THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

A Phase II Study of Nivolumab with Ipilimumab and Cabozantinib in Patients with Untreated Renal Cell Carcinoma Brain Metastases
2021-0520

Study Chair: Jianbo Wang

_____ _____
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 the combination of nivolumab, ipilimumab, and cabozantinib can help to control kidney cancer that has spread to the brain (brain metastases). The safety and effects of this combination will also be studied.

This is an investigational study. Ipilimumab is FDA approved and commercially available to treat kidney cancer when given with nivolumab. Cabozantinib is FDA approved and commercially available to treat kidney cancer when given alone or with nivolumab. Nivolumab is FDA approved and commercially available to treat kidney cancer when given alone or with ipilimumab or cabozantinib.

It is considered investigational to give all 3 drugs together to treat kidney cancer that has spread to the brain. The study doctor can explain how the study drugs are designed to work.

The study drugs 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 high blood pressure, fatigue, fever, pain, headache, itching/skin rash, nausea, diarrhea, loss appetite, constipation, low red blood cell count, and/or abnormal liver and/or kidney function tests. You can read a full list of potential side effects below in the Possible Risks section of this consent.

You may receive nivolumab and cabozantinib for as long as the study doctor thinks it is in your best interest. You may receive up to 4 doses of ipilimumab. You may no longer be able to take the study drug(s) if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

The study drugs will be provided at no cost to you during the study.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive radiation to treat brain metastases and/or surgery. You may choose to receive other drugs. The study doctor will discuss other treatment options with you. You may choose to receive other investigational therapy, if available. The study doctor will discuss the possible risks and benefits of these treatments. 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.
- You will have a neurocognitive exam (tests to check your memory and thinking abilities, for example).
- Blood (about 2 tablespoons) will be drawn for routine tests and to test for hepatitis and HIV.
- Blood (about 3 teaspoons) will be drawn for biomarker testing, including genetic biomarkers. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drugs.
- Urine will be collected for routine tests.
- You will have an EKG to check your heart function.
- You will have CT scans or an MRI to check the status of the disease.
- Tumor tissue left over from a previous procedure, if available, will be collected for biomarker testing, including genetic biomarkers. If there is not enough tissue for testing or there is no tumor tissue available, you will have a tissue biopsy. The type of biopsy will depend on where the disease has spread. The study staff will tell you more about the biopsy and its risks.
- If you can become pregnant, blood (about 1 teaspoon) will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

- If you are female under the age of 55 and the doctor thinks it is needed, blood (about 1 teaspoon) will be drawn for hormone tests to confirm that you cannot become 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 40 participants will be enrolled in this study. All will be enrolled at MD Anderson.

Study Drug Administration

If you are found to be eligible to take part in this study, you will begin taking the study drugs as follows:

- **Nivolumab** by vein every 3 weeks for 4 doses. After the 4th dose, you will receive nivolumab every 4 weeks. Your first dose of nivolumab will be given over about 60 minutes. If you tolerate the infusion well, all other doses will be given over about 30 minutes.
- **Ipilimumab** by vein over 30 minutes every 3 weeks for 4 doses.
- **Cabozantinib** tablets by mouth 1 time every day. Tablets should be swallowed whole with about 8 ounces of water. Do not cut, chew, crush, or dissolve the tablets. Do not eat for at least 2 hours before and 1 hour after each dose of cabozantinib. If you miss a dose and it is more than 12 hours until your next dose, you may take it as soon as you remember. Otherwise, skip that dose and take your next dose as scheduled.

You may be given standard drugs to help decrease the risk of side effects. You may ask the study staff for information about how the drugs are given and their risks.

Study Visits

On **Day 1 of Cycles 1-5:**

- You will have a physical exam.
- Blood (about 2½ teaspoons) and urine will be collected for routine tests.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test.
- Additionally, at certain cycles:
    - During Cycles 2 and 3, blood (about 1 teaspoon) will be drawn for biomarker testing, including genetic biomarkers, and pharmacogenomic (PGx) testing. PGx testing looks at how someone's genes may influence the study drug's effect on the disease.
    - During Cycle 3, you will have a tumor biopsy for biomarker testing, including genetic biomarkers.
    - During Cycle 4, you will have a neurocognitive exam.
    - During Cycles 3 and 5, you will have an EKG.

Every 4 weeks (about every month) **after Cycle 5:**

- You will have a physical exam.

- Blood (about 2½ teaspoons) and urine will be collected for routine tests.
- During Cycle 6, blood (about 4 teaspoons) will be drawn for biomarker testing, including genetic biomarkers, and PGx testing. If the disease gets worse, this blood draw will be repeated at that time.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test.

