THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Phase I/II Study of the Combination of Low-Intensity Chemotherapy, Venetoclax (ABT-199), and Navitoclax in Patients with Acute Lymphoblastic Leukemia (ALL)
2016-0629

Subtitle: AbbVie IIR

Study Chair: Elias Jabbour

_____ _____
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

This clinical research study has 2 parts.

The goal of Part 1 of this research study is to find the most tolerable study drug combination that can be given to patients with acute lymphoblastic leukemia (ALL). The two study drug combinations that will be tested in this study are venetoclax given in combination with navitoclax and chemotherapy and venetoclax given in combination with chemotherapy alone (without navitoclax). **Part 1 of the study is now completed.**

The goal of Part 2 of this study is to learn if the study drug combination found in Part 1 can help to control the disease. Participants will only be enrolled in Part 2.

The safety of this drug combination will also be studied.

Please note: If you take part in this study, you may be given either rituximab or a biosimilar of that drug (which means it is identical to the study drug). Everything stated in this document about rituximab also applies to its biosimilar, including information about FDA approval status, side effects, and cost.

This is an investigational study. Venetoclax and rituximab are FDA approved and commercially available for the treatment of a type of chronic lymphocytic leukemia (CLL). Navitoclax is not FDA approved or commercially available. It is currently being used for research purposes only. It is investigational to use these drugs as a treatment for relapsed or refractory ALL.

Hyper-CVD (cyclophosphamide, vincristine, and dexamethasone), methotrexate, cytarabine, pegasparaginase, and nelarabine are FDA approved and commercially available for the treatment of ALL.

The study doctor can explain how the study drugs are designed to work.

The study drugs may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. If you take part in this study, you may experience side effects, some of which may be severe or fatal.

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

Depending on the status of your disease when you enroll in the study and previous treatment that you have received, you will receive up to 8 cycles of venetoclax, navitoclax (if you are assigned to receive it), and chemotherapy, followed by about 2 years of maintenance therapy. Your doctor will discuss this with you.

While you are on this study, venetoclax and navitoclax (if you are assigned to receive it) will be provided at no cost to you. You and/or your insurance provider will be responsible for the costs of methotrexate, cytarabine, rituximab, Hyper-CVD, pegasparaginase, nelarabine, vincristine and prednisone.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive Hyper-CVD. You may choose to receive pegasparaginase and nelarabine if you have T-cell ALL. The study doctor will discuss the possible risks and benefits of these treatments. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have the following screening tests 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.
- Blood (about 4 teaspoons) will be drawn for biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug. This blood for biomarker testing may be performed anytime within 24 hours after your treatment starts, if it is not completed during screening.
    - Within 30 days before the start of the study, you may have a bone marrow aspirate and/or biopsy for biomarker testing, cytogenetic testing, and to check the status of the disease. If you have had bone marrow collected within the last 30 days of the planned first dose of venetoclax (Day 1 of Cycle 1), that tissue will be used instead of needing a biopsy. To collect a bone marrow aspirate/biopsy, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow and/or bone is withdrawn through a large needle. Cytogenetic testing looks at how genetic changes to cells may affect how the disease may react to the study drug.
- You will have a chest x-ray, CT scan, and/or PET scan to check the status of the disease.
- You will have an EKG and either an echocardiogram (ECHO) or a MUGA scan to check your heart function.
- Within 7 days before the start of the study, if you can become pregnant, blood (about 1 teaspoon) or urine will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

If some of these tests have been done recently, they may not need to be repeated. The study staff will discuss this with you.

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 Drug Dose Levels

If you are found to be eligible to take part in this study, you will be assigned to Part 2 of the study. Part 2 will enroll 2 groups of up to 37 participants in each group.

If you are enrolled in Part 2, you will receive the study drug combination that was tolerated in Part 1.

The study drug doses may be changed during the study, depending on how you are doing.

Up to about 80 participants will be enrolled in this study. All will take part at MD Anderson.

