THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Phase I/II Trial of MK-3475 and Hypofractionated Stereotactic Radiation Therapy in Patients with NSCLC

2014-1020

Subtitle: NSCLC 2014-1020

Study Chair: James Welsh

Participant's Name _____ Medical Record Number _____

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

STUDY SUMMARY

The goal of Phase 1 of this clinical research study is to find the highest tolerable dose of the combination of Keytruda (pembrolizumab, also called MK-3475) and radiation therapy (either conventional or stereotactic body radiation therapy [SBRT]). The safety of this combination will also be studied.

The goal of Phase 2 of this study is to learn if this combination therapy can help to control metastatic NSCLC.

This is an investigational study. Radiation therapy (both conventional and SBRT) is FDA approved for the local control of metastatic and primary tumors. Pembrolizumab is FDA approved and commercially available for the treatment of melanoma that is metastatic or cannot be removed by surgery. Its use in patients with metastatic NSCLC is investigational.

Treatment on this study may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side

effects, potential expenses, and time commitment. If you live outside of the Houston area, taking part in this study will require a prolonged stay out of town.

You can read a list of potential side effects below in the Possible Risks section of this consent.

You may receive up to 32 cycles of pembrolizumab. You will receive up to 15 radiation treatments, depending on what group you are in.

Pembrolizumab will be provided at no cost to you while you are on study. You and/or your insurance provider will be responsible for the costs of radiation.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard photon radiation therapy and/or standard chemotherapy outside of this study. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have screening tests to help the doctor decide if you are eligible. If you have had some of these tests or procedures done recently, they may not need to be repeated.

- You will have a physical exam.
- You will have a computed tomography (CT) scan, a positron emission tomography (PET) scan, magnetic resonance imaging (MRI), x-ray, and/or ultrasound to check the status of the disease.
- You will have breathing function tests to check your lung function.
- Blood (about 4 teaspoons) and urine will be collected for routine tests.
- If you can become pregnant, blood (about ½ teaspoon) or urine will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Study Groups

If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up to 24 participants will be enrolled in Phase 1 of the study, and up to 120 participants will be enrolled in Phase 2.

Up to 144 participants will be enrolled in this study. All will take part at MD Anderson.

Phase 1

If you are enrolled in Phase 1, the dose of pembrolizumab you receive will depend on when you join this study. The first set of participants will receive the lowest dose level of pembrolizumab. Each new set will receive a higher dose of pembrolizumab than the set before it, if no intolerable side effects were seen. This will continue until the highest tolerable dose of pembrolizumab is found.

In addition to pembrolizumab, you will receive either SBRT or conventional radiation therapy, depending on what type of radiation therapy the doctor thinks will be better for you.

Phase 2
If you are enrolled in Phase 2, you will receive pembrolizumab at the highest dose that was tolerated in Phase 1.

Your radiation therapy assignment will be decided based on what treatment your doctor thinks would be better for you:

If the doctor thinks SBRT would be better for you, you will be randomly assigned (as in the flip of a coin) to either Group 1 or Group 2:

- If you are in **Group 1**, you will receive SBRT and pembrolizumab.
- If you are in **Group 2**, you will receive pembrolizumab alone. However, if the disease has gotten worse after 5 weeks or possibly later, you may be able to also start receiving SBRT. If your doctor thinks it would be safer, you may cross over to Group 4 (described below) and receive conventional radiation therapy instead of SBRT.

If the doctor thinks conventional radiation therapy would be better for you, you will be randomly assigned to either Group 3 or Group 4:

- If you are in **Group 3**, you will receive conventional radiation therapy and pembrolizumab.
- If you are in **Group 4**, you will receive pembrolizumab alone. However, if the disease has gotten worse after 5 weeks or possibly later, you may be able to continue receiving pembrolizumab and start receiving conventional radiation therapy.

These treatments are randomly assigned because no one knows if one study group is better, the same, or worse than the other group. You will have an equal chance of being in either group.

Some participants will also be assigned to **Group 5** and will have their radiation treatment details decided by the treating doctor. If you are in Group 5, you will receive pembrolizumab along with SBRT or conventional radiation therapy to one or more tumors and low dose radiation to others.

Study Therapy Administration
You will receive pembrolizumab by vein over about 30 minutes on Day 1 of each 3-week cycle.

Radiation will consist of either 4 or 15 daily treatments lasting about 30-45 minutes each day while you stay in the same position. Depending on what group you are in and the status of the disease, you will either start radiation on the same day as your first pembrolizumab dose, or if the disease has gotten worse. The doctor will discuss the radiation therapy schedule with you.

