CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Trial of Pembrolizumab Sequentially Following Single Fraction Non-Ablative Radiation to One or More of the Target Lesions in Patients with Stage IV NSCLC (CASE 1516)

Clinical Trials Registration Number: NCT02658097

Sponsor: Cleveland Clinic/Case Comprehensive Cancer Center

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[redacted]

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered locally at Cleveland Clinic Main, CC regional sites including: Hillcrest Hospital, Fairview Hospital, Strongsville Family Health Center (FHC), and CC Florida.

External sites include Rush University Medical Center, Roswell Park Institute, and Alleghany Memorial Hospital.

What is the Usual Approach to My Stage IV Non-Small Cell Lung Cancer (NSCLC)?
The most common treatment approach to your cancer is treatment with chemotherapy or an immunotherapy. Palliative low dose radiation (such has the one being studied here) is considered standard treatment in patients who have cancer related symptoms.

What Are My Other Choices If I Do Not Take Part In This Study?
If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach described above
- You may choose to take part in a different study, if one is available
- Or, you may choose not to be treated for cancer. For example: comfort/palliative care

Why Is This Study Being Done?
Even though immunotherapy treatments such as pembrolizumab are new modes of treatment for patients with lung cancer, only about 20-30% of patients respond to such treatments. Recent research has shown that radiation treatment to cancers can increase the ability of patients' immune system to recognize cancer, and could serve as a useful addition to immunotherapy treatments.

The purpose of this study is to determine if low single palliative dose radiation to the lung cancer will improve your immune response against the tumor, and if sequential treatment with pembrolizumab (study drug) would offer superior results to pembrolizumab alone.

Pembrolizumab is an FDA approved drug (also known as Keytruda), which has been approved by the FDA for use in lung cancer and certain types of skin cancer (melanoma). Pembrolizumab is a monoclonal antibody that binds to the surface of some cells of the immune system and activates them against cancer cells. It is not chemotherapy.

The purpose of this research is also to study whether there are any changes present in the DNA, RNA, and proteins within your tumor or the blood cells that may contribute to a response to the study treatment or progression of cancer. This research will study your genome. The genome is the complete set of your genes. Your genes are made up of DNA, which contains the code for making a protein. DNA gives instructions to RNA to make proteins. Research on genes is called genomic research, research on RNA is called transcriptomic research, and research on large sets of proteins is called proteomic research. This research also looks at how your genes are "turned on" or "turned off" to give the messages that prompt the making of proteins.

This research may help the researchers in the future to learn more about the causes, risks, treatments, or prevention of cancers and other health problems. The research may be used to develop new ideas and medical products, including drugs, injections, and diagnostic tests. You will not own any idea or product created by the researchers using your samples. You will not receive any payment or financial benefit from the creation, use, or sale of such a product or idea.

How Long Will I Be In This Study?
This study is being conducted at 9 facilities: Cleveland Clinic's Main hospital and its regional facilities, Alleghany Memorial, Roswell Park, Rush University, and NYU Langone. Approximately 48 subjects will be enrolled in this trial overall. You can be on the core part of this treatment for up to 28 weeks. After that, you will continue on pembrolizumab standard of care and followed until your disease has progressed.

What Extra Tests and Procedures Will I Have If I Take Part in This Study?
Biopsies
Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there will be additional biopsies done after you have started the study drug that you must be willing to have if you take part in this study. These research biopsies will be performed on your tumor specimens and your blood to understand the factors in the tumor that may influence how your cancer responds to treatments.

A tumor biopsy is the removal of a small (pencil eraser-sized) circle of tumor using a cookie cutter-like instrument. The duration of the biopsy procedure is approximately 30 minutes. The biopsy may be done by a radiologist or a surgeon in a procedure room. The procedure will be done using local anesthesia to minimize discomfort from the biopsy. The doctor will then numb the area with a local anesthetic so that the biopsy is less uncomfortable. The doctor will ask you to hold your breath and not move while he or she places the needle into your tumor and withdraws a small core of tissue which remains trapped inside the needle. It is very important that you not move or breathe during the biopsy.

Blood Collection

Blood samples will be collected to test for biomarkers that help researchers understand the relationship between the study drug and your tumor.