Study Drug Administration - Chemotherapy + Venetoclax

Each study cycle is about 28 days, or possibly a different length if needed based on how you are doing.

The schedule of doses for some of the study drugs may vary +/- 3 days from what is listed below. The dosing cycle you start at study enrollment will depend on previous treatment that you have received. The study staff will discuss this with you.

During Cycles 1-8, you will be in the hospital up until the completion of chemotherapy. Your hospital stays may be longer if needed.

During **Cycles 1, 3, 5, and 7**:

- **On Days 1-21** of **Cycle 1**, you will take venetoclax by mouth 1 time a day, at about the same time each day.
- **On Days 1-7** of **Cycles 3, 5, and 7**, you will take venetoclax by mouth 1 time a day, at about the same time each day. However, depending on how the disease responds to treatment, you may be able to take venetoclax on Days 1-21 instead. You doctor will discuss this with you.
- **On Days 1-21** of **Cycle 1**, if you are assigned to receive it, you will take navitoclax by mouth 1 time a day, at about the same time each day.
- **On Days 1-7** of **Cycles 3, 5, and 7**, if you are assigned to receive it, you will take navitoclax by mouth 1 time a day. However, depending on how the disease responds to treatment, you may take navitoclax on Days 1-21 instead. You doctor will discuss this with you.
- **On Days 1-3**, you will receive cyclophosphamide by vein over about 3 hours 2 times a day.
- **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 and end about 12 hours after the last dose of cyclophosphamide.
- **On Days 1 and 11**, you will receive vincristine by vein over about 15 minutes.
- **On Days 1-4 and 11-14**, you will receive dexamethasone 1 time a day by vein over about 30 minutes or by mouth.
- If the doctor thinks it is appropriate, **on Days 1 and 11 of Cycles 1 and 3**, you may receive rituximab by vein over about 4-6 hours.
- **On Day 5**, you will receive either filgrastim-sndz or pegfilgrastim product (or drugs similar to filgrastim and pegfilgrastim). Pegfilgrastim product, if you receive it, will be a 1-time dose per cycle, injected under the skin. Filgrastim-sndz, if you receive it, would be injected under the skin every day until your white blood cell counts recover. You may ask the study staff for more information about how these standard drugs are given and their risks.
- **On Day 2 of Cycles 1 and 3**, you will receive methotrexate intrathecally (as a spinal tap). A spinal tap is when fluid surrounding the spinal cord is removed by inserting a needle into the lower back. The affected area is numbed with local anesthetic during the procedure. It can also be used to give chemotherapy.
- **On Day 7 of Cycles 1 and 3**, you will receive cytarabine intrathecally.

During **Cycles 2, 4, 6, and 8**:

- **On Days 1-7**, you will take venetoclax by mouth 1 time a day. However, depending on how the disease responds to treatment, you will take venetoclax on Days 1-21. You doctor will discuss this with you.

- **On Days 1-7**, if you are assigned to receive it, you will take navitoclax by mouth 1 time a day. However, depending on how the disease responds to treatment, you will take navitoclax on Days 1-21. You doctor will discuss this with you.
- **On Day 1**, you will receive methotrexate by vein over 24 hours.
- **On Days 2 and 3**, you will receive cytarabine by vein 2 times each day over about 3 hours.
- If the doctor thinks it is appropriate, **on Days 1 and 8 of Cycles 2 and 4**, you will receive rituximab by vein over about 4-6 hours.
- **On Day 4**, you will receive either filgrastim-sndz or pegfilgrastim product (or drugs similar to filgrastim and pegfilgrastim). Pegfilgrastim product, if you receive it, will be a 1-time dose per cycle, injected under the skin. Filgrastim-sndz, if you receive it, would be injected under the skin every day until your white blood cell counts recover.
- **On Day 2 of Cycles 2 and 4**, you will receive cytarabine intrathecally.
- **On Day 8 of Cycles 2 and 4**, you will receive methotrexate intrathecally.

