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 the Combination of Ponatinib with Mini-hyper CVD Chemotherapy and Venetoclax in Patients with Relapsed or Refractory T-cell Acute Lymphoblastic Leukemia

2021-0802

Subtitle: Protocol Version 08 – 12/21/2023

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.

If you are reading and signing this form on behalf of a potential participant, please note: Any time the words "you," "your," "I," or "me" appear, it is meant to apply to the potential participant.

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 ponatinib in combination with venetoclax and chemotherapy can help to control acute lymphoblastic leukemia (ALL) that is relapsed (has come back) or refractory (has not responded to treatment). The safety of this study drug combination will also be studied.

This is an investigational study. Ponatinib and venetoclax are each FDA approved and commercially available for the treatment of certain types of leukemia, but not for relapsed or refractory ALL. The chemotherapy given in this study (cyclophosphamide, mesna, vincristine, dexamethasone, methotrexate, solumedrol, cytarabine, pegfilgrastim, and leucovorin) consists of drugs that are FDA approved and commercially available for the treatment of ALL. It is considered investigational to give ponatinib in combination with venetoclax and chemotherapy to patients with relapsed or refractory ALL.

As part of this study, you may also receive maintenance therapy. The drugs given for maintenance therapy (prednisone and vincristine) are FDA approved and commercially available for this use. You will also continue to receive ponatinib and venetoclax during maintenance therapy.

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, hospitalization, potential expenses, and time commitment/prolonged stay out of town.

If you take part in this study, you may experience side effects, some of which may be severe or life threatening. Ponatinib may commonly cause a blood clot to form in an artery or vein. This may cause a heart attack, stroke, and/or severe tissue damage and may result in death. You can read a full list of potential side effects below in the Possible Risks section of this consent.

You may receive the study drugs for up to 32 study cycles (about 2½ years). You may receive ponatinib, venetoclax, and chemotherapy for up to 8 cycles followed by ponatinib, venetoclax, and maintenance therapy for up to 24 cycles (described in more detail below under “Study Drug Administration”).

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.

Ponatinib will be provided at no cost to you during this study. You and/or your insurance provider will be responsible for the cost of venetoclax, the chemotherapy drugs, and the maintenance therapy drugs.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive chemotherapy outside of this study or other standard-of-care treatment for the disease that may be available to you. You may choose to receive other investigational therapy, if available. The study doctor will discuss with you 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 be performed within 14 days before your first dose of study drug to help the doctor decide if you are eligible:

- You will have a physical exam.

- Blood (about 2-3 tablespoons) will be drawn for routine tests.
- You will have a chest x-ray to check your lung health.
- If you can become pregnant, blood (about 2-3 teaspoons) or urine will be collected for pregnancy test. To take part in this study, you must not be pregnant.

The following screening tests will be performed within 30 days before your first dose of study drug to help the doctor decide if you are eligible:

- You will have an EKG and either an echocardiogram (ECHO) or a MUGA scan to check your heart function.
- Blood (about 1-2 tablespoons) will be drawn for routine tests, including to test for infectious disease (HIV [the AIDS virus] and hepatitis B and C. Hepatitis testing must be done within 90 days before your first dose.
- You will have a bone marrow aspirate and/or biopsy performed to check the status of the disease and for genetic testing. The type of genetic testing performed in this study will be done to help researchers learn if your genetic information relates to the disease and/or how you respond to treatment. To collect a bone marrow aspirate and/or biopsy, an area of the hip is numbed with anesthetic, and a small amount of bone marrow and bone is withdrawn through a large needle.

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 26 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration

If you are found to be eligible to take part in this study, you will receive the following study drugs. Study Cycle 1 is 31 days. Study Cycles 2 and beyond are 28 days.

You will take **ponatinib** by mouth during this study. For the first 3 days of Cycle 1, you will take ponatinib alone each day (without other chemotherapy drugs or venetoclax). These are referred to as Days -3, -2, and -1 of Cycle 1. Starting with Day -3, you will take ponatinib 1 time each day on Days —3 to Day 14 of Cycle 1. You will not take ponatinib on Days 15 to 28 of Cycle 1. Then, starting on Day 1 of Cycle 2, you will take ponatinib 1 time every day for the rest of the treatment period.

Ponatinib may be taken with or without food. Swallow the tablets whole. Do not crush, break, cut or chew tablets. If you forget to take a dose or vomit a dose, do not take a makeup dose. Wait and take the next dose as scheduled.

The day after you complete 3 days of ponatinib dosing, you will start taking **venetoclax**. You will take venetoclax by mouth 1 time on Days 1-14 of Cycle 1, on Days 1-14 of Cycles 2-8, and then on Days 1-7 of Cycles 9 and beyond. Venetoclax must be taken in the morning with about 1 cup (8 ounces) of water and within 30 minutes after you eat a low-fat breakfast.

If you vomit a dose of venetoclax within 15 minutes after taking it and the expelled tablet(s) are all intact, you may take another dose. Otherwise, do not take another dose. Wait and take the next dose as scheduled. If you forget to take a dose and less than 8 hours have passed since the usual time you take the study drug, take another dose with food as soon as you remember. If more than 8 hours have passed, do not take another dose. Wait and take the next dose as scheduled.

You may continue taking ponatinib and venetoclax until you complete Maintenance Therapy (described below).