Neither you nor your insurance company will be charged for these biopsies or extra blood collections.

What Will Happen if I Take Part in This Study?

If you agree to take part in this research you will be asked to sign the study consent. The study includes a screening period, a core or treatment phase, and a post study (observation) phase. During the screening phase the research team will perform a series of tests to determine if you are eligible for the study.

SCREENING

- The study doctor will review:
  - Your medical history
  - Any prior or continuing medications
  - Any prior treatment(s) you may have had for your cancer
- You will be asked about your health
- You will have a complete physical exam
- Your vital signs will be taken(blood pressure, heart rate, temperature, breathing rate)
- Your height and weight will be measured
- Routine blood and urine samples will be collected to check your health and status of your disease
  - To check the function of your organs for safety.
  - To perform a pregnancy test for females who are able to have children.
- Extra blood collection for exploratory biomarker assessments that help researchers understand the relationship between the study drug and your tumor (that is genetic studies).
- If you are a woman:
  - Who is able to become pregnant you will be asked to have a serum pregnancy test that requires about 1ml (less than half a teaspoon) of blood serum, or a urine pregnancy test;
  - If you are considered postmenopausal or unable to reproduce, you may be asked to have different blood test to test a hormone in your body that determines your ability to become pregnant. This test requires about 1ml (less than half a teaspoon) of blood.

During your visits to the doctor, you will have extra blood drawn by taking additional blood from a vein in your arm (up to 3 ounces) during each study visit. If you have had a previous tumor biopsy, you may be eligible to use your old tumor samples. If you do not have archived tumor tissue, you will be required to have a new biopsy (fresh tissue sample taken) at the time of screening, unless waived by the sponsor.

Blood and tissue samples that are collected by the study doctor will be provided to collaborators who specialize in analyzing the tumor DNA, proteins and the immune cells.

We will request for review of your CT Scans to determine the location of the tumor for the biopsy and the radiation.

Please make your study doctor aware if you are receiving care elsewhere or plan to receive care elsewhere while on this study.
The following list of therapies are prohibited while on the screening and treatment period of this study:

- Other cancer therapies including immunotherapy and chemotherapy not specified in this protocol.
- Other investigational agents outside of pembrolizumab.
- Live vaccines prior to the first dose of trial treatment and while participating on trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- System-wide steroids for any purpose other than an event of clinical interest suspected to be originating from the immune system. Short courses of steroids unrelated to study treatment could be approved after consultation with your treating physician and the sponsor.

Please reach out to your treating physician if you have been prescribed or plan to take any of the above therapies throughout the course of this study.

CORE STUDY PERIOD (TREATMENT)
If from the screening it is determined you are eligible to participate in the study you will begin treatment. The core study period will start with the single dose of radiation and then you will continue for the first eight treatments of pembrolizumab; that is 24-28 weeks. Your disease will continue to be measured by CT or MRI scans as indicated.

You will also have:

- Vital Signs taken
- Weight Measured
- Safety Laboratory Blood tests
- Review of symptoms and side effects
- Directed Physical Exam as indicated by the research staff.
- Include - Extra blood for Exploratory Biomarker Assessment at every cycle during the treatment period, with the exception of cycle 1, and collection at the end of treatment visit.

The pembrolizumab will continue for up to 8 cycles unless any of the following reasons cause your treatment to stop before the 8 cycles:

- Your disease has progressed
- There has been a serious adverse event or medical emergency that prevents you from continuing treatment
- You withdraw or no longer wish to participate in the study
- Failure or inability to fulfill trial requirements
- Your doctor feels it is no longer in your best interest to remain on treatment

You will also be required to have a new biopsy after two treatments of your study drug, unless waived by the sponsor.

Following the 8 cycles, if the cancer is responding to treatment, your physician will continue treatment with pembrolizumab as a standard treatment (Pembrolizumab is already FDA approved treatment for lung cancer).