Intrathecal treatments are generally given on Cycles 1-4 but if one or more intrathecal treatments is missed, it can be made up on a later cycle. Your doctor will discuss this with you.

You will be given other drugs to help prevent side effects. The study staff will tell you about these drugs, how they will be given, and the possible risks.

Schedule Changes for T-cell ALL
If you have T-cell ALL, after the first 4 cycles you will receive 2 cycles of nelarabine and pegasparaginase (Cycles 4N and 5N) by themselves. Once Cycle 5N is complete, you will continue with Cycle 6 as described above. You will not take venetoclax or navitoclax (if you are assigned to receive it) or the other chemotherapy drugs during Cycles 4N and 5N.

During **Cycles 4N and 5N**:

- On Days 1-5, you will receive nelarabine by vein over 2 hours 1 time a day.
- On Day 5, you will receive pegasparaginase by vein over 2 hours 1 time a day.

Study Drug Administration - Maintenance Therapy
After completing the Chemotherapy with Navitoclax (if you are assigned to receive it) + Venetoclax portion of the study, you may be able to receive maintenance therapy in 28-day cycles for about 2 years:

- **On Days 1-5** of each Maintenance cycle, you will take prednisone by mouth 1 time a day.
- **On Day 1** of each Maintenance cycle, you will receive vincristine by vein over about 15 minutes.
- **On Days 1-14** of each Maintenance cycle, you will take venetoclax by mouth 1 time a day.
- **On Days 1-14** of each Maintenance cycle, if you are assigned to receive it, you will take navitoclax by mouth 1 time a day.

Schedule Changes for T-cell ALL
After the first 5 cycles of maintenance therapy, you will receive nelarabine and pegasparaginase in Cycles 6 and 7 if you received them earlier in the study. You will not take prednisone, vincristine, and venetoclax during Maintenance Cycles 6 and 7.

During Maintenance Cycles 6 and 7:

- **On Days 1-5**, you will receive nelarabine by vein over about 2 hours 1 time a day.
- **On Day 5**, you will receive pegasparaginase by vein over about 2 hours.

After Cycle 7, you will continue with the rest of the maintenance cycles (prednisone, vincristine, venetoclax, and navitoclax, if you are assigned to receive it).

If you have disease taking place outside of your bone marrow, you may receive radiation therapy. Your doctor will discuss this with you. You will sign a separate consent describing the radiation therapy and its risks.

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 - Chemotherapy + Venetoclax
Before or on **Day 1 of each cycle**, you will have a physical exam.

On **Days 14 and 28 of Cycle 1 and then every 1-3 cycles after that**, you will have a bone marrow biopsy/aspiration to check the status of the disease and for cytogenetic testing. You may have this done more or less often depending on how the disease responds to treatment. On **Day 28 of Cycle 1** and if your doctor thinks you may need more bone marrow biopsy/aspiration and cytogenetic testing during Cycle 1 to check the status of the disease, you will also have biomarker testing from your bone marrow.

On **Day 28 of Cycle 1**, you will also have an EKG.

One (1) to 2 times each week during Cycle 1, then every 1-3 weeks during Cycles 2-8, blood (about 2-3 teaspoons) will be drawn for routine tests.

On **Days 1 and 2 of Cycle 1,** before taking venetoclax and then 6 hours later, additional blood (about 2-3 teaspoons) will be drawn for routine tests.

You will have a chest x-ray, CT scan, or PET scan to check the status of the disease anytime the doctor thinks it is needed.

If the disease appears to be getting worse, you will have a bone marrow aspirate/biopsy to check the status of the disease and for cytogenetic and biomarker testing. Blood (about 4 teaspoons) will also be drawn for biomarker testing.

If you have T-cell ALL, blood (about 2-3 teaspoons) will be drawn for routine tests on Day 1 and 1-3 times each week during Cycles 4N and 5N.