Chemotherapy Phase (Cycles 1-8)
In addition to taking ponatinib and venetoclax as described above:

During **Cycles 1, 3, 5, and 7**:
- On **Days 1-3**, you will receive cyclophosphamide 2 times each day (about 12 hours apart) by vein over about 3 hours.
- On **Days 1-3**, you will receive mesna by vein non-stop to help prevent side effects. The mesna infusion will start about 1 hour before the cyclophosphamide infusion and end about 12 hours after the last dose of cyclophosphamide.
- On **Days 1 and 8**, you will receive vincristine 1 time a day by vein over about 15 minutes.
- On **Days 1-4 and 11-14**, you will receive dexamethasone 1 time a day by vein over 30 minutes or by mouth.
- On **Day 4**, you will receive either a biosimilar of pegfilgrastim (which means it is identical to that drug) as an injection under the skin as a 1-time dose or filgrastim product as an injection under the skin 1 time every day to help your blood counts recover.
- If the study doctor thinks it is needed, on **Day 2 of Cycles 1 and 3**, you may receive methotrexate intrathecally (as a spinal tap). Intrathecally means the chemotherapy will be given directly into the cerebrospinal fluid (CSF—the fluid surrounding the brain and spinal cord). For this procedure, your lower back will be numbed with an anesthetic and a needle will be inserted into the lower back. This will be discussed with you.
- If the study doctor thinks it is needed, in **Day 8 of Cycles 1 and 3**, you may receive cytarabine intrathecally.

During **Cycles 2, 4, 6 and 8**:
- On **Day 1**, you will receive methotrexate by vein non-stop over 24 hours.
- On **Days 1-3**, you will receive solumedrol 2 times each day (about 12 hours apart) by vein over about 2 hours.
- On **Days 2 and 3**, you will receive cytarabine by vein 2 times each day (about 12 hours apart) over about 3 hours.
- On **Day 4**, you will receive either pegfilgrastim biosimilar as an injection under the skin as a 1-time dose or filgrastim product as an injection under the skin 1 time every day to help your blood cell counts recover.
- If the study doctor thinks it is needed, on **Day 2 of Cycles 2 and 4**, you may receive cytarabine intrathecally.

- If the study doctor thinks it is needed, on **Day 8 of Cycles 2 and 4**, you may receive methotrexate intrathecally.
- If your doctor thinks it is needed to help reduce the risk of side effects, you may receive leucovorin by vein over about 15 minutes 4 times a day for up to 8 doses, beginning 12 hours after the methotrexate dose ends.

You will be hospitalized until chemotherapy is completed. If the study doctor thinks it is needed for your safety, you may stay in the hospital longer after completing chemotherapy. You and/or your insurance provider will be responsible for the cost of this hospital stay.

Maintenance Therapy (Cycles 9-32)
After completing chemotherapy, in addition to taking ponatinib and venetoclax as described above:

- On **Day 1 of each cycle**, you will receive vincristine 1 time by vein over about 15 minutes.
- On **Days 1-5 of each cycle**, you will take prednisone by mouth 1 time.

If the study doctor thinks it is in your best interest, you may start maintenance therapy before completing chemotherapy. This will be discussed with you.

During both the chemotherapy and maintenance therapy phases, you may also be given other 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

Within **48 hours before Day 1 of Cycle 1**:

- You will have a physical exam.
- Blood (about 2 tablespoons) will be drawn for routine tests.

One (1) time every week during Cycle 1 and then before each cycle after that, you will have a physical exam.

At least 1-3 times every week during Cycle 1, at least 1 time every week during Cycles 2-8, and then at least 1 time every month after that, blood (about 2 tablespoons) will be drawn for routine tests.

Before starting Cycles 2, 4, 6, and 8, you will have a chest x-ray to check your lung health.

At the end of Cycle 1 (before starting Cycle 2) and then before Cycles 3 and beyond, you will have a bone marrow aspirate and/or biopsy performed to check the status of the disease. This bone marrow sample may also be used for genetic testing. At the end of Cycle 1, these samples will also be used for correlative (research) tests to help the doctor understand the relationship between the study drugs, your body, and the disease. Based on how the disease responds to the study drugs, you may not have bone marrow aspirates/biopsies as often. The study doctor

will discuss this with you. If the disease gets worse, you will also have a bone marrow biopsy/aspirate to check the status of the disease and for correlative testing.

Long-Term Follow-up

After your last dose of study drugs, you will be called by a member of the study staff every 6 months. You will be asked how you are feeling and about any other drugs or treatments you are receiving. The call should last about 10 minutes. This will continue until you withdraw from the study.

Other Information

While on study:

- It is important to tell the study doctor/study staff about all medications you are taking or plan to take while on study, including prescription drugs, over-the-counter drugs, herbal remedies, supplements, and/or vitamins. This is especially important if you are taking medications that may cause heart-related side effects or may cause changes in your blood's ability to clot. Some medications may interact with the study drug. If you are taking a medication that is not allowed on study, the study doctor will prescribe you an alternative.
- Short-acting antacid drugs may be taken, but it is recommended that these not be taken from 2 hours before to 2 hours after your dose of ponatinib. Proton pump inhibitors (PPIs) may be given with ponatinib if the doctor tells you it is okay to do so.
- Herbal supplements are not allowed while on study. Do not take herbal medications, such as St. John’s Wort, Blue Cohash, and Estroven, for at least 7 days before the first dose of ponatinib or within 3 days before the first dose of venetoclax.
- Do not receive live vaccines while on study.
- Avoid having any grapefruit, Seville (sour) oranges, star fruit, and products containing juices of these fruits.

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.

Ponatinib, venetoclax, cyclophosphamide, mesna, vincristine, methotrexate, pegfilgrastim biosimilar, filgrastim product, and cytarabine each may cause a low blood cell count (red, 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.

