THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

A Pilot Trial to Replace Chemotherapy with Ipilimumab-Nivolumab in Local-Regionally Advanced Non Small Cell Lung Cancer (NSCLC)
2018-0836

Subtitle: IND Trial Supported by BMS

Study Chair: Anne S. Tsao

_____ _____
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 a treatment strategy combining ipilimumab and nivolumab with radiation therapy (RT) can be used for treating patients with local-regionally advanced non-small cell lung cancer (NSCLC). The safety of these study drugs in combination with RT will also be studied.

This is an investigational study. Nivolumab combined with ipilimumab is FDA approved and commercially available for the treatment of a type of melanoma. It is investigational to use this treatment for NSCLC. Radiation therapy is delivered using FDA-approved and commercially available methods. It is investigational to combine RT with immunotherapy in patients with NSCLC. The study doctor can explain how the study drugs in combination with RT are 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. If you take part in this study, you may experience side effects, some of which may be severe or fatal.

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

You may receive nivolumab for up to 58 weeks, ipilimumab for up to 25 weeks, and RT for up to 6 weeks.

Ipilimumab and nivolumab 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 RT.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard chemotherapy with radiation therapy followed by immunotherapy. You will not be able to receive treatment with platinum-based chemotherapy (followed by durvalumab for patients with stage 3 disease), which has been beneficial for some patients, if you take part in this study. The study doctor can explain which options are available to you. 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 help the doctor decide if you are eligible:

- You will have a physical exam.
- Blood (up to 3 teaspoons) will be drawn for routine testing.
- Blood (about 1 ½ to 2 teaspoons) will be drawn for biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug.
- You will have CT or MRI scans to check the status of the disease.
- Leftover tumor tissue from a previous procedure within the last 6 weeks will be collected for biomarker testing, including genetic biomarkers. If you do not have enough tumor tissue available, you will have a biopsy. The study doctor will tell you what type of biopsy you will have.
- A stool sample will be collected for microbiome testing.
- If your doctor thinks it is needed, you will have an EKG to check your heart function.
- If you can become pregnant, blood (about ½ teaspoon) will be drawn 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 20 participants will take part in this study. All will take part at MD Anderson.

Study Drug Administration

For nivolumab, each study cycle is 21 days (3 weeks). For ipilimumab, each cycle is 42 days (6 weeks). After Week 25, each cycle of nivolumab is 28 days (4 weeks).

During Weeks 1 to 25, you will receive nivolumab and ipilimumab by vein over about 30 minutes. You will receive nivolumab on Day 1 of each nivolumab cycle for 8 cycles (24 weeks total) and ipilimumab on Day 1 of each ipilimumab cycle for 4 cycles (24 weeks total). Within a day of starting your first dose of study drugs, you will have radiation therapy 5 days a week, Monday through Friday.

During Weeks 25-58, you will receive nivolumab on Day 1 of each nivolumab cycle for 8 cycles (32 weeks).

You will no longer be able to take the study 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 after the follow-up visits.

Study Visits

On Day 1 of Weeks 1, 4, 7, and then every 3 weeks until Week 25 and then every 4 weeks after that:

- You will have a physical exam.
- Blood (about 3 teaspoons) will be drawn for routine tests.
- Blood (about 2 teaspoons) will be drawn for biomarker testing (Week 10 only).
- A stool sample will be collected for microbiome testing (Week 10 only).

You will have a CT and/or MRI scan 4 to 6 weeks after finishing the combined ipilimumab-nivolumab-radiation therapy. These scans will be repeated every 12 weeks. If your doctor thinks it is needed, these scans may be repeated at any time.

End of Treatment Visit

After your last dose of nivolumab:

- You will have a physical exam.
- Blood (about 5 teaspoons) will be drawn for routine and biomarker tests.
- You will have CT/MRI scans to check the status of the disease.
- A stool sample will be collected for microbiome testing.

Long-term Follow-Up

Every 3 months for 2 years after the End of Treatment visit:

- You will have a physical exam.
- Blood (about 5 teaspoons) will be drawn for routine and biomarker tests.
- You will have CT/MRI scans 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 drugs/procedures.

Nivolumab and ipilimumab may cause low blood cell counts (red blood cells, platelets, 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 platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet 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.

