THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Neoadjuvant Pembrolizumab for Patients with Mismatch Repair Deficient Locally Advanced Solid Cancers
2018-1182

Subtitle: Main

Study Chair: Michael Overman

_____ _____
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.

This research has been reviewed and approved by an Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

The goal of this clinical research study is to learn if pembrolizumab can help to control the disease in patients with locally advanced solid cancers caused by a deficient mismatch repair (dMMR) mutation, which is a type of genetic mutation (change) that may affect response to cancer therapy.

This is an investigational study. Pembrolizumab is FDA approved and commercially available for the treatment of several types of cancer, but not all locally advanced cancers. It is considered investigational to use pembrolizumab alone to treat some advanced solid tumor cancers.

The study doctor can explain how the study drug is designed to work.

The study drug 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.

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

You may receive the study drug for up to about 1 year.

Pembrolizumab will be provided to you at no cost while you are on this study.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive other standard drugs (including chemotherapy) or surgery. The study doctor will discuss the possible risks and benefits of these treatments. 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. The following screening tests will be performed within 28 days before your first dose of study drug to help the doctor decide if you are eligible:

- You will have a physical exam.
- Leftover tissue from a previous tissue biopsy will be collected to check the status of the disease.
- Blood (about 12 teaspoons) will be drawn for routine tests, tumor marker testing, ctDNA testing, to check the status of the disease, and to check for viruses (HIV and hepatitis). Tumor markers may be related to the status of the disease. ctDNA testing is a measure of how many tumor cells are in the blood.
- Urine will be collected for routine tests.
- You will have an MRI or CT scan to check the status of the disease.
- If you can become pregnant, blood (about 2 teaspoons) 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.

Up to 35 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration

If you are found to be eligible to take part in this study, you will receive pembrolizumab by vein over about 30 minutes on Day 1 of each cycle. Each cycle is 21 days long.

After 6 months of receiving pembrolizumab, the study doctor may recommend surgery if they think it is in your best interest. However, you and your study doctor may decide to forgo surgery and continue treatment with pembrolizumab for a total of 1 year.

You will no longer be able to receive the study drug if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

Study Visits

On **Day 1 of Cycle 1:**

- You will have a physical exam.
- Blood (about 5 teaspoons) will be drawn for routine tests. If you can become pregnant, part of this sample will be used for a pregnancy test. To participate in this study, you must not be pregnant.

During **Day 1 of Cycle 2:**

- You will have a physical exam.
- Blood (about 12 teaspoons) will be drawn for routine tests, tumor marker testing, ctDNA testing, and to check the status of the disease.

During **Day 1 of Cycle 3:**

- You will have a physical exam.
- Blood (about 12 teaspoons) will be drawn for routine tests, tumor marker testing, and to check the status of the disease.
- You will have an MRI or CT scan to check the status of the disease.

During **Day 1 of Cycle 4, 5, 7, 9, 11, 13, and 15:**

- You will have a physical exam.
- Blood (about 5 teaspoons) will be drawn for routine tests.

During **Day 1 of Cycles 6, 8, 10, 12, 14, and 16:**

- You will have a physical exam.
- Blood (about 12 teaspoons) will be drawn for routine tests, tumor marker testing, and to check the status of the disease.

During **Day 1 of Cycles 6, 9, 12, and 15**:

- You will have an MRI or CT scan to check the status of the disease.

End-of-Treatment Visit

After **6 months** if you have surgery, or after **12 months** if you do not have surgery):

- Leftover tissue from a previous tissue biopsy will be collected to check the status of the disease.

- Blood (about 6 teaspoons) will be drawn to check the status of the disease.

Safety Follow-Up Visit
Thirty (30) days after the End-of-Treatment visit, the study staff will call you to check on your health, any side effects you may be experiencing, and any new cancer therapies you may have started. This phone call should take about 5-10 minutes.

Follow-Up Visits
Every 12 weeks after the End-of-Treatment visit:
- Blood (about 6 teaspoons) will be drawn for tumor marker testing.
- You will have an MRI or CT scan to check the status of the disease.

Long-Term Follow-Up
Every 6 months after the End-of-Treatment visit, the study staff will call you to check on how you are doing. Each call should take about 5-10 minutes.

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. 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 the study drug is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Side effects will vary from person to person, and some may occur after you have stopped receiving the study drug. Tell the study doctor as soon as possible about any side effects or you may have or changes in how you feel, even if you do not think they are related to the study product/procedures.