OBSERVATION PHASE (POST STUDY)

Following the 8 cycles of study period or treatment, you will be entering the observation part of the study. In the observation part of the study, if your physician determines your cancer is continuing to respond to pembrolizumab, you will be continuing the treatment with pembrolizumab. The investigators will be collecting information regarding your outcome and future treatment for your cancer you may be receiving. Your study doctor will provide the blood samples and the cancer tissue to collaborators for research. The collaborators will conduct research on your blood and cancer tissue samples.

Your blood and tissue samples, as well as the research data obtained from the analyses of your samples, will be kept for an indefinite time and may be used in potential unspecified future research. Although the researchers or the partners may store and maintain your samples for possible use, they do not promise to keep or store them at all. In addition, even if the researchers or the partners do store your samples, there is no guarantee that the samples will not run out, be lost or be damaged.

Once you complete the 8 cycles of study period or treatment ends for any of the above reasons, you will be in what is called follow-up. During follow-up period, you will be asked to return to the clinic approximately 30 days after you stop taking the study drug or before you start a new treatment for your cancer, whichever comes first. If during follow-up period, your cancer gets worse or you start a new treatment for your cancer, you may be contacted for survival follow-up by telephone about every 12 weeks.

How Will The Confidentiality of My Tumor Samples Be Protected?

The study doctor, study staff, and Sponsor will make reasonable efforts to keep and maintain the confidentiality of your personal health information and the study records relating to your samples, as well as your samples themselves. However, your study doctor and researchers cannot guarantee absolute confidentiality of the samples that you provide for the research described in this consent form. The samples collected by your study doctor and sent to the collaborators or partners will not be labeled to identify you by name, your hospital/clinical medical record number, address or any contact information. The samples provided to the researchers, or its partners, will only be labeled with a subject identification number. Only the study doctors will keep a code key that makes it possible to link your study number to your name and contact information.

The complete analysis and any research findings derived from the studies will be considered "complete research data." Complete research data will not be given to you or your family members. The complete research data belongs to the study research team and may be used for any purpose. For example, some of the ways the study researchers may use and share the research data include for publication, further research, validation, quality control, commercial applications, and all other reasonable purposes. The researchers will use reasonable efforts to protect the confidentiality of your samples and the data acquired from analyzing your samples. Any reporting of your research data will not use any individual identification, and the use and tracking of your samples is described below.

For more information please refer to the section on genetic testing on pages 9-10, and/or ask your doctor.

What is known about this Study Drug?
Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer. Pembrolizumab can also be known as KEYTRUDA and is approved to treat a type of skin cancer called malignant melanoma.

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.

What possible risks can I expect from taking part in this study?
If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.
- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.

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 be testing your blood and will let you know if

changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

The study doctors do not know who will or will not have side effects.

- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

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

If you experience severe side effects associated with the study drug, your doctor may prescribe medications to treat the side effect(s), future treatments may be delayed, or treatment may be stopped permanently. Any significant new findings that develop during the course of the research and may relate to your willingness to continue participation will be provided to you.

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.

Possible side effects of **pembrolizumab (KEYTRUDA):**

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, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired confused, have a headache, muscle cramps, and/or feel sick to your stomach

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:

- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Inflammation of the lungs so you may feel short of breath and cough. Sometimes this might lead to death
- Inflammation of the bowels/gut that may cause pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Infusion reaction, where you may feel dizzy or faint, 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 pain at the site of infusion.
- Inflammation of the skin- you may have peeling of the skin, itchiness, skin and/or skin redness. The skin inflammation (i.e. peeling itching and redness) could also be widespread 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. These severe conditions can sometimes lead to death. This may be called Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).

RARE, 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 liver that may make you feel sick to your stomach and vomit, feel like not eating,, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- It may also cause 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.
- Adrenal glands (on top of the kidneys) that may not make enough hormone, which causes tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and abdominal aches,

nausea, vomiting, loose watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan.

- Inflammation of the kidney so you may pass less urine, or have cloudy or bloody urine, swelling and low back pain, even to the point of requiring dialysis.
- Inflammation of the muscles so you may feel weak or pain in the muscles
- 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, sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- 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 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
- 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 dizziness or fainting. Sometimes this condition can lead to death
- 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.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- 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

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side 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 may include joint pain, stiffness and/or swelling.
- 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.

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.

If you have 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.