Nivolumab Side Effects

Common (occurring in more than 20% of patients)

• fatigue/lack of energy • headache • fever • skin rash • 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 levels of fat (possible heart disease and/or stroke)	• high blood sugar (possible diabetes) • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • abdominal pain • diarrhea • loss of appetite • nausea • constipation • abnormal digestive blood test (possible inflammation of the pancreas)	• low blood cell counts (red, white, platelets) • abnormal liver test (possible liver damage and/or yellowing of the skin and/or eyes) • pain • abnormal kidney test (possible kidney damage) • weakness • difficulty breathing • cough • infection

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • dizziness • skin redness • patches of skin color loss • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating) • inflammation of the thyroid gland (possible tenderness in the neck) • vomiting • inflammation of the intestines • hole in the intestines (possibly leaking contents into the abdomen)	• mouth blisters/sores (possibly difficulty swallowing) • abnormal blood test (possible pancreas damage) • nerve damage (possible numbness, pain, and/or loss of motor/sensory function) • inflammation of nerves (possible pain and/or loss of motor or sensory function) • peripheral nerve palsy (weakness, numbness, tingling) • muscle damage causing weakness	• joint disease • build-up of fluid around the lungs • lung inflammation (possible difficulty breathing) • stuffy nose • immune reaction (possible organ damage) • immune system disease (possible dry mouth/eyes, fatigue, joint pain, and/or organ failure) • infusion reaction (possible chills and/or hives)

If you have a stem cell transplant from a donor before or after you receive nivolumab, you may have an increased risk of complications, such as severe graft-versus-host disease (when transplanted donor tissue attacks the recipient's organs such as skin, liver, and/or intestines) and/or clotting of blood within the liver. Deaths have been reported in patients who received stem cell transplant from a donor before or after nivolumab therapy. If you decide to receive a stem cell transplant from a donor, please tell your transplant doctor that you received nivolumab in the past.

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

• blood vessel inflammation (possible bleeding and/or bruising) • heart inflammation • brain inflammation (possible paralysis and/or coma) • damage to the nervous system (causing numbness and/or paralysis) • paralysis of the nerves controlling the head and neck • skin blisters • diabetes requiring insulin • severe high blood sugar due to uncontrolled diabetes	• hormonal deficiency that affects the body's ability to control blood pressure and react to stress • inflammation of the pancreas (possible abdominal pain) • liver damage (possibly due to blood clots) • paralysis (face) • uncontrolled movements • inflammation inside the eye (possible vision problems) • kidney failure • breakdown of muscle tissue (possibly kidney failure)	• blockage in the lung (possible pain and/or shortness of breath) • multi-organ disease causing lesions, most often in the lungs (sarcoidosis) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • Vogt Koyanagi Harada syndrome -- pigmented tissue (possible eye pain/swelling, hearing loss, and/or loss of skin color)

Frequency unknown

• migraine • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract)	• hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering)	• weight loss

You may need to take drugs to reduce inflammation while taking nivolumab. Long-term use of these drugs may increase your risk of infection. These infections may occur anywhere and may be fatal. Treatment with antibiotic or antifungal drugs may be required to treat these infections.

The study drug 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.

Nivolumab may cause serious side effects that affect your immune system. Some of these side effects start as inflammation in different areas of the body like the skin, hormone glands, pancreas, or appendix. Tell the study staff right away if you have diarrhea, nausea, vomiting, blurred vision, dizziness, fainting, or you are feeling cold all the time.

If you had an organ transplant, nivolumab may increase your risk for the transplant to be rejected by your body.

