THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Ipilimumab Combined with Ibrutinib and Nivolumab for Patients with Chronic Lymphocytic Leukemia (CLL) and Richter Transformation (RT)

2020-0571

Subtitle: Ipilimumab combination of Ibrutinib and Nivolumab with Ibrutinib for CLL

Study Chair: Nitin Jain

_____ _____
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 find the recommended dose of ipilimumab that can be given in combination with either ibrutinib alone or with ibrutinib and nivolumab to patients with chronic lymphocytic leukemia (CLL) and Richter transformation (RT).

The safety of these drug combinations will also be studied.

This is an investigational study. Nivolumab is FDA approved and commercially available for use in melanoma patients. Ipilimumab is FDA approved and commercially available for use in melanoma patients and renal cell carcinoma. Ibrutinib is FDA approved and commercially available for the treatment of patients with CLL/RT. The combination of nivolumab and ipilimumab is FDA approved for the treatment of mesothelioma. The use of these drugs in combination is considered investigational.

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 have to spend long periods of time out of town.

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

You may receive the study drugs for up to 2 years as long as the doctor thinks it is in your best interest.

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

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive treatment with other chemotherapy or targeted therapy drugs. You may choose to receive Ibrutinib without being part of this study. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all.

There may be other FDA approved therapies for your disease type that have been shown to be safe and effective. Your doctor will discuss with you the risks and benefits of participation in this research study versus treatment with other established therapies.

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 an EKG and either an echocardiogram (ECHO) or multigated acquisition (MUGA) scan to check your heart function.
- Blood (about 3-5 tablespoons) will be drawn for routine tests, antibody testing, and to test for hepatitis and HIV (the AIDS virus). If you can become pregnant, the routine blood draw or a urine sample will be used for a pregnancy test. To take part in this study, you cannot be pregnant.
- Urine will be collected for routine tests.
- You will have a bone marrow biopsy and/or aspirate to test for tumor markers. Tumor markers may be related to the status of the disease. To collect a bone

marrow biopsy/aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow and bone is withdrawn through a large needle.
- You will a CT or PET scan to check the status of the disease.

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

Study Groups

If you are found to be eligible to take part in this study, you will be assigned to a study part based on when you join this study. If you are enrolled in Part A (up to 18 participants), you will receive ipilimumab and ibrutinib. If you are enrolled in Part B (up to 32 participants), you will receive ipilimumab, ibrutinib, and nivolumab.

Up to 50 participants will be enrolled in this study. All will take part at MD Anderson.

Participants in all parts will receive the same dose of ibrutinib. If you were already receiving ibrutinib before enrolling in this study, you may continue your assigned dose and dose schedule.

The dose of ipilimumab you receive will depend on when you join this study.
- **Participants in Part A:** The first group of participants will receive the lowest dose level of ipilimumab.
- **Participants in Part B:** The first group of participants will receive the recommended dose found in Part A.

In all parts, each group will receive a higher dose of ipilimumab than the group before it, if no intolerable side effects were seen. This will continue until a recommended tolerable dose of ipilimumab is found.

All participants in Part B will also receive the same dose of nivolumab.

Study Drug Administration

Cycles 1-4 will be 21 days long. After that, each cycle will be 28 days.

All patients will receive:
- Ipilimumab by vein over about 90 minutes on Day 1 of Cycles 1-4.
- Ibrutinib by mouth 1 time every day starting on Day 1 of Cycle 1 (if enrolled in Part A) or Day 7 of Cycle 1 (if enrolled in Part B).

Ibrutinib capsules should be taken with a full glass (about 8 ounces) of water. The capsules should be swallowed whole and should not be opened or dissolved in water. Each dose of ibrutinib should be taken about 2 hours after a meal or at least 30 minutes before the next meal, at about the same time each day. If you miss a dose, you should take it as soon as you remember on the same day. The next dose

should be taken at the normally scheduled time the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose.

If you are enrolled in Part B, you will also receive nivolumab by vein over about 30 minutes on Day 1 of Cycles 1-4. After that, you will receive it every cycle for 9 cycles (1 year total).

If ipilimumab or nivolumab (if you receive it) are helping to control the disease and you are not having serious side effects, you may be able to continue taking ipilimumab (1 time every 12 weeks) or nivolumab (1 time every 3 weeks) for up to 2 years.

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.

Study Visits

Day 1 of Cycles 1-5 (+/- 3 days):
- You will have a physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests and antibody testing (Cycles 2-4 only).
- Urine will be collected for routine tests (Cycles 2-5 only).
- If you can become pregnant, blood (about 1 tablespoon) or urine will be collected for a pregnancy test (Day 22 of Cycles 2-5).