Every 12 weeks (about every 3 months) **after Cycle 5:**
- You will have an EKG.
- You will have a neurocognitive exam.

At **Cycles 3 and 5, then every 8 weeks after that for 1 year, then every 12 weeks after that,** you will have a CT scan and MRI to check the status of the disease.

Treatment Beyond Progression
If the disease appears to be getting worse or the tumors appear to be getting larger, you may still be able to receive the study drugs if your doctor decides it is in your best interest. If you still want to take part in the study and you are eligible you will continue to receive the same drugs. Sometimes the disease appears to get worse but the study drugs are actually working.

However, there are risks of continuing to receive the study drugs because the disease may actually be getting worse. You are still at risk for side effects due to the study drugs. This could also delay starting other treatments. The disease may get worse to the point that you are no longer able to receive other treatments.

If you choose to receive the study drugs after the disease gets worse, you will continue to have study visits as described above and be asked to re-sign the consent. The study doctor will discuss this option with you.

Follow-Up Visits
About 1 month and 3 months after your last study drug dose:
- You will have a physical exam.
- Blood (about 2½ teaspoons) will be drawn for routine tests.
- If you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test.
- At the 1 month visit only:
    - You will have an EKG.
    - Urine will be collected for routine tests.

If you stop taking the study drugs for reasons other than the disease getting worse, you will continue having CT scans or MRIs every 8-12 weeks. This will continue during Follow-Up and Long-Term Follow-Up (described below). If the disease gets worse or you start a new anti-cancer therapy, these scans will stop.

Long-Term Follow-Up

Every 3 months after your last follow-up visit, you will be asked how you are doing and if you have started any new anticancer therapies or had any side effects. This may be asked during a routine clinic visit or you may be called. The calls should last about 10-20 minutes.

If the safety or effectiveness of the drug needs to be studied further, the study doctor may try to collect study-related information about your health from you or from other sources, including your regular care doctor and public sources such as national patient registries (such as cancer registries). This may also include contacting you again by phone or letter.

Other Information

- Tell the study doctor about all medications you are taking or plan to take, including prescriptions, herbal supplements, and over-the-counter medications.
- Certain medications cannot be taken while you are participating in this study. Your study doctor will explain what these medications are. If you need treatment with any medications that are not allowed during your participation in this study, you must tell the study doctor or the study staff. If this happens, you may need to stop taking the study drug(s). This is for your safety, since some medications may not work well with the study treatment, and side effects may occur.
- Tell the study doctor about any medical treatments that you plan to receive during the study (such as surgery you choose to have, or radiation).
- Bring back empty cabozantinib packages and any unused study medication to each study visit.
- Tell your study doctor or staff if you change your address, phone number, or other contact information.
- You will be given a Subject Alert Card. You must carry this card with you at all times.
- If your study doctor needs to follow up with you but cannot find you, she may try to learn your new address, telephone number, or current health status by calling or writing to the person(s) named as your secondary contacts.

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 the drugs are stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even lead to 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 and procedures.

Nivolumab, ipilimumab, and cabozantinib each may cause low blood cell counts (red blood cells, platelets, and 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 10%)

• fatigue/lack of energy	• diarrhea • itching	• skin rash

Occasional (occurring in 3-10%)

• fever • underactive thyroid gland (possible increased thyroid stimulating hormone lab test result, weight gain, heart failure, and/or constipation)	• abnormal digestive blood test (possible inflammation of the pancreas) • nausea/vomiting • abdominal pain • loss of appetite • low red blood cell count	• abnormal liver test (possible liver damage and/or yellowing of the eyes and/or skin) • pain (including muscle/bone) • lung inflammation (pneumonitis), and/or bronchitis (possible difficulty breathing)

Rare (occurring in fewer than 3% of patients)

• fast heartbeat • abnormal EKG • heart inflammation/ inflammation of the tissue around the heart (possible chest pain) • high blood pressure • low blood pressure (possible dizziness and/or fainting) • swelling of the brain (possible headache and/or mental status changes)	• decreased production of adrenal hormones (possible weakness and/or low blood pressure) • inflammation of the thyroid gland (possible tenderness in the neck) • pituitary gland failure (possible hormone imbalance) • blood vessel inflammation	• abnormal kidney test (possible kidney damage) • kidney failure • breakdown of muscle tissue (possible kidney failure) • damage to the nervous system (causing numbness and/or paralysis) • nerve damage (possible numbness, pain, and/or loss of motor function

