effects from the investigational study treatment, we will make appropriate adjustments as defined by the study protocol. You may need to discontinue the investigational study treatment if the side effects are too serious.

Side Effects ASSOCIATED WITH Pemetrexed

The following side effects have been described with pemetrexed use when given as a single agent or in combination with other chemotherapy:

- Nausea, vomiting, diarrhea, or constipation
- Low blood cell counts
- Tiredness
- Redness or sores in the mouth, throat, lips or esophagus
- Loss of appetite
- Rash or itching

The following table describes side effects reported with pemetrexed. For complete information regarding pemetrexed, please refer to the ALIMTA®(pemetrexed) prescribing information or ask your doctor.

Side Effects with Pemetrexed		
Common (occurring in 10% or more of patients)	• Your body's ability to fight infections may be affected (Leukopenia: Decrease in white blood cells in the blood, including low levels of neutrophils) • Fatigue or shortness of breath (Anemia: decrease in red blood cells in the blood) • More likely to bruise or bleed (Thrombocytopenia: low platelet count)	• Increase in creatinine (marker of kidney function) • Fatigue • Nausea • Vomiting • Loss of appetite • Constipation • Diarrhea • Inflammation of the mouth and lips (Stomatitis) • Hair loss
Less common (less than 10% of patients)	• Heartburn • Taste alteration • Numbness, tingling, and burning sensation in hands and feet (Peripheral neuropathy) • Dehydration	• Abnormal liver tests (may suggest liver damage) • Infection • Painful, red eyes (Conjunctivitis) • Rash • Itching
Rare (less than 1% of patients)	• Abnormal heart rhythm (Arrhythmia) • Allergic reaction • Damage to the nerves affecting movement (Motor neuropathy)	• Kidney failure (Renal failure) • Heart attack (Myocardial infarction) • Lung disease (Radiation pneumonitis)

Side Effects ASSOCIATED WITH CARBOPLATIN

When receiving carboplatin, you may experience side effects. Side effects when carboplatin is administered alone are described in the table below. For complete information, please refer to the carboplatin (PARAPLATIN®) prescribing information or ask your doctor.

Side Effects with Carboplatin		
Common (occurring in 10% or more of patients)	• Your body's ability to fight infections may be affected (Leukopenia: decrease in white blood cells in the blood, including low levels of neutrophils) • Fatigue or shortness of breath (Anemia: decrease in red blood cells in the blood) • More likely to bruise or bleed (Thrombocytopenia: low platelet count)	• Abnormal kidney test (increase blood urea nitrogen and/or creatinine, may suggest kidney damage) • Abnormal liver tests (may suggest liver damage) • Electrolyte loss (low blood sodium, potassium, calcium, or magnesium) • Generalized pain • Feeling weak or lack of energy • Nausea • Vomiting
Less common (less than 10% of patients)	• Numbness, tingling, and burning sensation in hands and feet (Peripheral neuropathy) • Sores in mouth (Mucositis) • Hair loss • Hearing loss • Infection	• Diarrhea • Constipation • Allergic reaction (symptoms include rash, hives, redness of the skin, itching, breathing difficulty and decreased blood pressure)
Rare (less than 1% of patients)	• Heart failure • Stroke • Liver failure	• Blood clot • Changes in taste • Red blood cells that prevent filtering in the kidneys, which can lead to kidney failure (Hemolytic uremic syndrome)

Side Effects ASSOCIATED WITH PEMBROLIZUMAB

Pembrolizumab is a drug that may treat certain cancers by working with your immune system. Pembrolizumab can cause your immune system to attack normal organs and tissues in many areas of the 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. For complete information, please refer to the pembrolizumab (Keytruda®) prescribing information or ask your doctor.

The following side effects may be caused by pembrolizumab.

VERY COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening or where noted, may cause death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Cough
- Loose or watery stools

COMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Fever
- Back pain
- Rash
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps and/or feel sick to your stomach (hyponatremia)

UNCOMMON, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough (pneumonitis).
- Inflammation of the bowels/gut that may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools, or stools with blood or mucus (colitis)
- Too much thyroid hormone so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching, and redness) could also be wide spread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and /or may cause the top layer of your skin to peel from all over your body which can cause severe infection. (Severe skin reactions, including Stevens-Johnson syndrome/or toxic epidermal necrolysis)

RARE, SOME MAY BE SERIOUS (i.e. causing hospitalization, life-threatening, or where noted, may cause death)

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)

- Inflammation of the pituitary gland (a gland in the head) which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting (hypophysitis)
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the muscles so you may feel weak or pain in the muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and/or have vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches (uveitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle and abdominal aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain-Barre syndrome)
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause you dizziness or fainting. (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms, and legs or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis)

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which include joint pain, stiffness, and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)

- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation oof the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

If you had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

Risks of CT Scan
The contrast substance injected during the CT scan may cause pain, burning feeling, sweating and rarely a severe allergic reaction that can be serious. If you know you're allergic to iodine you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated and if you're older. In addition, your thyroid function may be affected. Please inform your doctor if this is the case.

CT imaging uses ionizing radiation, which increases your risk to develop cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation. The estimated additional lifetime risk of developing a fatal cancer from a standard CT scan is approximately 1 in 2,000.

Risks of MRI Scan
Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation.

The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF) This causes a thickening of the skin, organs and other tissues, and is a rare complication in patients with kidney disease that undergo an MRI with contrast material. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

Blood tests
Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include dizziness and fainting.