You will no longer be able to take the study drug if intolerable side effects occur or if you are unable to follow study directions.

If the disease has gotten worse, you may be able to continue study therapy, as described above.

Your participation on the study will be over after the follow-up visits.

Study Visits

On **Day 1 of each cycle**:

- You will have a physical exam.
- Blood (about 1 tablespoon) will be drawn for routine tests.

One (1) day before the start of Cycles 3, 5, 8, 11, and 14, you will have a CT, PET, MRI, x-ray, and/or ultrasound scan.

Leftover tumor tissue from an earlier procedure will be used for biomarker testing. Biomarkers are found in the blood and tissue and may be related to your reaction to the study treatment.

Follow-Up Visits

About 30 days after your last dose of pembrolizumab

- You will have a physical exam.
- Blood (about ½ teaspoon) will be drawn for routine tests.
- You will have a CT, PET, MRI, x-ray, and/or ultrasound scan.
- You may have lung function tests performed.

About every 12 weeks for 2 years after you finish your last pembrolizumab cycle, the following tests and procedures may be performed. Instead of any of these follow-up visits, it is possible the study staff may call you instead and ask how you are doing.

- You may have a physical exam.
- Blood (about 1 tablespoon) may be collected for routine tests.
- You may have a CT, PET, MRI, x-ray and/or ultrasound scan.

Starting 2 years after you finish your last pembrolizumab cycle, you will have a physical exam and/or a CT, PET, MRI, x-ray, and/or ultrasound scan every 12 weeks if your doctor thinks it is needed. If you have these procedures performed at another hospital, information about your medical history, physical exam, lung function, and scans will be sent to MD Anderson for review.

Other Information

You are not allowed to receive any types of vaccinations while receiving the study drug.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. You should discuss these with the study doctor. You may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study treatment.

Radiation Side Effects

It is not known how often the side effects of radiation therapy may occur.

• decreased blood supply to the heart • chest pain • spinal cord and/or nerve damage (possible weakness, loss feeling, and/or loss of coordination)	• tiredness • skin redness, irritation, scarring, scaling, and/or blistering • abdominal pain • diarrhea	• abnormal liver tests (possible liver damage) • difficulty breathing • problems swallowing • choking

Radiation therapy may cause you to develop another type of cancer. Side effects may not occur for up to 6 months after radiation therapy is over. Side effects will vary depending on what part of the body is receiving radiation therapy.

Pembrolizumab Side Effects

Common (occurring in more than 20% of patients)

• fatigue • fever • skin rash and/or itching • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental	• high blood sugar (possible diabetes) • high blood levels of fat (possible heart disease and/or stroke) • nausea • constipation • loss of appetite	• abnormal liver test (possible liver damage) • pain • abnormal kidney test (possible kidney damage) • cough

status, and/or seizure)		

Pembrolizumab may cause low blood cell counts (red and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.

Occasional (occurring in 3-20% of patients)

• swelling (face/arm/leg) • headache • confusion • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating)	• weight loss • diarrhea • vomiting • abdominal pain • blood in the urine • abnormal liver tests (possible yellowing of the skin and/or eyes)	• weakness • nerve damage (possible numbness, pain, and/or loss of motor function) • difficulty breathing (possibly due to lung inflammation) • infusion reaction (possible dizziness, low blood pressure, nausea, pain, and/or difficulty breathing)

Rare but serious (occurring in fewer than 3% of patients)

• heart inflammation • blood vessel inflammation (possible bleeding and/or bruising) • seizure • immune system damage to the nervous system (causing muscle weakness, numbness and/or paralysis) • spinal cord inflammation (possible pain, weakness, loss of	• hormonal deficiency that affects the body's ability to control blood pressure and react to stress • pituitary gland inflammation (possible headaches) • decreased production of adrenal hormones (possible weakness and/or low blood pressure)	• inflammation inside the eye (possible vision problems) • kidney inflammation (possible kidney damage/failure) • kidney failure • build-up of fluid around the lungs • immune response that causes the body to attack itself (possible organ damage) • multi-organ disease causing

feeling or movement, and/or paralysis) • brain inflammation (possible paralysis and/or coma) • shedding, scaling and/or inflammation of the skin (possible fatal loss of bodily fluids) • large skin blisters • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract	• inflammation of the thyroid gland (possible tenderness in the neck) • diabetes requiring insulin • severe high blood sugar due to uncontrolled diabetes • inflammation of the pancreas (possible abdominal pain) • anemia due to destruction of red blood cells • liver damage (hepatitis)	lesions, most often in the lungs (sarcoidosis) • immune response (causing muscle weakness) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

If you have a solid tumor type and you have an organ transplant, pembrolizumab may increase your risk for the transplant to be rejected by your body.