Ponatinib Side Effects

Common (occurring in more than 20% of patients)

• high blood pressure • swelling (arm/leg) • heart attack • blood clots in an artery (possible organ damage such as stroke and/or heart attack) • blood clots in a vein (possible pain, swelling, and/or redness) • blood vessel disorder (possible tissue death) • fatigue • weakness • headache • fever • bleeding in the brain • stroke	• skin rash • dry skin • high blood sugar (possible diabetes) • low blood sugar • 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) • abdominal pain • constipation • nausea • loss of appetite • diarrhea	• vomiting • mouth blisters/sores (possible difficulty swallowing) • digestive system bleeding • abnormal digestive blood test (possible pancreas inflammation/damage) • low blood counts (white, red, platelet) • abnormal liver tests (possible liver damage) • pain (joint/muscle) • difficulty breathing • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Ponatinib may cause a blood clot to form in an artery or in a vein. Depending on the location of the clot, this could cause a heart attack, a stroke, severe damage to other tissue, or death. A blood clot may occur within 2 weeks after you start taking the drug. About 41% (about 2 in 5) of patients taking the drug form an abnormal clot. Blood clots can occur in patients that do not have other known risk factors for forming clots. If you develop a blood clot, you will need to stop taking ponatinib. In some cases, emergency surgery could be needed to remove the clot and restore blood flow.

Occasional (occurring in 3-20% of patients)

• fast/irregular heartbeat • heart and/or lung failure • decreased blood supply to the heart • heart and/or blood vessel disease • shock caused by heart damage • build-up of fluid in the tissue around the heart • decreased supply of blood through the arteries (possible tissue death) • difficulty sleeping • dizziness • chills • sweating • flushing • itching • hair loss (partial or total) • high blood levels of fat (possible heart disease and/or stroke) • inflammation of the pancreas (possible abdominal pain)	• weight loss • abdominal swelling • upset stomach • dry mouth • problems with urination • high blood levels of uric acid (possible painful joints and/or kidney failure) • impotence • abnormal liver tests (possible yellowing of the skin and/or eyes) • blood clots in a vein to the liver (possible liver and/or digestive system damage) • pain (arm/leg/back/bone) • muscle spasms • nerve damage (possible numbness, pain, and/or loss of motor function) • abnormal sensation (such as pins and needles)	• blood clot inside the eye (possible blindness) • eye irritation/pain • swelling under the central part of the retina (possible vision loss) • bleeding in the eye • dry eyes • blurry vision • blood clot inside the eye (possible blindness) • abnormal kidney test (possible kidney damage) • fluid in or around the lung (possible difficulty breathing) • blockage in the lung (possible pain, shortness of breath, and/or failure to breathe) • cough • voice changes (possible hoarseness) • infection

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

• slow heartbeat • reduced blood supply to the arms and legs • narrowing of the arteries (possible high blood pressure, fatigue, and/or weakness) • swelling of the brain (possible headache and/or mental status changes) • temporary stroke symptoms • painful skin bumps • fluid in the abdomen	• abnormal connections or passageways between different parts of the digestive system • hole in the intestines (possibly leaking contents into the abdomen) • nerve damage (affecting the head and neck) • blindness • cataracts (clouding of the lens of the eye) • increased pressure in the eye (possible vision	• inflammation of the eye and/or inside the eye (possible sores on the eye) • allergic reaction (such as a skin reaction) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

	loss)	

Frequency unknown

• severe increase in blood pressure (possible stroke) • blocked blood vessel (such as an artery in the abdomen)	• decreased blood circulation • blood clots in the heart (possible heart attack) • increased sensitivity of the senses	• liver failure • irritation in the tissue lining the eye • amputation due to tissue death • wound healing problems

Venetoclax Side Effects

Common (occurring in more than 20% of patients)

• swelling (arm/leg) • fatigue • 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)	• diarrhea • nausea • low blood counts (red, platelets, and white) • abnormal liver tests (possible liver damage)	• muscle and/or bone pain • upper respiratory tract infection • cough

Occasional (occurring in 3-20% of patients)

• fever • headache • dizziness • skin rash • vomiting • constipation • abdominal pain • mouth blisters/sores (possible difficulty swallowing) • joint pain	• high blood levels of uric acid (possible painful joints and/or kidney failure) • pneumonia • difficulty breathing • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)	• bacteria in the blood • tumor lysis syndrome (TLS)--breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

TLS is a problem that can occur when cancer cells break down rapidly and the body has to get rid of the broken-up cell parts. Sometimes your body, especially the kidneys, cannot remove the cell parts quickly enough, so the level of some of these

cell products in your blood, such as salts and acids, can rise. This can happen especially in participants with large tumors or a high number of cancerous white cells in the blood. TLS can lead to serious problems, such as effects on your kidneys and heart (including abnormal heart rhythms), seizures, or even death.

If you develop TLS, your urine may look dark, thick, or cloudy. You may have fever, chills, nausea/vomiting, diarrhea, confusion, shortness of breath, irregular heartbeat, fatigue, muscle pain, joint discomfort, and/or seizure. If you notice any of these, tell your doctor or nurse right away. Your study doctor will closely watch and treat you as needed to lower the risk of any serious changes in your blood or other complications of TLS. You may need to have extra blood tests or EKGs to check for signs of TLS.

You should wear ear plugs or other hearing protection when involved in a loud activity.

If you notice any rash, hives, itching, or other signs of an allergic reaction such as swelling, wheezing, or you are having a hard time breathing, tell your doctor right away.

At this time, there are no known serious side effects that **occur in fewer than 3% of patients**.