Study Visits - Maintenance Phase

Before or on Day 1 of Maintenance Cycle 1, the following tests will be performed:

- Every 3 cycles, you will have a physical exam.
- Every 4-8 weeks (usually every 1-2 cycles), blood (about 2-3 teaspoons) will be drawn for routine tests.
- Every 3-6 cycles, you will have a bone marrow biopsy/aspiration and cytogenetic testing to check the status of the disease. You may have this done more or less often depending on how the disease responds to treatment.

You will have a chest x-ray, CT scan, and/or PET scan to check the status of the disease anytime the doctor thinks it is needed.

If the disease appears to be getting worse, you will have a bone marrow aspirate/biopsy and cytogenetic testing to check the status of the disease and for biomarker testing, and also blood (about 4 teaspoons) will be drawn for biomarker testing.

Before or on Day 1 of Maintenance Cycles 6 and 7, if you have T-cell ALL and are taking nelarabine and pegasparaginase:

- You will have a physical exam.
- Blood (about 2-3 teaspoons) will be drawn for routine tests.

Follow-Up

About 30 days after your last dose of study drugs and every 3 months after that, you will be asked in clinic or called by the study staff and asked about your health. If you are called, the calls should last about 10 minutes each.

Other Instructions

While taking part in this study, you should not take part in any other research study without checking with the doctors first.

It is very important that you tell your study doctor what prescription and non-prescription drugs, vitamins, and/or nutritional and herbal supplements you are taking. The study doctor will review these drugs with you before you start the study.

You must not eat grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), pomegranate, or star fruit. There are also some drugs that may interfere with the study drugs and cannot be taken while you are on the study. The study staff will let you know which drugs to avoid while you are taking part in this study.

You may be able to have some of the study tests done and/or study drug doses given at a clinic closer to your home. The study staff will discuss this with you.

2. POSSIBLE RISKS

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

may also want to ask about uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after treatment is stopped, but in some cases side effects may be serious, long-lasting or permanent, and may even result in hospitalization and/or death.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs/procedures.

Venetoclax, navitoclax, rituximab, cyclophosphamide, mesna, vincristine, methotrexate, cytarabine, pegasparaginase, nelarabine, pegfilgrastim product, and filgrastim-sndz each may cause low blood cell counts (red blood cells, platelets, and/or white blood cells):

- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

Venetoclax Side Effects

Common (occurring in more than 20% of patients)

• fatigue • fever due to low white blood cell count • diarrhea	• constipation • nausea/vomiting • low blood counts (red, platelets, white)	• infection (including and upper respiratory tract infection)

Occasional (occurring in 3-20% of patients)

• swelling (arm/leg) • fever • headache • 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)	• vomiting • back pain • high blood levels of uric acid (possible painful joints and/or kidney failure)	• pneumonia • cough • 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)

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

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

Navitoclax Side Effects

It is not known how often the side effects of navitoclax may occur. Based on studies in humans, navitoclax may cause the following side effects:

• abnormal EKG (possible irregular heartbeat and/or serious heart problems) • blood clot (possible pain, swelling, redness, and/or organ damage such as stroke and/or heart attack) • bleeding inside the head • progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in paralysis and/or coma, which may be permanent, or death)	• fatigue • swelling of the lips • skin redness/ swelling/itching • nausea/vomiting • diarrhea • loss of appetite • abnormal pancreas tests (possible pancreas damage) • digestive system bleeding • blood in the urine	• low blood cell count (red/white/platelets) • abnormal liver tests (possible liver damage) • nosebleed • tumor lysis syndrome (TLS)--breakdown products of the cancer cells entering the blood stream (possible heart rate abnormalities, kidney failure, muscle twitching, and/or muscle cramps)

Based on studies in animals, navitoclax may also cause the following side effects:

• high blood pressure • brain damage (seen only in infant animals)	• low sperm count or decrease in ovary size	• lung damage

You should call the study doctor or staff if you are hospitalized for any reason or if you experience any of the following:

- Easy or excessive bruising.
- Bleeding from the nose or gums.
- Prolonged bleeding from cuts.
- Blood in urine or stools (stools may appear like tar or dark in color).
- Rash of reddish-purple spots the size of pin points.
- Unusually heavy menstrual periods.
- Feeling excessively tired or sleepy.
- Shortness of breath.
- Chest pain.

