THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Phase II Study of Pembrolizumab and Fractionated External Beam Radiotherapy in Patients with Relapsed and Refractory Non-Hodgkin Lymphoma
2017-0341

Study Chair: Chelsea C. Pinnix

_____ _____
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 this clinical research study is to learn if the combination of external beam radiation therapy (EBRT) and pembrolizumab can help control relapsed (has come back) and refractory (has not responded to treatment) non-Hodgkin's Lymphoma (NHL). The safety of this combination will also be studied.

This is an investigational study. Pembrolizumab is FDA approved and commercially approved for many types of cancer, including classical Hodgkin Lymphoma. EBRT will be performed using FDA approved and commercially available methods. The combination of EBRT with Pembrolizumab to treat NHL is investigational.

The study doctor can describe how the study drug and radiation therapy combination are designed to work.

Treatment with the study drugs may help to control the disease. Future patients may benefit from what is learned on this study. 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 may choose not to take part in

this study because of potential costs, prolonged stay out of town, and/or because you want to do other standard options.

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

You may receive radiation therapy for up to 15-25 doses. You may take pembrolizumab for up to 35 doses, which may take about 2 years.

While you are on this study, pembrolizumab will be provided at no cost to you. You and/or your insurance company will be responsible for the cost of the EBRT.

You may choose not to take part in this study. Instead of taking part in 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. The following screening tests will be performed to help the doctor decide if you are eligible:

- You will have a physical exam.
- Blood (about 2½ tablespoons) will be drawn for routine tests, HIV testing, hepatitis testing, blood-clotting tests, thyroid function tests, and immune system testing.
- Urine will be collected for routine tests.
- You will have a chest x-ray and a PET/CT scan to check the status of the disease.
- If the study doctor thinks that it is needed, you will have a bone marrow biopsy and aspirate to check the status of the disease. To collect a bone marrow aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone and/or bone marrow is withdrawn through a large needle.
- 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 21 patients will take part in this study. All will be enrolled at MD Anderson.

Study Drug Administration and EBRT

If you are found to be eligible for this study, you will have a CT scan while lying still on your back. This is called a "CT simulation." You will not be injected with a contrast agent (part of the normal CT process) during the CT simulation. After you complete the CT simulation, your radiation oncologist will need about 1 week for radiation therapy planning before you begin your radiation therapy treatment.

You will receive **EBRT** 1 time each day for a total of 15-25 treatments, depending on the type of NHL you have.

EBRT is considered part of your standard care. You will be given a separate consent form which will discuss this procedure and its risks in greater detail.

Starting the day after you begin EBRT, you will receive **pembrolizumab** by vein over about 1 hour, every 21 days for up to 35 doses.

Study Visits
Each cycle of pembrolizumab treatment is 21 days.

On **Day 1 of Cycle 1**, you will have a physical exam.

On **Day 1 of Cycles 2-16**:

- You will have a physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests.
- Every 2 cycles (Cycles 2, 4, 6, and so on), part of this blood sample will also be used to check your thyroid function.
- Every 4 cycles (Cycles 2, 6, 10, and so on), part of this blood sample will also be used to check the status of your immune system.
- During Cycle 4 only, you will have a CT scan to check the status of the disease.
- During Cycle 5 only, urine will be collected for routine tests.
- During Cycle 8 only, you will have a PET/CT scan to check the status of the disease.

At any time, if your doctor thinks it is needed, you may have a bone marrow biopsy and aspirate and/or a CT or PET/CT scan to check the status of the disease.

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

Your participation on the study will be over once you have completed follow-up.

End-of-Treatment Visit
After you stop receiving the study drug(s):

- You will have a physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests.
- If your doctor thinks it is needed, you will have a PET/CT scan to check the status of the disease.

Long Term Follow-Up

About 30 days after your End-of-Treatment visit:

- You will have a physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests, thyroid function testing, and immune system testing.
- Urine will be collected for routine tests.

Every 3 months for 1 year, and then every 6 months after that until you start a new therapy, the disease gets worse, or the study ends:

- You will have a physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests, thyroid function testing, and immune system testing.
- You will have a CT scan to check the status of the disease.