For Radiation Treatment
The risks of radiation are related to the part of the body that is radiated. All radiation on this study is being done as "standard of care", meaning that the dose and the regimen of radiation that is being used is a dose that is routinely used to treat lung cancer for improving symptoms from the cancer. The most common side effect (30-50%) of radiation is mild fatigue which may last for up to 1-2 months after treatment. The specific part(s) of the body radiated will be determined by your medical team, with radiation given to cancer containing regions which are causing you symptoms for the purpose of relieving these symptoms.

Radiation to bone or muscle produces minimal side effects, though occasionally cancer related bone pain may increase slightly for 12-24 hours after the first treatment (prior to improving 5-14 days after radiation).

Radiation to the skin may produce a mild darkening of the skin similar to a suntan, as well as dryness in the shape of the radiation field. This typically occurs 5-10 days after radiation, but should be relatively rare at this treatment dose (less than <10%).

Radiation to the bowel or stomach may produce nausea or diarrhea (20% at this dose level). If needed, appropriate medication will be prescribed by your medical team to relieve symptoms.

Radiation to the lungs may produce mild scaring, though at this dose level this would be extremely rare (<1%).

Radiation exposure can cause risk of developing a second cancer 5-20 years after radiation exposure, though the risk of this is very low (<1 per 5,000 patients treated).

What Are The Possible Risks With The Research Analysis On The Tumor and Blood?
Physical risks with this study are no different from the risk of having blood taken for routine clinical practice and risks associated with the research biopsies as described above.

<u>Genetic Testing</u>
Risks of being in genetic testing include the misuse of personal, genetic information. All personnel who will have access to genetic information about you are ethically and legally obligated to maintain the confidence of that information. However, there can be no absolute guarantees. Although rare, misuse of such information has caused problems for persons related to their employment and/or their life and/or health insurance and other benefits or entitlements.

The researchers will use commercially reasonable efforts to protect your confidentiality by using codes to identify and track your samples. The samples and any personal study data collected from

you, as well as the complete research data, will not be labeled with any information such as your name, contact information, or date of birth.

If the researchers share your study data or your samples with outside researchers, the outside researchers must promise not to use information from your genes or proteins to identify or contact you.

There is a risk that someone could gain access to your samples, or the personal research information from the study of your samples. Even without your name or other identifiers, your genetic information is unique to you. If future research is done on your genes and proteins, there is a chance that someone could learn about your risk for certain diseases and link that information back to identify you. In some cases, it could be used to make it harder for you to get or keep a job or insurance.

Information on Genetic Studies:
A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

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

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Reproductive Risks
It is not known if the study drug, pembrolizumab/Keytruda may affect an unborn or nursing baby, or has an adverse effect on sperm. If you are pregnant, trying to become pregnant or breast-feeding, you may not be in the study. The study doctor will perform a blood or urine pregnancy test before the start of and during the study, if you are able to have a baby.

Females who are able to have a baby, must use 2 methods of birth control from study Visit 1, during the study, and for a period of 120 after your last dose of pembrolizumab/Keytruda. The requirement to use contraception does not apply to women who are postmenopausal (a woman who is $\geq$ 45 years of age and has not had menses for greater than 2 years), surgically sterilized, or not heterosexually active.

Women of childbearing potential must use 2 barrier methods, or 1 barrier and 1 hormonal method, or be abstinent. The following birth control methods are allowed during the study:

Barrier Methods:

- Copper Intra-uterine device (IUD)
- Diaphragm
- Sponge
- Condom (by the partner)
- Spermicide

Hormonal method:

- Hormonal contraceptives (such as the birth control pill)

Abstinence (no heterosexual activity)

If you become pregnant during the study you must notify the study doctor right away. The study drug will be stopped and you will be taken out of the study.

There may be risks if you are male and your partner is pregnant or trying to become pregnant. If you are male and your partner is able to have a baby, you and your partner must use 2 methods of birth control during the study and for a period of 120 days after your last dose of pembrolizumab/Keytruda.