- Swelling (especially in the legs).
- Sensation of feeling the heart beat or throb.
- Flu-like symptoms, such as tiredness, nausea, abdominal pain or itchy skin.
- If your skin turns yellow (jaundice) or if your urine turns tea-colored.
- Rash.
- Raised, red, patches on your skin that itches (hives).
- Swelling around the mouth, throat, or eyes.
- Wheezing when you take a breath.

As stated above, navitoclax may cause low platelet counts. This may cause you to have an episode of excessive bleeding or hemorrhage. Below are some tips to try to prevent excessive bleeding if your platelet count is low:

- Use a very soft toothbrush when cleaning your teeth, and do not brush vigorously.
- Avoid forcefully blowing your nose; blow very gently into a soft tissue.
- When shaving, use an electric shaver instead of a razor.
- Avoid activities that put you as risk for falling.

Rituximab Side Effects

Common (occurring in more than 20% of patients)

• fever • fatigue • chills	• nausea • low blood cell counts (red, white) • weakness	• nerve damage (loss of motor or sensory function) • infection

Rituximab may commonly cause infusion reactions such as difficulty breathing and/or tissue swelling. In some cases, life-threatening reactions such as sudden stopping of the heart and/or shock caused by heart damage may occur. It is not known how often these more serious reactions may occur.

Because rituximab is a mouse antibody that has been changed to make it similar to a human antibody, treatment with rituximab may commonly cause the body to make human antibodies to the mouse-based antibody. These antibodies are called HAMA or HACA. The potential response of your body to rituximab may lead to decreasing the effectiveness of mouse-based antibody therapies for you in the future. If you receive other drugs in the future that contain mouse proteins, you could develop an allergic reaction to those drugs.

Occasional (occurring in 3-20% of patients)

• high blood pressure • low blood pressure (possible dizziness/fainting)	• itching • night sweats • hives	• abnormal liver and/or bone tests (possible liver damage)

• swelling (arm/leg/ • tissue) • flushing • anxiety • headache • difficulty sleeping • dizziness • skin rash	• high blood sugar (possible diabetes) • abnormal blood test • diarrhea • abdominal pain • weight gain • vomiting • upset stomach • low platelet counts	• pain (back/joint/muscle) • muscle spasms • difficulty breathing (possibly due to narrowing of the airways) • cough • runny nose • nosebleed • sore throat

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

• sudden stopping of the heart • fast and/or irregular heartbeat • chest pain due to heart trouble • heart failure • heart attack • blood vessel inflammation (possible bleeding, bruising, and/or rash) • shock caused by heart damage • inflammation of the brain and spinal cord (possible altered consciousness) • progressive multifocal leukoencephalopathy (PML – a disease with brain damage that may likely result in paralysis and/or coma, which may be permanent, or death) • brain injury that may be reversible (possible headache, confusion, seizures, and/or vision loss)	• severe painful blisters • severe skin rash • infections of skin and mucous membrane • very severe blistering skin disease (loss of large portion of skin and/or ulcers of the skin and digestive tract) • blockage and/or hole in the intestines (possibly leaking contents into the abdomen) • anemia due to destruction of red blood cells • thick blood (possible blockage of blood flow) • condition that looks like lupus (an immune system disease) • immune system reaction (possible organ damage) • decreased bone marrow function and inability to make red blood cells • liver damage/failure • muscle inflammation and weakness	• abnormal sensation (such as pins and needles) • kidney damage/failure • inflammation inside the eye and/or of an eye nerve (possible vision problems) • bronchiolitis obliterans (damage of the small airways with difficulty breathing) • lung inflammation (possible difficulty breathing) • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • worsening of Kaposi's sarcoma • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor right away. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Rituximab may also cause other viruses to reactivate. This includes JC virus (PML), cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C.