Richter's Transformation (RT) is a change of chronic lymphocytic leukemia (CLL) into a more aggressive lymphoma. Richter's Transformation has happened to a small number of people that received venetoclax. It is not clear at this time if venetoclax treatment caused it to happen, or if it is a complication from the disease.

<u>Cyclophosphamide Side Effects</u>

Common (occurring in more than 20% of patients):

• hair loss (partial or total) • mouth blisters/sores (possible difficulty swallowing) • nausea/vomiting • inability to regulate water/salt balance which can cause frequent urination and dehydration	• headache • abdominal pain • loss of appetite • diarrhea • problems with production of sperm and eggs • inability to have children • stopped menstrual cycle • low blood counts (red, platelet, white)	• fever with dangerously low white blood cell count (febrile neutropenia) • bladder inflammation and bleeding (possible pain and/or urge to urinate) • infection

Cyclophosphamide may cause you to develop another type of cancer (such as bladder cancer, acute leukemia [a type of blood cancer], lymphoma [a type of lymph

node cancer], thyroid cancer, and/or sarcoma [a type of cancer that can start in the soft tissue, bone, or other tissue].

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

• irregular heartbeat • build-up of fluid around the heart (possible heart failure) • build-up of blood in the sac around the heart (possible impaired heart function) • inflammation of the heart and/or the tissue around the heart (possible chest pain and/or bleeding) • heart damage/failure, death of heart tissue, or other severe heart problems • heart attack, which can be serious and life-threatening • blood clots in a vein (possible pain, swelling, and/or redness) • blood clots in an artery (possible organ damage such as stroke and/or heart attack) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss) • dizziness • very severe blistering skin disease (with ulcers of the skin and digestive tract) • severe sunburn-like rash at site of previous radiation (called radiation recall)	• wound healing problems • low blood levels of potassium (possible weakness) • low blood levels of sodium (possible headache, confusion, seizures, and/or coma) • hormonal deficiency that affects the body's ability to control blood pressure and react to stress • decreased supply of blood to the abdomen • digestive system bleeding • enlarged bowel (possible abdominal pain) • inflammation of the intestines (possible bleeding) • inflammation of the pancreas (possible abdominal pain) • liver damage (possibly due to blood clots) • jaundice (yellowing of skin and/or eyes) • high blood levels of uric acid (possible painful joints and/or kidney failure) • ovarian scarring • urinary tract or bladder scarring • decreased testicle size and function • blood in the urine • blurry vision	• hearing loss • breakdown of muscle tissue (possible kidney failure) • death of kidney tissue (possible kidney failure) • difficulty breathing • lung inflammation (possible difficulty breathing) • problems with blood carrying oxygen (possible blue skin) • lung damage due to blood clots • increased blood pressure in the lungs (possible difficulty breathing and/or heart failure) • multiorgan 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) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

• very severe blistering skin disease (loss of large portion of skin)		

Mesna Side Effects

It is not known how often the following side effects of mesna may occur.

• flushing • dizziness • fever • increased sensitivity of the senses • headache • sleepiness • very severe blistering skin disease (with ulcers of the skin and digestive tract)	• skin rash, blisters, and/or sores • very severe blistering skin disease (loss of large portion of skin) • loss of appetite • constipation • diarrhea • gas • nausea/vomiting • abnormal taste/change in taste	• blood in the urine • pain • shivering • painful red eyes • cough • sore throat • runny nose • flu-like symptoms • injection site swelling, pain, and/or heat

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

• high blood pressure • low blood pressure (possible dizziness/fainting)	• fast heartbeat • low platelet count	• allergic reaction that may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure)

Vincristine Side Effects

Common

• hair loss (partial or total)	• constipation	• nerve damage (possible numbness, pain, and/or loss of motor function)

Rare

• hormonal deficiency that affects the body's ability to control blood pressure and react to stress	• allergic reaction that may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure)

It is not known how often the following side effects of vincristine may occur.

• swelling • high blood pressure • low blood pressure (possible dizziness/fainting) • heart attack • decreased blood supply to the heart • multiple blood clots (possible organ dysfunction and/or failure) • vein inflammation • difficulty walking • coma • decreased function of nerves controlling the head and neck (possible hearing damage and/or damage to the nerves serving the muscle to the eye and/or voicebox [causing vision and speech problems]) • dizziness • fever • headache • depression • confusion • difficulty sleeping • seizure • skin rash	• tissue irritation and/or tissue death • abdominal cramps/pain • loss of appetite • diarrhea • decreased blood flow to part of the bowel (possibly causing death of tissue) • hole in the intestines (possibly leaking contents into the abdomen) • nausea/vomiting • mouth ulcers • weight loss • bladder weakness • inability to urinate • difficult, frequent, and/or painful urination • low blood cell counts (red, white, platelets) • destruction of red blood cells (possible kidney damage and/or failure) • liver damage due to blood clots • pain • loss of deep tendon reflexes (possible weakness)	• loss of muscle • paralysis (possibly of the intestines) • nerve damage (foot/ankle weakness causing abnormal walking) • loss of motor and/or sensory function • abnormal sensation (such as pins and needles) • blindness • eye twitching • damage to an eye nerve (possible vision changes) • deafness • inner ear damage (possible dizziness and/or problems with balance) • high blood levels of uric acid (possible painful joints and/or kidney failure) • difficulty breathing (possibly due to narrowing of the airways)

Dexamethasone Side Effects

It is not well known how often the following side effects may occur.