Potential Risk or Discomfort from Research Procedures

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is usually brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

CT Scans

If you take part in this research, you will have one or more medical imaging studies which use radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may not have received or will receive from other tests. The CT scan that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation." No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer. The amount of radiation that scientists think can cause harmful side effects equals more than 15 times the amount of extra radiation you would receive from being in this study. Also, scientists believe the number of people who would be at risk for developing a second cancer from being exposed to large amounts of radiation to be about 1 out of every 1,000.

X-ray

We are all exposed to radiation on a daily basis both from natural (sun and earth) and man-made

sources that we call background radiation. The amount of radiation from an x-ray is lower than what you are exposed to through natural sources of radiation in the environment.

The x-ray technologists and radiologists use the smallest possible dose of radiation and provide a protective lead apron when multiple x-rays are necessary.

Biopsies

Risks associated with biopsies include pain, redness, swelling, low blood pressure, excessive bleeding, bruising, or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site. Two to 3% of patients require hospitalization after a tumor biopsy. Rarely, an infection can occur. The risks involved with the biopsy depend on the location of the tumor that has to be biopsied. Your physician will determine the safest area of the tumor to biopsy and the risks of the procedure will be discussed in detail prior to the procedure by the physician performing the biopsy. Very rarely, a complication from having a biopsy could be fatal.

Risks specifically associated with lung biopsy are pneumothorax (collapse of lung), air embolus (air in a blood vessel), hemopericardium (blood around the heart), and lung torsion (twisting that interrupts the blood supply to the lung).

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.

What Possible Benefits Can I Expect From Taking Part In This Study?

We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your cancer, which may give you relief from some symptoms, improve your quality of life or prolong your survival. However, it is possible that your condition could worsen. Your participation in this study will help to obtain information about treating subjects with non-small cell lung cancer.

Can I Stop Taking Part In This Study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The 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.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.
- If you become pregnant

What Are My Rights In This Study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What Are The Costs Of Taking Part In This Study?
Your involvement in this research study is voluntary and you will not be paid for your participation.

The study agent, pembrolizumab, will be provided free of charge by Merck, over the 8 treatment infusions while you are on study treatment. Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures. The blood work for research purposes will not be charged to you. It will be paid for by the research study.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., radiation therapy, medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.
For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

What Happens If I Am Injured Or Hurt Because I Took Part In This Study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury".

In the event that a research activity results in injury, you/your medical insurance may be charged for the cost of diagnosing and treating your condition. You will be responsible for co-pays or deductibles. A research injury is an injury that happens as a result of taking part in this research study.

The costs of such medical care will be billed to you or your insurance company. There are no plans to provide compensation for lost wages, direct or indirect losses. The Cleveland Clinic will not voluntarily provide compensation for research related injury. You are not waiving any legal rights by signing this form.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924.

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to: Dr. Nathan Pennell and the research study staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- The Cleveland Clinic, its monitors and representatives
- Merck Pharmaceutical, its study monitors and representatives
- Merck Pharmaceutical collaborators and licensees *(people and companies who partner with Merck)*
- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Nathan Pennell, MD, PhD
Case Comprehensive Cancer Center
Cleveland Clinic Taussig Cancer Institute, [redacted]

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, you can ask the Principal Investigator, Nathan Pennell, MD and/or research staff at [redacted].

Emergency or after-hours contact information
If you are a **Cleveland Clinic** patient, you should contact the page operator at [redacted] or toll free at [redacted] and ask for the oncologist (cancer doctor) that is on call. Florida patients should call ([redacted].

If you are a **Cleveland Clinic-Fairview** participant, you may contact Dr. Timothy Spiro at [redacted] This number can be used 24 hours a day 7 days a week.

If you are a **Cleveland Clinic-Hillcrest** Hospital participant, you may contact Dr. Vinit Makkar at [redacted]. This number can be used 24 hours a day 7 days a week.

If you are a **Cleveland Clinic-Strongsville** participant, you may contact Dr. Abramovich from 8:00 am to 4:30pm at [redacted] After 4:30pm, please ask to speak to the doctor on call.

If you are a **Cleveland Clinic-Florida** participant, please call [redacted]. This number can be used 24 hours a day, 7 days a week.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924.

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, 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.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Signature of Participant	Date	Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

Signature of Person Obtaining Consent	Date

Printed Name of Person Obtaining Consent