Pembrolizumab works by boosting the immune system. This may cause unknown side effects resulting from your immune system attacking your organs. This may cause inflammation and inflammation-related side effects in any organ or tissue.

Other Risks

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active.

Birth Control Specifications: Acceptable forms of birth control include:

- Birth control pills plus a barrier method, such as a condom or diaphragm
- Intrauterine devices (IUD) plus a barrier method
- Implantable or injectable birth control (such as NorplantR or Depo-ProveraR started at least 3 months before joining the study) plus a barrier method
- Double-barrier methods, such as a condom used in combination with a diaphragm

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

If you agree, you will have a core biopsy performed at screening and at Week 3 of Cycle 4 for immune system testing. To perform a core biopsy, you will be given local anesthesia and a sample of tissue is removed using a hollow core needle that has a cutting edge.

If you agree, tissue left over from the procedures performed while on this study will be collected and stored in a research bank at MD Anderson for use in future research related to immune system testing.

Before your samples can be used for research, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson. The IRB is a committee of doctors, researchers, and community members. The IRB is responsible for protecting study participants and making sure all research is safe and ethical.

Your samples will be given a code number. No identifying information will be directly linked to your samples. Only the researcher in charge of the bank will have access to the code numbers and be able to link the samples to you. This is to allow medical data related to the samples to be updated as needed.

There are no benefits to you for taking part in the optional procedures. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedures.

Optional Procedure Risks

Having biopsies performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

MD Anderson and others can learn about cancer and other diseases from your banked samples. In the future, people who may do research with these samples may need to know more information about your health. This information may be collected from your medical record. MD Anderson will make reasonable efforts to preserve your privacy, but cannot guarantee complete privacy. Sometimes your samples may be used for genetic research about diseases that are passed on in families. Genetic research may result in the development of beneficial treatments, devices, new drugs, or patentable procedures. If this happens, there are no plans to compensate you. MD Anderson will not be able to give you, your family, or your

doctor the reports about the research done with these samples, and these reports may be put in your medical record. If this information were released, it could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty getting insurance coverage and/or a job.

If you withdraw your consent to the storage of leftover samples in the tissue bank, then they will no longer be collected for storage. Any of your samples that remain in the tissue bank will no longer be used for research and will be destroyed.

However, if any of your de-identified samples were already released for research purposes before you withdrew consent, MD Anderson will not be able to destroy them.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

Circle your choice of "yes" or "no" for each of the following optional procedures:

Optional Procedure #1: Do you agree to allow leftover tissue (from a research sample bank, or from your diagnosis) to be obtained for immune system testing?

YES **NO**

Optional Procedure #2: Do you agree to have a tumor tissue biopsy after completion of radiation therapy for immune system testing?

YES **NO**

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Merck for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance

provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. James Welsh, at 713-563-2300) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, Merck, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: Merck.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Data
Your personal information is being collected as part of this study. These data may be used by researchers at MD Anderson and Merck and/or shared with other researchers and/or institutions for use in future research.

Samples
Samples (such as blood and/or tissue) are being collected from you as part of this study. Researchers at MD Anderson may use any leftover samples that are stored at MD Anderson in future research. Leftover samples stored by Merck may be used in future research.

Before being used or shared for future research, every effort will be made to remove your identifying information from any data and/or research samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data or research samples are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or research samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research
Research samples collected from you as part of this study may be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment.

Conflict of Interest

Dr. James Welsh (Study Chair) has received compensation from Merck & Co. as a Scientific Advisor. The financial interests are within the limits of the conflict of interest policy

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:

- Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
- The IRB and officials of MD Anderson
- Merck, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. 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.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)
The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

_____ _____
SIGNATURE OF LAR DATE

_____
PRINTED NAME and RELATIONSHIP TO PARTICIPANT

WITNESS TO CONSENT
I was present during the explanation of the research to be performed under Protocol **2014-1020**.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE
A witness signature is only required for vulnerable adult participants. If witnessing the assent of a pediatric participant, leave this line blank and sign on the witness to assent page instead.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT
I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL TRANSLATION DATE
(OTHER THAN TRANSLATOR, PARENT/GUARDIAN,
OR STUDY CHAIR)

_____
PRINTED NAME OF WITNESS TO THE VERBAL TRANSLATION