• high blood pressure • irregular, fast, and/or slow heartbeat • enlarged heart • heart failure • tearing of the walls of the heart (post-heart attack) • blood vessel inflammation (possible bleeding and/or bruising) • blood clots in a vein (possible pain, swelling, and/or redness) • blood clots in the arteries • swelling (such as tissue and/or abdominal swelling) • dizziness • shock • fainting • headache • increased pressure in the skull or between the skull and brain (possible headache, vision changes, and/or mental status changes) • seizure • depression • fatigue and anxiety • mood swings • personality changes • mental disorders • euphoria (unusual feelings of happiness or well-being) • difficulty sleeping • fatigue/lack of energy • darkening and/or lightening of the skin • tiny dots on the skin • impaired wound healing	• decreased ability to process carbohydrates • high blood sugar (possible diabetes) • diabetes • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • abnormal blood acid/base balance (possible organ damage) • low blood levels of potassium (possible weakness and/or muscle cramps) • high blood levels of sodium (possible weakness and/or swelling) • sugar in the urine • body-wide loss of proteins (possible weakness and/or swelling) • build-up of fat in abnormal areas • weight gain • increased appetite • digestive system bleeding • small red or purple spots in the mouth • esophageal sore • hole in the intestines (possibly leaking contents into the abdomen) • nausea • itching near the anus • inflammation of the pancreas (possible abdominal pain) • stomach ulcer	• inflammation of nerves (possible pain and/or loss of motor or sensory function) • joint disease (possible pain) • pain or loss of function of the hips or shoulders due to bone death • broken bones • loss of muscle • muscle damage causing weakness • nerve damage (loss of motor or sensory function) • loss of bone strength (possible broken bones) • abnormal sensation (such as pins and needles) • tendon tear • collapse of bones in the spine • enlarged liver • abnormal liver tests (possible liver damage) • bulging eye • increased pressure in the eye (possible vision loss, pain, and/or blurry vision) • cataracts (clouding of the lens of the eye) • hiccups • fluid in the lung (possible difficulty breathing) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney

• skin rash, redness, and/or dryness • fragile and/or thinning skin • skin test reaction impaired (due to a lowered immune system) • stretch marks • hives • acne-like rash • hair loss (partial or total) • hair growth • sweating • tissue death • Cushing's syndrome (possible weakness, diabetes, and/or bone weakness)	• changes to the menstrual cycle • problems with production of sperm • bruising • muscle weakness	damage, and/or other organ damage) • infection • allergic reaction (such as skin reaction) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure)

Dexamethasone may cause you to develop another type of cancer.

Dexamethasone may cause a false-positive or false-negative skin test (such as a test for tuberculosis [TB]). If you need to have a skin test performed, tell the doctor that you are taking dexamethasone.

Stopping dexamethasone suddenly may cause withdrawal symptoms (such as fever, muscle/joint pain, and fatigue). This is because dexamethasone affects your adrenal glands and may cause your body's hormone levels to change. The study doctor will help you stop dexamethasone safely, if you want to stop taking the study drug. Do not just stop taking dexamethasone.

Methotrexate Side Effects

Exact frequency unknown but occurring in more than 10% of patients:

• mouth blisters/sores	• diarrhea	• abnormal liver test (possible live damage)

Exact frequency unknown but occurring in between 1 and 10% of patients:

• dizziness • nausea • vomiting	• hair loss (partial or total) • skin rash and/or itching	• burning sensation of the skin • low blood cell counts (red/white/platelets)

	• skin sensitivity to sunlight or lamps	

Frequency Unknown

• chest pain • low blood pressure (possible dizziness/fainting) • blood clots in an artery (possible organ damage such as stroke and/or heart attack) • blood clots in a vein (possible pain, swelling, and/or redness) • blood clots in the brain • inflammation of and/or build-up of fluid in the tissue around the heart (possible chest pain) • blood clot inside the eye (possible blindness) • blood vessel inflammation (possible bleeding and/or bruising) • dilated red blood vessels • blockage in the lung (possible pain and/or shortness of breath) • inflammation of the membrane around the spinal cord and brain (possible headache, vomiting, and fever) • damage to the spinal cord (possible paralysis, weakness, and/or abnormal sensation) • fever • chills • abnormal sensation on the scalp	• very severe blistering skin disease (loss of large portion of skin) • shedding and scaling of the skin (possible fatal loss of bodily fluids) • red, dry, scaly patches of thickened skin (psoriasis) • allergic skin reaction • lightening or darkening of skin • skin rash • acne-like rash • severe sunburn-like rash at site of previous radiation (called radiation recall) • death of skin • skin redness • hives • decreased sex drive • enlarged breasts in males • failure of the ovaries to produce hormones (possible stopped menstrual cycle) • low blood level of albumin (possible swelling, weakness, and/or fatigue) • diabetes • abdominal pain • loss of appetite • gum disease • stomach ulcer • inflammation of the intestines • digestive system bleeding	• birth defects • miscarriage • impotence • inability to have children • low sperm count • decreased egg production • vaginal discharge • liver damage due to scarring • liver failure • liver damage due to inflammation • bone destruction and soft tissue death of tissue (with radiotherapy) • broken bone(s) • loss of bone strength (possible broken bones) • joint/muscle pain • blurry vision • temporary blindness • painful red eyes • eye pain • blindness • ringing in the ears • abnormal kidney test (possible kidney damage) • decreased kidney function • kidney failure • difficulty breathing • lung inflammation (possible difficulty breathing) • difficulty breathing due to lung damage

• brain damage that may be reversible (possible headache, confusion, seizures, and/or vision loss) • mental status change (such as memory loss and impaired thinking) • fatigue/lack of energy • decreased brain function (possible paralysis and/or coma) • mood swings • confusion • weakness on one side of the body • inability to speak • difficulty forming or speaking words • seizures • coma • sweating • very severe blistering skin disease (with ulcers of the skin and digestive tract)	• hole in the intestines (possibly leaking contents into the abdomen) • inflammation of the pancreas (possible abdominal pain) • vomiting of blood • tarry or coffee ground-like blood in the stool • build-up of bodily waste products in the blood (possible kidney damage) • bladder inflammation (possible pain and/or urge to urinate) • difficult and/or painful urination • blood in the urine	• increase in infection-fighting cells • infection • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • sore throat • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart 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) • cough

Methotrexate may rarely cause you to develop another type of cancer (such as lymphoma, a type of lymph node cancer).