• inflammation of the brain and spinal cord (possible altered consciousness) • inflammation of the membrane around the spinal cord and brain (possible headache and/or coma) • swelling (face/arms/legs) • chills • headache • difficulty sleeping • dizziness • dry/red skin • hives • skin blisters • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract) • red, dry, scaly patches of thickened skin (psoriasis) • allergic skin reaction • hair loss (partial or total) • overactive thyroid gland (possible decreased thyroid stimulating hormone lab test result, weight loss, heart rate changes, and/or sweating)	• low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • abnormal blood test (possible pancreas damage) • high blood sugar (possible diabetes) • diabetes • abnormal blood acid/base balance due to uncontrolled diabetes (possible organ damage) • mouth blisters/sores (possible difficulty swallowing) • constipation • dehydration • dry mouth • inflammation of the intestines • hole in the intestines (possibly leaking contents into the abdomen) • liver inflammation • liver failure/damage • low blood cell count (platelets, white) • destruction of red blood cells due to the body attacking itself (called autoimmune hemolytic anemia)	and/or “pins and needles” sensation) • nerve damage (affecting the head and neck) • muscle inflammation • joint pain/stiffness • dry eye • blurry/double vision • difficulty breathing • cough • infusion reaction (possible fever, rash, pain, and/or swelling) • immune response causing the body to attack itself (possibly causing muscle weakness) • immune system reaction (possible fever, jaundice, liver/spleen enlargement, irritability, and/or seizures) • multi-organ disease causing lesions, most often in the lungs (sarcoidosis) • allergic reaction, possibly life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure) • patches of skin color loss • inflammation of multiple areas of the body (see below)

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, eye, kidney, or stomach. Tell the study staff right away if you have diarrhea, nausea, vomiting, blurred vision, dizziness, fainting, or you are feeling cold all the time.

Frequency Unknown

• graft-versus-host disease (when transplanted donor tissue attacks the tissues of the recipient's body) • Hemophagocytic lymphohistiocytosis (HLH) syndrome (see below)	• Vogt Koyanagi Harada syndrome -- pigmented tissue (possible eye pain/swelling, hearing loss, and/or loss of skin color) • risk of organ transplant rejection

Nivolumab may cause Hemophagocytic lymphohistiocytosis (HLH) syndrome at an unknown frequency. HLH is a disease that may affect your body's defense system, (your immune system) and certain white blood cells made by your immune system may attack other blood cells. These abnormal blood cells collect in your spleen and liver, causing these organs to enlarge, possibly causing fever, rash, and low blood cell counts.

<u>Ipilimumab Side Effects</u>

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)	• 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 liver tests (possible yellowing of the skin and/or eyes) • liver damage • abnormal kidney test (possible kidney damage) • dry eyes • cough • difficulty breathing

• very severe blistering skin disease (with ulcers of the skin and digestive tract)	• abnormal blood test (possible pancreas damage)	

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) • 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.

Cabozantinib Side Effects

Common (occurring in more than 20% of patients)

• high blood pressure • fatigue • weakness • changes in hair color • hand-foot syndrome (palms of hands/soles of feet having pain, swelling, and blistering) • skin rash • high blood levels of fat (possible heart disease and/or stroke) • high blood sugar (possible diabetes)	• 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) • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • mouth blisters/sores (possible difficulty swallowing) • mouth pain • abnormal taste	• loss of appetite • weight loss • diarrhea • nausea • abdominal pain • constipation • vomiting • low blood counts (red/white/platelets) • abnormal liver or bone tests (possible liver damage and/or yellowing of the skin and/or eyes) • abnormal kidney test (possible kidney damage)

Occasional (occurring in 3-20% of patients)

• blood clots in a vein (possible pain, swelling, and/or redness) • blood vessel disorder (possible tissue death) • chest pain • low blood pressure possible dizziness/fainting) • headache • dizziness • depression/anxiety • fainting • sores • skin redness/dryness/ • thickening • hair loss (partial or total) • upset stomach	• hemorrhoids • hole in the stomach or intestines (possibly leaking contents into the abdomen) • dehydration • abnormal connections or passageways between organs or vessels (such as between different parts of the digestive system) • difficulty swallowing • pain	• muscle spasms • abnormal sensation (such as pins and needles) • nerve damage (possible numbness, pain, and/or loss of motor and/or sensory function) • kidney failure • difficulty breathing • cough • blockage in the lung (possible pain and/or shortness of breath) • voice changes • infection

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

• severe increase in blood pressure (possible stroke) • blood clots in the arteries (possible organ damage, stroke, and/or heart attack) • seizure	• brain damage that may be reversible (possible headache, confusion, seizures, and/or vision loss) • inflammation of the pancreas (possible abdominal pain)	• severe bleeding • inflammation of the bile tract (possible blockage) • bone destruction (jaw bone) • wound healing problems

You should not take St. John's Wort while on this study. In addition, you should not eat grapefruit, Seville (sour) oranges, star fruit, pomegranate, or products made with these fruits (including juice, jams, or candies) while you are taking cabozantinib.