On Day 8 and 15 of Cycles 1-4 (+/- 3 days):
- You will have a physical exam (Cycle 1 only).
- Blood (about 2 tablespoons) will be drawn for routine tests.

At the end of Cycle 4 (+/- 1 week):
- You will have a bone marrow aspiration to check the status of the disease.
- You will a CT or PET scan to check the status of the disease.

After Cycle 4:
- About 1 time every month:
  - You will have a physical exam.
  - Blood (about 2 tablespoons) will be drawn for routine tests.
- About 1 time every 3 months:
  - Blood (about 3 tablespoons) will be drawn for antibody testing.
  - Urine will be collected for routine tests.
  - If you can become pregnant, blood (about 1 tablespoon) or urine will be collected for a pregnancy test.
- At end of Cycles 6 and 12, and then about every 12 months:
  - You will have a bone marrow aspiration.
  - You will have a CT or PET scan.

If you complete nivolumab and ipilimumab doses but continue taking ibrutinib, you will have the following tests/procedures until you leave the study:

- At least 1 time every month for the first 12 months, and then about every 3 months:
  - Blood (about 2 tablespoons) will be drawn for routine tests.
- About 1 time every 3 months:
  - Blood (about 3 tablespoons) will be drawn for antibody testing.
  - You will have a physical exam.
- At end of Cycles 6 and 12, and then about every 12 months:
  - You will have a bone marrow aspiration.
  - You will have a CT or PET scan.

End-of-Study Visit

Within 30 days after your last dose of study drugs:

- You will have a physical exam.
- Blood (about 2-3 tablespoons) will be drawn for routine tests, antibody testing, and to check the status of the disease.
- If you can become pregnant, blood (about 1 tablespoon) or urine will be collected for a pregnancy test.
- If the doctor thinks it is needed:
  - You will have a bone marrow aspirate.
  - You will have a CT or PET scan.

Additional Information

While you are on study, do not have any foods or drinks containing grapefruit, star fruit, or Seville (sour) orange.

Ask the study doctor before taking any new drugs during the study. This includes over-the-counter drugs and herbal and natural remedies. Your study doctor will review all of the drugs you are taking and let you know if they can be taken during the study.

While you are receiving Ibrutinib, it is very important that you DO NOT take the drug Coumadin (warfarin), which is a blood thinner that is usually given to treat blood clots or to prevent blood clots from happening. You also must not take any of the drugs, herbal supplements, or fruit juices listed in the table below. You should tell the study doctor or staff right away if you take warfarin or anything listed in the table below.

• drugs or supplements that increase your risk of bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs)	• clarithromycin • itraconazole • ketoconazole • nefazodone • saquinavir • telithromycin • carbamazepine	• phenytoin • pioglitazone • rifabutin • rifampin • St. John's Wort • troglitazone • aprepitant

• drugs used to prevent or treat blood clots or stroke • blood thinners such as vitamin K antagonists • supplements such as fish oil and vitamin E • indinavir • nelfinavir • ritonavir	• efavirenz • nevirapine • barbiturates • carbamazepine • glucocorticoids • modafinil • oxcarbazepine • phenobarbital	• erythromycin • diltiazem • fluconazole • grapefruit or its juice • Seville oranges or their juice • verapamil • cimetidine

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. You should discuss these with the study doctor. The more commonly occurring side effects are listed in this form, as are rare but serious side effects. 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.

Side effects will vary from person to person, and some may occur after you have stopped receiving treatment. 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, ibrutinib, and ipilimumab may each 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.

<u>Nivolumab combined with ipilimumab</u>

Common (occurring in more than 10%)

• fatigue/lack of energy • fever • itching • skin rash	• overactive thyroid gland (possible decreased thyroid stimulating hormone lab test result,	• diarrhea • loss of appetite • nausea/vomiting

• underactive thyroid gland (possible increased thyroid stimulating hormone lab test result, weight gain, heart failure, and/or constipation)	weight loss, heart rate changes, and/or sweating) • abnormal digestive blood test (possible inflammation of the pancreas)	• abnormal liver test (possible liver damage and/or yellowing of the eyes and/or skin)

Occasional (occurring in 3-10% of patients)