When given intrathecally, methotrexate may cause inflammation of the membrane around the spinal cord and brain (possible headache).

Pegfilgrastim Biosimilar Side Effects

Common (occurring in more than 20% of patients)

• bone and/or muscle pain

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • headache	• vomiting • constipation	• pain (joint/arm/leg) • weakness

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

• leakage of fluids from blood vessels into surrounding tissue (possible difficulty breathing) • chest pain • inflammation of blood vessels • fever • skin condition with fever and skin lesions	• ruptured spleen • enlarged spleen • decreased kidney function (possible kidney failure) • low platelet counts • diarrhea • high blood levels of uric acid (possible painful joints and/or kidney failure) • muscle tightness • difficulty breathing	• sickle cell crisis in patients with sickle cell disease • flu • immune reaction (possible loss of drug function or organ damage) • allergic reaction that may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure)

Filgrastim Product Side Effects

Common (occurring in more than 20% of patients)

• fever • fatigue	• nausea • enlarged spleen	• low platelet counts • bone pain

Occasional (occurring in 3-20% of patients)

• chest pain • high blood pressure • dizziness • headache • skin rash • abnormal blood test • vomiting	• high blood levels of uric acid (possible painful joints and/or kidney failure) • abnormal liver tests (possible liver damage) • pain	• muscle spasm • lung inflammation • cough • difficulty breathing • nosebleed • reaction to a blood transfusion

The drug may occasionally cause an increased risk of infection, such as pneumonia. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

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

• low blood pressure (possible dizziness/fainting) • irregular heartbeat • heart attack • fast heartbeat • swelling (arm/leg/face) • bleeding in the brain	• leakage of fluids from blood vessels into surrounding tissue (possible difficulty breathing) • diarrhea • low red blood cells • blood in the urine • enlarged liver	• loss of bone strength (possible broken bones) • decreased kidney function (possible kidney failure) • coughing up blood • bleeding in the lungs and/or airways

• hair loss (partial or total) • skin condition with fever and skin lesions • painful skin bumps • worsening of existing skin disease (psoriasis)	• sickle cell crisis in patients with sickle cell disease • ruptured spleen	• life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • immune reaction

Frequency unknown

• blood vessel inflammation (possible bleeding and/or bruising)

<u>Solumedrol (Methylprednisolone) Side Effects</u>

It is not well known how often the following side effects of solumedrol may occur.

• irregular, slow, and/or fast heartbeat • sudden stopping of the heart • enlarged heart • shock • heart failure • swelling • blood vessel blockage by fat • high blood pressure • tearing of the walls of the heart • fainting • blood clots in a vein (possible pain, swelling, and/or redness) • blood vessel inflammation (possible bleeding and/or bruising) • delirium (loss of contact with reality) • anxiety • depression • mood swings • euphoria (unusual feelings of happiness or well-being)	• bruising • skin redness • hair growth • hair loss (partial or total) • darkening or lightening of skin • wound healing problems • tiny dots on the skin • skin rash • skin thinning • skin tests (such as for TB) may not be accurate • stretch marks • tissue swelling • death of tissue • hives • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • stopped menstrual cycle • decreased ability to process carbohydrates	• abdominal swelling • increased appetite • digestive system bleeding • nausea • inflammation of the pancreas (possible abdominal pain) • stomach ulcer • hole in the intestines (possibly leaking contents into the abdomen) • esophageal sore • vomiting • weight gain • increase in infection-fighting cells • enlarged liver • abnormal liver tests (possible liver damage) • joint pain • joint disease (possible pain) • pain or loss of function of the hips or shoulders due to bone death) • weakness • loss of muscle

• hallucinations (seeing or hearing things that are not there) • headache • increased pressure between the skull and brain (possible vision changes and/or headaches) • difficulty sleeping/fatigue/lack of energy • nervousness • inflammation of nerves (possible pain and/or loss of motor or sensory function) • personality change • increased pressure in the skull (possible headache, vision changes, and/or mental status changes) • seizure • dizziness • sweating • acne • dry, scaly skin	• Cushing's syndrome (possible weakness, diabetes, and/or bone weakness) • diabetes • high blood or urine sugar levels (possible diabetes) • high blood levels of fat (possible heart disease and/or stroke) • low blood levels of potassium (possible weakness and/or muscle cramps) • high blood levels of sodium (possible weakness and/or swelling) • abnormal blood acid/base balance (possible organ damage) • changes to the menstrual cycle • hormonal deficiency that affects the body's ability to control blood pressure and react to stress • body-wide loss of proteins (possible weakness and/or swelling)	• muscle damage causing weakness • nerve damage (loss of motor or sensory function) • loss of bone strength (possible broken bones) • stunted growth (children) • abnormal sensation (such as pins and needles) • tendon tear • collapse of bones in the spine • cataracts (clouding of the lens of the eye) • bulging eye • increased pressure in the eye (possible blurry vision and/or vision loss) • fluid in the lung (possible difficulty breathing) • abnormal fat deposits • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • hiccups • blood clots in a vein (possible pain, swelling, and/or weakness)

Solumedrol may cause you to develop another type of cancer.