Tumor Biopsy
Risks associated with biopsy should be discussed with your study doctor and may include pain, bleeding, and infection. It is also possible to have an allergy to the anesthesia used. There is a risk that cancer cells spread to other parts of your body when the needle is removed from your tumor.

- Genetic material, including DNA and RNA, will be obtained from samples, stored in freezers, and used for profiling and analyzing your cancer. Specifically, the study includes DNA sequencing of your tumor and normal cells as a comparison. The goal is to identify key changes in the genes important to cancer cells that could potentially influence clinical decision making for your cancer. However, success or clinical benefits from the profiling of your cancer DNA is not guaranteed.

- It is possible that a mutation found in the tumor DNA is also a mutation in your normal tissue (inheritable or passed down in families). If your test results show that you have gene mutations that are inherited, your doctor should recommend that you meet with a genetic counselor. This referral is considered standard care and is not part of this study.

- As with all medical screening tests, there is a chance of a false positive or a false negative result. A "false positive" refers to the identification of a genetic change that is not present. A "false negative" is the failure to find a genetic change that indeed exists. The tests have been designed to ensure that the possibility of incorrect results is low.

Pregnancy
Taking the study interventions may involve unknown risks to a fetus (unborn baby) if pregnancy were to occur during the study.

If you are a woman of child bearing potential, you must not have sexual intercourse, or you must use a reliable form of birth control throughout the study and for 120 days after the last dose of study drug. The study doctor will discuss methods of birth control with you if needed. If you choose to use an oral contraception you need to start taking the oral contraception at least 14 days prior to starting the study interventions.

If you are pregnant or become pregnant or are nursing a child during the study, there may be risks to your unborn baby or nursing child. Some drugs cause premature (early) birth or birth defects. Nobody knows what all of these risks are right now.

If you become pregnant or think you may be pregnant during the study, immediately stop using the study drugs and contact the study doctor's office **immediately**. You must not breast-feed an infant during the study. Please also inform the study doctor if you become pregnant up to 120 days after the completion of the study drug.
If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use acceptable birth control (see below).

You must use acceptable birth control for medical reasons all during treatment (including during temporary breaks from treatment), and for at least 120 days after treatment has stopped. You must talk to the doctor before changing any birth control methods you have already agreed to use.

Acceptable methods of contraception are:

Single method (one of the following is acceptable):
- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):
- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)

- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Any birth control method can fail. The reports of birth control failing are more frequent for female patients who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

MEN
All men must use an acceptable form of birth control while taking part in the study and for 120 days after treatment has stopped because the effects on sperm are not known. Acceptable forms of birth control are noted above. Also, men should not donate sperm or semen while taking part in the study because the effects on sperm are not known.

The study doctor must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you become pregnant during the study, the study doctor or his/her staff will ask to contact you and your pregnancy physician for information about the pregnancy until the child is born and may share this information with the sponsor.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. However, information gained in this study may help future patients who are diagnosed with metastatic NSCLC cancer.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
You do not have to be in this study to get treatment for your cancer. Other possible options include:

- Additional treatment with standard of care drugs such as
    - If you have a tumor with EGFR: afatinib, erlotinib, gefitinib, osimertinib
- You could participate in other research trials using drugs not already approved for NSCLC patients with EGFR or other genetic alterations following other appropriate targeted therapy
- You could receive palliative radiation
- You could choose not to receive any treatment.

You should talk to your study doctor and your regular physician about each of your options and their risks and benefits before you decide if you want to take part in this study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

If you decide to leave the study early, please notify someone on the study team. They will instruct you on how to stop the study safely and you will be advised whether any additional test may need to be done for your safety.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

The study drug pembrolizumab will be provided by Merck free of charge.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Pemetrexed and carboplatin
- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services
- Treatment of complications

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Kalemkerian, at 734-647-8902 or 734-936-4000 (Hospital Operator – 24 hour paging). The doctor will either treat you or send you to another doctor for treatment.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will not be paid to take part in this study.

8.3 Who could profit or financially benefit from the study results?
Information obtained from this study may help the supporter Merck and/or the University of Michigan learn more about the causes, risks, treatments, or how to prevent this and other health problems. Merck, the University of Michigan, or physicians at the university could profit financially from this information.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researches, their organizations and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
The University of Michigan has rules to protect information about you. Federal and state laws also protect your privacy. Upon enrolling in this study, you will be assigned a unique identification number. All records and research blood samples related to the study will use this identification number instead of your name or other personally identifying information whenever possible. We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

You have the right to request access to your protected health information that is used or shared during this research and that is related to your study treatment for your study treatment, but you may access this information only after the study is completed. To request this information, please contact the researchers listed in Section 10 “Contact Information” (below).

The federal 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 does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain 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 obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service

Federal employees receiving care through the Federal Employees Health Benefits Plans

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.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease or other communicable disease status
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University of Michigan, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Merck, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular University of Michigan medical record.

- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?
As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University of Michigan and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	Gregory Kalemkerian, MD
Mailing Address:	University of Michigan Comprehensive Cancer Center 1500 East Medical Center Drive C350 Med Inn Building - SPC 5848 Ann Arbor, MI 48109
Telephone:	734-647-8902 734-936-6267 (Hospital Operator – 24 hour paging)

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214

Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

You will receive a copy of the signed and dated informed consent

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

PERSONAL CENSUS FORM

UMCC # 2017.057

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]
2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as "Haitian" or "Negro" are sometimes used in addition to "Black" or "African American.")

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" is sometimes used in addition to "Hispanic" or "Latino."