• chills • headache • dizziness • dry/red skin • patches of skin color loss • low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • inflammation of the pituitary gland (possibly headaches) • abnormal blood test (possible pancreas damage)	• high blood sugar (possible diabetes) • constipation • abdominal pain • dry mouth • inflammation of the intestines • mouth blisters/sores (possible difficulty swallowing) • low red blood cell count • liver inflammation • abnormal kidney test (possible kidney damage) • nerve damage (possible numbness, pain, and/or loss of motor function and/or “pins and needles” sensation)	• pain (including muscle/bone) • lung inflammation (pneumonitis), and/or bronchitis (possible difficulty breathing) • difficulty breathing • cough • infusion reaction (possible fever, rash, pain, and/or swelling) • allergic reaction, possibly life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure)

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	• blood vessel inflammation • abnormal blood acid/base balance due to uncontrolled diabetes (possible organ damage) • diabetes complications resulting in diabetic coma • dehydration	• muscle inflammation • joint pain/stiffness • dry eye • blurry/double vision • immune response causing the body to attack itself (possibly causing muscle weakness) • neuromuscular disease (possible weakness of eye, face, breathing

and/or mental status changes) • inflammation of the brain and spinal cord (possible altered consciousness) • swelling (face/arms/legs) • difficulty sleeping • 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) • inflammation of multiple areas of the body (see below) • inflammation of the thyroid gland (possible tenderness in the neck) • pituitary gland failure (possible hormone imbalance)	• hole in the intestines or stomach (possibly leaking contents into the abdomen) • liver failure/damage • low blood cell count (platelets, white) • viral/bacterial infection that affects nose, throat and airways (upper respiratory tract infection) • destruction of red blood cells due to the body attacking itself (called autoimmune hemolytic anemia) • kidney failure • breakdown of muscle tissue (possible kidney failure) • Guillain-Barre syndrome--damage to the nervous system (causing numbness and/or paralysis) • nerve damage (affecting the head and neck)	and swallowing muscles) (myasthenic syndrome, myasthenia gravis) • multi-organ disease causing lesions, most often in the lungs (sarcoidosis) • abnormally excessive sweating involving the arms, legs, hands and feet, underarms, and face, usually unrelated to body temperature or exercise • flu-like symptoms (which may include fever, chills, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, feeling tired) • lung infiltrates (possible infection or inflammation) • Hemophagocytic lymphohistiocytosis (HLH) syndrome (see below)

You may need to take drugs to reduce inflammation while taking nivolumab and ipilimumab. 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(s) work 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 and ipilimumab may cause serious side effects that affect your immune system. Some of these side effects can be rare or occasional and start as inflammation in different areas of the body like the skin, hormone glands, pancreas, pituitary gland, 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.

At this time, it is not known whether taking a COVID-19 vaccine may affect the way that the study drug(s) work in your body or if the study drug(s) may affect the way the vaccine works in your body. No information is known about the interaction between a COVID-19 vaccine and nivolumab or ipilimumab.

Nivolumab and ipilimumab may cause Hemophagocytic lymphohistiocytosis (HLH) syndrome at a rare 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.

Frequency Unknown

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

<u>Ibrutinib Side Effects</u>

Common (occurring in more than 20% of patients)

• swelling (arm/leg) • fatigue • fever • skin rash • diarrhea • nausea	• mouth blisters/sores (possible difficulty swallowing) • constipation • abdominal pain • vomiting • loss of appetite • low blood cell counts (white/platelets/red)	• bleeding (such as in the digestive system, around the brain, and blood in the urine) • pain (muscle/joint) • muscle spasms • difficulty breathing • cough • infection

Ibrutinib may increase the risk of bleeding with any surgical procedure. Ibrutinib should be stopped at least 3-7 days before and after surgery, depending on the type of surgery and the risk of bleeding. Be sure to contact your study doctor if you have any planned surgical procedures. For emergency surgical procedures, ibrutinib should be stopped after the procedure until the surgical site is reasonably healed (not oozing fluid).

You should contact the study doctor as soon as possible and you will be told when to stop ibrutinib and when to restart it after a surgical procedure.

If you have diarrhea, tell your study doctor right away. The study doctor may ask you to come into the clinic for additional blood draws and tests/procedures to check your health. This is very important.