When given intrathecally, solumedrol may cause bladder/bowel dysfunction.

<u>Cytarabine Side Effects</u>

Frequent:

• fever • skin rash	• diarrhea	• abnormal liver tests (possible liver damage

• anal and/or rectal inflammation • anal sores • loss of appetite	• mouth sores and/or blisters • nausea • vomiting • low blood cell counts (red, white, platelet)	and/or yellowing of the skin and/or eyes) • blood clots in a vein (possible pain, swelling, and/or redness)

Less Frequent:

• chest pain • inflammation of the tissue around the heart (possible chest pain) • dizziness • headache • nerve damage (possible dizziness and/or headache) • inflammation of nerves (possible pain and/or loss of motor or sensory function) • hair loss (partial or total) • itching • skin freckling	• skin sores • hives • abdominal pain • death of tissue in the intestines • esophageal sore • throat inflammation • inflammation of the pancreas (possible abdominal pain) • sore throat • inability to urinate • jaundice (yellowing of skin and/or eyes) • painful red eyes • decreased kidney function	• difficulty breathing • injection site swelling • allergic reaction (swelling of face, mouth, and/or tongue) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Infrequent:

• chest pain due to heart trouble • stoppage of heart and lung function • inflammation of the membranes around the spinal cord and brain (possible headache and/or coma) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss)	• mental status change • paralysis • enlarged bowel (possible abdominal pain) • high blood levels of uric acid (possible painful joints and/or kidney failure) • abnormal blood test (possible pancreas inflammation and/or damage) • liver damage due to blood clots	• breakdown of muscle tissue (possible kidney failure) • lung inflammation (possible difficulty breathing) • injection site pain and/or swelling • cytarabine syndrome (bone/chest/muscle pain, painful red eyes, fever, skin rash, and/or fatigue/lack of energy)

Additional side effects seen only in high dose cytarabine:

It is not well known how often the following side effects may occur.

• enlarged heart • decreased brain function affecting movement • coma • nervous system damage (possible seizure and/or coma) • nerve damage (possible numbness, pain, and/or loss of motor function) • personality change • sleepiness • skin peeling	• stomach and/or small intestine ulcer • abdominal wall inflammation • inflammation of the pancreas (possible abdominal pain) • air-filled cysts in the intestines • decreased blood flow to part of the bowel (possibly causing death of tissue)	• pus-filled areas in the liver • liver damage • damage to the surface of the eye • bleeding in the eye • difficulty breathing • fluid in the lung (possible difficulty breathing)

When cytarabine is given directly into the spine, it may also cause the following side effects:

• decreased brain function (possible paralysis and/or coma) • fever • nausea/vomiting	• paralysis (possibly of the nerves in the neck and/or both legs) • difficulty swallowing • blindness	• double vision • cough • hoarseness • voice loss

<u>Leucovorin Side Effects</u>

Common (occurring in more than 20% of patients)

• skin rash • hair loss (partial or total)	• mouth blisters/sores (possible difficulty swallowing) • loss of appetite	• nausea • vomiting • diarrhea

Occasional (occurring in 3-20% of patients)

• fatigue/lack of energy • constipation

The drug may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Exact frequency unknown:

• fainting • hives	• abdominal pain • seizure	• allergic reaction that may be life threatening (such as difficulty breathing, low blood pressure, and/or organ failure)

Prednisone Side Effects

It is not known how often the side effects of prednisone may occur:

• enlarged heart • heart failure • high blood pressure • swelling (such as of the face) • headache • increased pressure between the skull and brain (possible headaches, vision changes, and/or mental status changes) • weakness • difficulty sleeping • mood swings • euphoria (unusual feelings of happiness or well-being) • personality changes • depression • seizure • fatigue/lack of energy • fatigue and anxiety • dizziness • bruising • nervousness • tiny dots on the skin • skin tests (such as for TB) may not be accurate • redness (face) • hair growth • thin fragile skin • hives	• stunted growth • decreased ability to process carbohydrates • high blood sugar (possible diabetes) • diabetes • abnormal blood acid/base balance (possible organ damage) • body-wide loss of proteins (possible weakness and/or swelling) • low blood levels of potassium (possible muscle cramps) • high levels of salt in the body (possible swelling) abnormal blood acid/base balance (possible organ damage) • abdominal swelling • inflammation of the pancreas (possible abdominal pain) • weight gain • increased appetite • indigestion	• nausea • stomach ulcer • esophagus sore • abnormal liver or bone tests (possible liver damage) • changes to the menstrual cycle • joint pain • pain or loss of function of the hips and/or shoulders due to bone death • muscle weakness • loss of bone strength (possible broken bones) • broken bone(s) • decreased muscle mass • decreased muscle mass • muscle damage causing weakness • tendon tear • increased pressure in the eye (possible vision loss, pain, and/or blurry vision) • cataracts (clouding of the lens of the eye) • eye irritation • swelling (eyelid) • nosebleed

• sweating • wound healing problems • Cushing's syndrome (possible weakness, diabetes, and/or bone weakness)		• allergic reactions that may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure)

Rarely (in fewer than 3% of patients)

• blood clots in a vein (possible pain, swelling, and/or redness)

Prednisone may cause an increased risk of infection, such as pneumonia. This infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and/or difficulty breathing.

Prednisone may cause you to develop another type of cancer (such as Kaposi's sarcoma).

Study Drug Combination Side Effects

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 biopsy/aspiration. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy/aspiration 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.