Ipilimumab Side Effects

Common (occurring in more than 20% of patients)

• fatigue • headache • itching and/or skin rash • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • weight loss • nausea • diarrhea	• loss of appetite • vomiting • abnormal digestive blood test (possible inflammation of the pancreas)	• constipation • low red blood cell counts • abnormal liver tests (possible liver damage) • muscle/bone pain

Occasional (occurring in 3-20% of patients)

• fast heartbeat • fever • dizziness • difficulty sleeping • death of skin tissue and skin sores • very severe blistering skin disease (with loss of large portion of skin) • very severe blistering skin disease (with ulcers of the skin and digestive tract)	• skin rash with blisters or bleeding • pituitary gland failure (possible endocrine gland abnormality) • Type 1 diabetes, which may require insulin • abdominal pain • inflammation of the intestines • abnormal blood test (possible pancreas damage)	• abnormal liver tests (possible yellowing of the skin and/or eyes) • liver damage • abnormal kidney test (possible kidney damage) • dry eyes • cough • difficulty breathing

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

• blood vessel disease • blood vessel inflammation (possible bleeding and/or bruising) • leakage of fluids from blood vessels into surrounding tissue (possible difficulty breathing) • heart inflammation • inflammation of the tissue around the heart (possible chest pain) • brain inflammation (possible paralysis and/or coma) • immune system damage to the nervous system (causing numbness and/or paralysis) • immune response (causing muscle weakness) • nerve damage (loss of motor or sensory function) • Cushing's syndrome (possible weakness, diabetes, and/or bone weakness) • red, dry, scaly patches of thickened skin (psoriasis)	• skin rash (possible fever/lymph node swelling/inflammation of internal organs/abnormal blood cell counts) • large skin blisters • allergic skin reaction • inflammation of the thyroid gland (possible tenderness in the neck) • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • overactive thyroid gland (possible weight loss, heart rate changes, and/or sweating) • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • hole in the intestines (possibly leaking contents into the abdomen) • inflammation of the pancreas (possible abdominal pain) • stomach and/or small intestine ulcer	• anemia due to destruction of red blood cells • bone marrow failure due to abnormal tissue growth • liver failure • liver damage due to inflammation • muscle inflammation and weakness • inflammation inside the eye (possible vision problems) • partial hearing loss • kidney failure • bronchiolitis obliterans (damage of the small airways with difficulty breathing) • lung inflammation (possible difficulty breathing) • multi-organ disease causing lesions, most often in the lungs • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • immune response • infection

Ipilimumab may cause dehydration that may be severe enough to require hospitalization.

Ipilimumab may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere (such as the brain/spinal cord, lungs, and/or blood). It

may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Radiation Therapy Side Effects

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

• swelling • swelling of the arms or torso • skin changes (possible dryness, itching, peeling, and/or blistering)	• hair loss at the treatment site • mouth problems • trouble swallowing • nausea • vomiting • diarrhea	• urinary and/or bladder changes • sexual changes • inability to produce children • joint problems • secondary cancers

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

Using the study drugs together may cause side effects that are not seen when each is given alone. The study drug combination may also increase the frequency and/or severity of the side effects listed above.

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** 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.

EKGs may cause discomfort while lying on the exam table, and the tape on the EKG pads may cause skin irritation.

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.

If you can become pregnant or father a child, you must use medically acceptable forms of birth control during the study and for at least 5 months after the last dose of study drugs/radiation therapy.

Birth Control Specifications: Medically acceptable methods of birth control include hormonal birth control (oral birth control pills, vaginal ring, injectables, implants, transdermal, and intrauterine hormone-releasing system [IUS]) or barrier methods (male or female condom, diaphragm, cervical cap, or sponge).

Males: You should not donate sperm during study treatment and for 7 months after treatment. Tell the doctor right away if your partner becomes pregnant or suspects pregnancy. If your partner/spouse becomes pregnant while you are on this study, the sponsor would like to collect information about the pregnancy. The study sponsor's contact information will be made available so that, if you and your partner wish to, you can share information about the outcome of the pregnancy with the sponsor. If you and/or your partner choose not to share this information, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

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 and the disease has gotten worse, you will have a tumor biopsy for biomarker testing.

There are no benefits to you for taking part in the optional procedure. 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 procedure.

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.

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 have a tumor biopsy for biomarker testing if the disease gets worse?

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 Bristol-Myers Squibb (BMS) 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. Anne S. Tsao, at 713-792-6363) 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, Bristol-Myers Squibb (BMS), 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: Bristol-Myers Squibb (BMS).

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 will 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.

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
- Bristol-Myers Squibb (BMS), who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
- Any licensees, licensors, and collaborators of BMS
- 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 _____

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 _____

RELATIONSHIP TO PARTICIPANT _____

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2018-0836.

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.

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 _____

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)