Occasional (occurring in 3-20% of patients)

• irregular heartbeat • high blood pressure • falls • chills • headache • dizziness • anxiety • stroke (with possible bleeding in the brain) • itching • low blood levels of albumin (possible swelling, weakness, and/or fatigue) • dehydration	• low blood levels of potassium (possible weakness and/or muscle cramps) • high blood levels of uric acid (possible painful joints and/or kidney failure) • chronic heartburn and indigestion • upset stomach • weakness • nerve damage (possible numbness, pain, and/or loss of motor function) • mouth/throat pain • joint disease (possible pain)	• blurred vision • dry eyes • teary eyes • abnormal kidney test (possible kidney damage) • nosebleed • lung inflammation (possible difficulty breathing) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure) • increase in specific white blood cells (possible abnormal clumping or bleeding)

Ibrutinib may occasionally cause you to develop a new type of cancer (such as skin cancer, carcinoma, and/or rarely, histiocytic carcinoma [a type of cancer that can start in the bone marrow]).

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

• abnormal fast and irregular heartbeat rhythm that starts from the lower chambers (ventricles) of the heart • fast heartbeat • tissue swelling (face/mouth/throat) • progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in	• inflammation of the fatty layer under the skin • very severe blistering skin disease (with ulcers of the skin and digestive tract) • skin condition with fever and skin lesions • abnormal blood clotting • kidney and/or liver failure	• breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage) • allergic reaction, possibly life-threatening (such as difficulty breathing,

paralysis and/or coma, which may be permanent, or death)	• reactivation of hepatitis B (liver damage)	low blood pressure, and/or organ failure)

Your study doctor may start or continue medication to help prevent or treat an infection.

Ipilimumab Side Effects

Common (occurring in more than 20% of patients)

• fatigue • headache • itching and/or skin rash • low blood levels of calcium (possible weakness and/or cramping) • low blood levels of sodium (possible headache, confusion, seizures, and/or coma)	• high blood sugar (possible diabetes) • weight loss • diarrhea • loss of appetite • nausea • inflammation of the intestines	• abnormal digestive blood test (possible inflammation of the pancreas) • pain • low blood cell counts (red/white) • abnormal liver tests (possible liver damage) • cough

Occasional (occurring in 3-20% of patients)

• high blood pressure • fever • difficulty sleeping • hives • patches of skin color loss • underactive thyroid gland (possible weight gain, heart failure, and/or constipation)	• vomiting • low platelet blood cell count • 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) • difficulty breathing • infusion reaction (possible chills and/or hives)

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

• blood vessel disease (possible tissue death) • blood vessel inflammation (possible bleeding and/or bruising) • body-wide inflammation • heart inflammation	• nerve damage (loss of motor or sensory function) • Cushing's syndrome (possible weakness, diabetes, and/or bone weakness)	• stomach and/or small intestine ulcer • bone marrow failure due to abnormal tissue growth • liver failure • liver damage due to inflammation

• inflammation of the tissue around the heart (possible chest pain) • brain inflammation (possible paralysis and/or coma) • paralysis of nerves controlling the head and neck • immune system damage to the nervous system (causing numbness and/or paralysis) • immune response (causing muscle weakness)	• pituitary gland failure (possible endocrine gland abnormality) • red, dry, scaly patches of thickened skin (psoriasis) • 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) • inflammation of the pancreas (possible abdominal pain)	• muscle inflammation and weakness • breakdown of muscle tissue (possible kidney failure) • uncontrolled movements • paralysis • inflammation inside the eye (possible vision problems) • hearing loss • kidney failure • kidney damage • lung inflammation (possible difficulty breathing) • multi-organ disease causing lesions, most often in the lungs

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

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.

Frequency unknown

• leakage of fluids from blood vessels into surrounding tissue (possible difficulty breathing) • large skin blisters • skin rash (possible fever/lymph node swelling/inflammation of internal	• Type 1 diabetes, which may require insulin • gallbladder inflammation (possible abdominal pain) • bronchiolitis obliterans (damage of the small airways with difficulty breathing) • decreased bone marrow function and	• graft-versus-host disease (when transplanted donor tissue attacks the tissues of the recipient's body) • immune system disease (possible dry mouth/eyes, fatigue, joint pain, and/or organ failure)

organs/abnormal blood cell counts) • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract)	inability to make red blood cells	• Vogt Koyanagi Harada syndrome -- pigmented tissue (possible eye pain/swelling, hearing loss, and/or loss of skin color)

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 **bone marrow 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.

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

MUGA scans may cause allergic reactions to the radioactive tracer, injection site soreness, and/or swelling. They may cause damage to cells or tissue from being exposed to the radiation used in the scan. These side effects may occur in less than 10% of patients.

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.

A **PET scan** may cause you to 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 technicians will give comfort or the scanning will be stopped.

The PET scan exposes your body to radiation. The radioactive solution does not remain in your system for a long period of time. However, you should wait 2 hours before holding an infant or getting close to a pregnant woman to avoid exposing them to radiation. You should drink fluids after the scan to help remove the solution from your system.