Diagnostic procedures, such as **X-rays**, are part of your standard of care. You may discuss the risks of these scans with your doctor if you have questions about them.

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.

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.

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 or breastfeed a baby while on this study. You must use birth control during the study and for 30 days after your last dose of study drug(s) if you are sexually active.

Birth Control Specifications: If you can become pregnant or father a child, you must use a highly effective birth control method while on study, such as birth control pills or injections, intrauterine devices (IUDs), or double-barrier methods (for example, a condom in combination with spermicide). The study will discuss with you what method of birth control you should use.

If your or your female partner's period is late, you must take an at-home pregnancy test and report the results to the study staff/study doctor.

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

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away. The supporter will ask for information about the pregnancy.

Getting pregnant may result in your removal from this study.

Optional Procedures for the Study

You do not have to agree to the optional procedure in order to take part in this study. There are no benefits to you for taking part in the optional procedure. Future patients may benefit from what is learned. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedure.

Optional Procedure #1: If you agree, blood (about 2 tablespoons each time) will be drawn before your first dose of study drugs, on Day 4 of Cycle 1, and if the disease comes back (relapses). These samples will be stored in MD Anderson's Leukemia Research Bank for use in future research related to cancer and/or other diseases.

Optional Procedure #2: If you agree, additional bone marrow samples will be collected during your bone marrow aspirate procedure before your dose of study drugs, at the end of Cycle 1, and if the disease comes back (relapses). These samples will be stored in MD Anderson's Leukemia Research Bank for use in future research related to cancer and/or other diseases.

If you agree to either Optional Procedure, you will not receive the results of any research testing done on the blood and/or aspirate samples. Samples will be labeled with a unique code number instead of your name so you cannot be linked to the samples/data.

Samples may also be sent to Dr. Jun Yang at St. Jude Children's Research Hospital in Memphis, TN.

Optional Procedure Risks

The risks of **blood draws and bone marrow aspirate** collections are the same as those described above in the main study.

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 blood drawn and stored at MD Anderson's Leukemia Research Bank as described above?

YES NO

Optional Procedure #2: Do you agree to allow additional bone marrow aspirate samples to be collected and stored at MD Anderson's Leukemia Research Bank as described above?

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 Takeda Pharmaceuticals USA, Inc. for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 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 who can then decide if you need to have any visits or tests to check on your health. 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 at any time by the study chair, Amgen, Takeda Pharmaceuticals USA, Inc., the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

   Your participation in the study may be stopped if the disease gets worse, if the disease does not get better after completing at least 2 chemotherapy cycles, if intolerable side effects occur, if you are unable to follow study directions, or if the study doctor thinks taking part in this study is no longer in your best interest.

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.

   Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the researchers will not contact you to let you know what they have found.

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

9. This study is supported by: Takeda Pharmaceuticals USA, Inc.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study 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 Takeda Pharmaceuticals USA, Inc. 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 stored by Takeda Pharmaceuticals USA, Inc. may be used in future research.

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
Samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. 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.

Financial Interest Disclosure

Outside relationships are disclosed to and approved by the Conflict of Interest Committee, which reviews these relationships for compliance with institutional policy. This review helps the IRB to assure that financial relationships do not have an impact on the conduct of this study. The following members of the study staff have disclosed compensation from the funding source(s) of this study:

- Hagop Kantarjian (Co-Principal Investigator)
- Courtney DiNardo (Study Co-chair)

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
   - Takeda Pharmaceuticals USA, Inc., who is the supporter of this study
   - Any future sponsors/supporters of the study
   - 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.

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

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

   Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

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

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under this protocol**.**

_____ _____
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) and patients who are illiterate.

_____
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

PARENT/GUARDIAN PERMISSION

I have read and understand the description of this research. I have had a chance to discuss the study and ask questions. My questions have been answered. I give permission for my child or ward to take part in this study.

_____ _____
SIGNATURE OF PARENT/GUARDIAN DATE

_____
PRINTED NAME OF PARENT/GUARDIAN

_____ _____
SIGNATURE OF PARENT/GUARDIAN DATE
Signature of Other Parent (Optional, unless required by the IRB.)

_____
PRINTED NAME OF PARENT/GUARDIAN

____The IRB has determined that the signature of both parents is required.

If not obtaining both parental signatures, please indicate reason below:

____Other parent is deceased, unknown, incompetent, or not reasonably available.

____Parent/Guardian signing above has sole legal responsibility for the care and custody of the child.

__X__ The IRB has determined that the signature of both parents is NOT required.

ASSENT OF MINOR

(Entire section must be completed if the participant's intellectual age is at least 7 and less than 18 years. Participants with an intellectual age of 7 - 12 are not required to sign.)

If written assent is not obtained on an age-appropriate participant, check reason why not:

____ 1.) The participant's intellectual age is less than seven.

____ 2.) The participant dissented, but the participant's parent(s)/guardian felt that the intervention(s) or procedure(s) involved in the research hold out the possibility of a direct benefit that is important to the health and/or well being of the participant and is available only in the context of this research study.

____ 3.) Other:_____

I have been told what I will be asked to do in this study.

I have been told that I do not have to be in this study. If I decide not to be in this study, no one will be mad at me. I may quit at any time, but if I do, I may need to take a different treatment.

I have had a chance to talk about the study and ask the study doctor questions. All of my questions have been answered. I agree to be in this study and do what I am asked to do so long as I want to stay in this study. I agree that the study doctor can put me on this study. By signing this paper, I am not giving up any of my legal rights. I have been given a copy of this document.

_____ _____
SIGNATURE OF MINOR (Age 13-17) DATE

_____
PRINTED NAME OF MINOR

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.)