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. Rarely (in fewer than 3% of patients), major bleeding may occur.

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

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.

Genetic research may result in the development of beneficial treatments, devices, new drugs, or patentable procedures. There are no plans to provide you compensation from such developments. The results of any genetic tests may be put in your health records. 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 obtaining insurance coverage and/or a job.

Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen, which may result in a **loss of confidentiality**. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study.

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. Please speak with your doctor if you would like to consider having children after treatment. You may want to talk with a specialist about preserving ovum (eggs) or sperm for the future.

If you are sexually active and can become pregnant or father a child, you must use birth control during the study and for up to 5 months (females) or 7 months (males) after the last study drug dose.

Birth control specifications: Acceptable methods of birth control for females include the following:

- Hormonal methods of birth control, including birth control pills (combination of estrogen and progesterone)
- Progestogen-only hormonal birth control
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion (also called having your “tubes tied”)
- Vasectomized male partner
- Male condoms (female partner must also use an acceptable form of birth control)

You should contact your study doctor right away if there is a change in your method of birth control or if you start any prescription drug or other drug (including over-the-counter drugs and herbal supplements) not prescribed by the study doctor.

Males: Do not donate sperm during the study and for at least 7 months after your last dose of study drugs.

You must tell your female partners who can become pregnant about the birth control requirements. 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, we would like to collect information about the pregnancy. The study supporter will provide you with a document and 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: You should not breastfeed while taking the study drug or for up to 5 months after the last dose of study drug. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away. The sponsor will ask for information about the pregnancy

Getting pregnant may result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If the disease gets worse and you agree, you will have a tumor biopsy for biomarker testing.

Optional Procedure #2: If you agree, you will have a lumbar puncture to collect cerebrospinal fluid (CSF, the fluid that surrounds the spinal cord and brain) at screening and on Day 1 of Cycle 3. If the disease gets worse, you will also have a lumbar puncture at that time.

A lumbar puncture (also called a spinal tap) is when fluid surrounding the spinal cord is removed by inserting a needle into the lower back. The affected area is numbed with local anesthetic during the procedure.

Optional Procedure #3: If you need surgery as part of your standard of care to remove the worsening brain metastasis, leftover tissue from that surgery will be collected for biomarker testing.

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:

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. Rarely (in fewer than 3% of patients), major bleeding may occur.

Spinal taps may cause headaches, sensitivity of the eyes to light, nausea, vomiting, confusion, drowsiness and/or pain at the injection site. They may cause fever, infection, and/or bleeding. Spinal taps may cause inflammation/bleeding around the brain and/or the covering of the spinal cord, which can lead to nerve damage. In rare instances, spinal taps may cause seizures, leakage of spinal fluid, and/or blockage of spinal fluid, which can lead to brain swelling. Severe infections of the spinal fluid or bleeding within the brain can result in coma and/or death. Repeated spinal taps may result in learning or memory difficulties.

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

Optional Procedure #2: Do you agree to have a lumbar puncture?

YES NO

Optional Procedure #3: If you have surgery as part of your standard of care to remove brain metastasis, do you agree to allow researchers to collect leftover tissue?

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, Bristol-Myers Squibb, or Exelixis 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. Jianbo Wang, at 713-792-2830) 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. It may be dangerous to suddenly stop study treatment, and the study doctor can discuss ways to safely withdraw. If you withdraw from this study, you can still choose to be treated at MD Anderson.

   If you stop being in the research, already collected data may not be removed from the study database. The study staff may ask if they can continue collecting the results of routine care from your medical record.

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, Exelixis, 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, including the results of all of your standard tests performed as part of this research, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

   The results for most of the non-optional study tests will be placed in your medical record.

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

9. This study is sponsored by MD Anderson and supported by: Bristol-Myers Squibb and Exelixis.

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 Bristol-Myers Squibb and Exelixis 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 will not be stored by Bristol-Myers Squibb and Exelixis.

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 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.

If you do not want your samples or data to be used for future research, tell the study doctor. You may withdraw your samples at any time by telling your study team. If you decide to withdraw your samples, they will be returned to the lab they came from or destroyed. However, the data and test results already collected from your samples will be kept and may be used.

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.

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.

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 and Exelixis, who are supporters 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.

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 **2021-0520**.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE
A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS).

_____
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.)