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,	• high blood sugar (possible diabetes) • high blood levels of fat (possible heart disease and/or stroke) • loss of appetite • nausea • constipation	• abnormal liver test (possible liver damage) • pain • abnormal kidney test (possible kidney damage) • cough

heart problems, changes in mental status, and/or seizure)	• low blood cell count (white/red/platelets)	

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

- 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, diarrhea, mood swings, difficulty sleeping, heart rate changes, and/or sweating)	• weight loss • diarrhea • abdominal pain • blood in the urine • vomiting • abnormal liver test (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 numbness and/or paralysis)	• hormonal deficiency that affects the body's ability to control blood pressure and react to stress • pituitary gland inflammation (possible headaches) • inflammation of the thyroid gland (possible tenderness in the neck)	• 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

• spinal cord inflammation (possible pain, weakness, loss of 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 with ulcers of the skin and digestive tract)	• diabetes requiring insulin • severe high blood sugar due to uncontrolled diabetes • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • inflammation of the pancreas (possible abdominal pain) • anemia due to destruction of red blood cells • liver damage (hepatitis)	attack itself (possible organ damage) • multi-organ disease causing 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.

During the **MRI**, you may feel mild vibrations throughout your body. The machine will produce a loud knocking noise. This is normal. You will be given earplugs to protect your ears. Some people, especially those who tend to feel uncomfortable in small or closed spaces, may feel “closed in” and become anxious while in the scanner. The scanner has an intercom, which will allow you to speak to the staff during the procedure. If you feel ill or anxious during scanning, tell the MRI staff and the scanning will be stopped if you wish. The MRI will require a catheter to be inserted into one of your veins in order to inject the MRI contrast agent. This may cause skin irritation, bleeding, and/or infection. You may have an allergic reaction to the contrast agent.

The magnetic field used in MRI scanning may harm you if you have certain types of metal in your body (as might be found in pacemakers, neurostimulators, or certain clips). It may cause problems with devices, such as pacemakers. If you have metal in

your body or devices such as a pacemaker, you should discuss this with the study doctor.

CT scans send x-rays through the body at many different angles. You will be exposed to a small dose of radiation. All radiation adds up over a lifetime and may increase the risk of new cancer forming. Some people may feel "closed in" while lying in the scanner. However, the scanner is open at both ends, and an intercom allows you to talk with doctors and staff. If you feel ill or anxious during scanning, doctors and/or radiology technicians will give comfort, or the scanning will be stopped. Solution may also be given by vein to make the x-ray pictures more accurate. This may cause an uncomfortable feeling of warmth, nausea, and/or severe allergic reactions. The solution injection may also cause pain, bleeding, bruising, hives, and/or itching.

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: If you can become pregnant or father a child, you must use a highly effective method of birth control during the study and for 120 days after taking the study drug. Acceptable methods of birth control include:

- Combined (estrogen- and progestogen-containing) hormonal birth control (including pills, patches, or injections)
- Progestogen-only hormonal birth control (pills, injections, or implants)
- Intrauterine hormone-releasing system (IUS) or device (IUD)
- Bilateral tubal occlusion ("tubes tied")
- Vasectomy of yourself or a partner

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

Optional Procedure #1: If you agree, leftover blood from the study procedures will be collected and stored by the sponsor (Merck) for future research related to cancer.

Before your samples are sent to the sponsor for banking, your name and any personal identifying information will be coded to protect your privacy. The sponsor will not have access to the codes that link the samples to your identity. MD Anderson will not have oversight of any leftover samples that will be banked by the sponsor for additional research.

Optional Procedure #2: If you agree, a core tumor biopsy will be performed at screening and during Cycle 2 for future research related to cancer. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge.

There are no benefits to you for taking part in the optional procedures. Future patients may benefit from what is learned. 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

Researchers 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 by researchers under the supervision of the study chair. Sometimes your samples may be used for genetic research about diseases that are passed on in families.

Having a **biopsy** 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.

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 your leftover blood to be stored by the sponsor for use in future research?

YES **NO**

Optional Procedure #2: Do you agree to have a core biopsy during screening and Cycle 2?

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. Michael Overman, at 713-792-2828) 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, 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 material that is stored at MD Anderson in future research. Leftover material stored by Merck may be used in future research if you consent to it in the optional procedure above.

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. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you. The same level of data protection that covers your individual data does not apply to summary results (when data from the whole study is combined).

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

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding 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. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Conflict of Interest

Dr. Jaffer Ajani (Collaborator) has received compensation from Merck & Co. as a Scientific Advisor and Consultant. The financial interests are within the limits of the conflict of interest policy.

Dr. Scott Kopetz (Study Co-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.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

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. If you withdraw from the study, the study staff may ask if they can continue collecting the results of routine care from your medical record.

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

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol **2018-1182**.

_____ _____
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 (OTHER THAN TRANSLATOR, PARENT/GUARDIAN, OR STUDY CHAIR) DATE

_____

PRINTED NAME OF WITNESS TO THE VERBAL TRANSLATION