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. You must use birth control during the study and for 23 weeks (females) or 31 weeks (males) after the last dose of study drugs, if you are sexually active.

Speak with your doctor about effective methods of birth control that can be used during the study.

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 may result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, extra blood (about 2 tablespoons) will be drawn before you begin treatment, on Day 1 of Cycle 1-5, and at the end of Cycles 6, 9, 12, 18, and 24. These samples will be stored at MD Anderson for use in future research related to cancer.

Optional Procedure #2: If you agree, extra bone marrow (about 1 teaspoon) will be collected during regularly scheduled aspirates/biopsies at the end of Cycles 4, 6, 12, 24, and at any additional bone marrow aspirates/biopsies performed after Cycle 24. These samples will be stored at MD Anderson for use in future research related to cancer.

Optional Procedure #3: If you agree, saliva will be collected 1 time at any time during the study and compared with the blood and/or bone marrow samples

collected. To collect the sample, you will be asked to spit in a tube. The sample will be stored at MD Anderson for use in future research related to cancer.

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

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

Optional Procedure #4: If you agree, extra blood (about 4 teaspoons) will be collected at the regularly scheduled times on Day 1 of Cycles 1, 2, and 5 and at the end of Cycles 6, 9, and 12, and additional bone marrow aspirate (about 1 teaspoon) will be collected before treatment and at the end of Cycles 4, 6, and 12. These samples will be sent to and stored by the Dana-Farber Cancer Institute to learn about the disease by studying tumor and immune cells in the bone marrow and blood.

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

You do not have to agree to the optional procedures in order to take part in this study. 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 procedure.

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

MD Anderson and others can learn about cancer and other diseases from your **banked samples**. In the future, people who may do research with these samples may need to know more information about your health. This information may be

collected from your medical record. MD Anderson will make reasonable efforts to preserve your privacy, but cannot guarantee complete privacy. 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.

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

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

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

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

Optional Procedure #1: Do you agree to have extra blood drawn and stored in a research bank at MD Anderson for use in future research related to cancer?

YES **NO**

Optional Procedure #2: Do you agree to have extra bone marrow collected during regularly scheduled aspirates/biopsies and stored in a research bank at MD Anderson for use in future research related to cancer?

YES **NO**

Optional Procedure #3: Do you agree to have saliva collected for comparison with other blood and/or bone marrow samples and stored in a research bank at MD Anderson for use in future research related to cancer?

YES **NO**

Optional Procedure #4: Do you agree to have extra blood drawn and bone marrow collected and sent and stored in a research bank at Dana-Farber Cancer Institute for testing of tumor and immune cells?

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 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. Nitin Jain, at 713-745-6080) 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 will be removed from the study drug and will be asked to take part in follow-up tests for your safety. 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. You may be asked whether the study doctor can collect data from your routine medical care. If you agree, this data will be handled the same as

research data.

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, 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.

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/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. Bristol Myers Squibb will not store leftover samples.

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

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

If 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.

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

Genetic Research
Research samples collected from you as part of this study may be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you. The same level of data protection that covers your individual data does not apply to summary results (when data from the whole study is combined).

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

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Outside Care

Part of your care, such as blood draws and physical exams, may be provided outside of MD Anderson by your home doctor(s).

Conflict of Interest

Nitin Jain (Study Chair) has received compensation from Bristol Myers-Squibb as a Scientific Advisor. The financial interests are within the limits of the conflict of interest policy.

Prithviraj Bose (Collaborator) has received compensation from Bristol Myers-Squibb as a Consultant. The financial interests are within the limits of the conflict of interest policy.

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

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson
   - Bristol Myers Squibb, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
   - Regulatory agencies in other countries where the study may be conducted and contracted CROs (contract research organization) such as Bristol Myers Squibb to monitor the progress of the study or analyze the study data and any future sponsors and/or licensees of the study technology
   - 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.

   If study results are published in books, magazines, journals, and scientific meetings, your name and other identifying information will not be used.

   Blood, tissue, and bone marrow samples will be sent to a central laboratory by the sponsor. These samples will be destroyed at the end of this study.

   You will have several imaging scans performed while you are on study. Your scans will be coded with your participant number that you are given at the time you enter the study. No identifiable information from these scans will ever be sent to the sponsor or anyone else outside of this institution.

   Your scans, labelled only with your participant number, may be transferred to a central imaging company for storage and analysis. The scans may be stored indefinitely.

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 **2020-0571**.

_____ _____
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