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 drug/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, heart problems, changes in mental status, and/or seizure)	• high blood sugar (possible diabetes) • high blood levels of fat (possible heart disease and/or stroke) • loss of appetite • nausea • constipation • diarrhea • abdominal pain •	• low blood cell counts (red, white, platelets) • abnormal liver test (possible liver damage) • pain • abnormal kidney test (possible kidney damage) • cough • difficulty breathing

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) • inflammation of the tissue around the heart (possible chest pain) • irregular heartbeat • headache • confusion • patches of skin color • 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) • low blood sugar • weight loss • fluid in the abdomen • 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) • flu-like symptoms • infusion reaction (possible dizziness, low blood pressure, nausea, pain, and/or difficulty breathing)

Frequency Unknown

• heart failure • heart attack • build-up of fluid around the heart (possible heart failure)	• abnormal connections or passageways between organs or vessels • bleeding in the rectum and/or uterus	• blockage in the lung (possible pain and/or shortness of breath) • nosebleed • coughing up blood

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

• low blood pressure (possible dizziness/fainting) • heart inflammation • build-up of fluid in the tissue around the heart • blood vessel inflammation (possible bleeding and/or bruising) • seizure • immune system damage	• 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) • diabetes requiring	• 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 lesions, most often in the lungs (sarcoidosis)

to the nervous system (causing muscle weakness, numbness and/or paralysis) • 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)	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) • inflammation inside the eye (possible vision problems) • kidney inflammation (possible kidney damage/failure)	• immune response (causing muscle weakness) • immune system reaction (possible fever, jaundice, liver/spleen enlargement, irritability, and/or seizures) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • Vogt Koyanagi Harada syndrome -- pigmented tissue (possible eye pain/swelling and changes in vision, hearing loss, and/or white patches on the skin)

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. These side effects can affect more than one of your normal organs and tissues at the same time.

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.

Having **biopsies/aspirations** 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.

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 and for 120 days after your last dose of pembrolizumab if you are sexually active.

Birth Control Specifications: If you or your partner can become pregnant or father a child, you and/or your partner must use 2 methods of birth control during the study and for 120 days after the last dose of pembrolizumab.

You must use either 2 barrier methods or 1 barrier and 1 hormonal method.

The following birth control methods are allowed during the study:

- Barrier Methods: copper intrauterine device (IUD), diaphragm, sponge, condom, spermicide
- Hormonal Method: birth control pill or patch, implantable or injectable birth control

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, tissue will be collected at screening for genetic research and biomarker studies. Biomarkers are found in the blood and may be related to your reaction to the study drug. If possible, leftover tissue from a previous procedure will be collected for this research. If you do not have previously collected tissue available, you will have a core needle biopsy and fine needle aspiration. To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge. To collect a fine needle aspirate, a small amount of tissue is withdrawn through a needle. The tissue samples will be stored in Dr. Neelapu's lab at MD Anderson until the study has ended.

Optional Procedure #2: If you agree, extra blood (about 2 ¾ tablespoons each time) will be drawn for biomarker testing at screening, on Day 1 of Cycle 1, on Day 1 of Cycles 2 and 4, and at the end-of-treatment visit

Optional Procedure #3: If you agree, tissue will be collected on Day 1 of Cycle 4 for genetic research and biomarker studies. If possible, leftover tissue from a previous procedure will be collected. If you do not have previously collected tissue available, you will have a core needle biopsy and fine needle aspiration. The tissue samples will be stored in Dr. Neelapu's lab at MD Anderson until the study has ended.

Optional Procedure Risks:

Having **aspirations/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.

The type of **genetic testing** being performed in this study will not provide you or your doctor information about diseases that are passed down in families. It will not tell the study researchers anything that will prevent you from getting health insurance, and it will not tell the study researchers anything about any diseases or conditions you may get in the future.

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.

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 tissue to be collected and used for genetic research and biomarker testing at the time of screening?

YES NO

Optional Procedure #2: Do you agree to allow extra blood to be drawn for biomarker testing?

YES NO

Optional Procedure #3: Do you agree to allow tissue to be collected and used for genetic research and biomarker testing on Day 1 of Cycle 3?

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. Chelsea C. Pinnix, 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

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

Before being shared for future research, every effort will be made to remove your identifying information from any data and/or 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 samples are used for future research. If this 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 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

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).

Conflict of Interest

Dr. Sattva Neelapu (Collaborator) has received compensation from Merck as a Consultant. The amount received was 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.

Dr. Neelapu's lab at the South Campus Research Bldg. I, Room 4.3206, at M. D. Anderson Cancer Center (MDACC) will receive tissue samples.

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.

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 **2017-0341.**

_____ _____
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