Talk to the study doctor before receiving any vaccines (for example, vaccines for measles, mumps, rubella, or polio). Receiving a vaccine while taking rituximab may increase the risk of serious infection or make the vaccine less effective.

Cyclophosphamide Side Effects

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

• hair loss (partial or total) • mouth blisters/sores (possible difficulty swallowing) • nausea/vomiting • 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) • 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)	• wound healing problems • low blood levels of potassium (possible weakness) • low blood levels of sodium (possible headache, confusion, seizures, and/or coma)	• blood in the urine • blurry vision • hearing loss • breakdown of muscle tissue (possible kidney failure) • death of kidney tissue (possible kidney failure)

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

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	• skin rash, blisters, and/or sores • very severe blistering skin disease (loss of large portion of skin) • loss of appetite • constipation	• blood in the urine • pain • shivering • painful red eyes • cough • sore throat • runny nose

• very severe blistering skin disease (with ulcers of the skin and digestive tract)	• diarrhea • gas • nausea/vomiting • abnormal taste/change in taste	• 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	• 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	• 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

• 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	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)	• 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)

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 • skin sensitivity to sunlight or lamps	• burning sensation of the skin • low blood cell counts (red/white/platelets)

Frequency Unknown

• chest pain • low blood pressure (possible dizziness/fainting)	• very severe blistering skin disease (loss of large portion of skin) • shedding and scaling of the skin (possible	• birth defects • miscarriage • impotence • inability to have children

• 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 • brain damage that may be reversible (possible headache,	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 • hole in the intestines (possibly leaking contents into the abdomen) • inflammation of the pancreas (possible abdominal pain) • vomiting of blood	• 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 • increase in infection-fighting cells • infection • life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • sore throat

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)	• 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	• 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).

Cytarabine Side Effects

Frequent:

• fever • skin rash • anal and/or rectal inflammation • anal sores • loss of appetite	• diarrhea • mouth sores and/or blisters • nausea • vomiting • low blood cell counts (red, white, platelet)	• abnormal liver tests (possible liver damage 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	• stomach and/or small intestine ulcer • abdominal wall inflammation	• pus-filled areas in the liver • liver damage • damage to the surface of the eye

• nervous system damage (possible seizure and/or coma) • nerve damage (possible numbness, pain, and/or loss of motor function) • personality change • sleepiness • skin peeling	• 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)	• bleeding in the eye • difficulty breathing • fluid in the lung (possible difficulty breathing)

When cytarabine is given intrathecally, 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>Dexamethasone Side Effects</u>

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

• high blood pressure • irregular and/or slow heartbeat • sudden stopping of the heart • 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)	• hives • acne • hair loss (partial or total) • hair growth • sweating • tissue death • Cushing's syndrome (possible weakness, diabetes, and/or bone weakness) • decreased ability to process carbohydrates • high blood sugar (possible diabetes) • diabetes • decreased production of adrenal hormones (possible weakness and/or low blood pressure)	• changes to the menstrual cycle • problems with production of sperm • bruising • weakness • inflammation of nerves (possible pain and/or loss of motor or sensory function) • joint pain • 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

• 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 • 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 • skin rash, redness, and/or dryness • fragile and/or thinning skin • skin test reaction impaired (due to a lowered immune system) • stretch marks	• low blood levels of potassium (possible weakness and/or muscle cramps) • high blood levels of sodium (possible weakness and/or swelling) • body-wide loss of proteins (possible weakness and/or swelling) • build-up of fat in abnormal areas • pituitary gland failure (possible hormone imbalance) • weight gain • increased appetite • digestive system bleeding • 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	• 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) • 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.

Nelarabine Side Effects

Common (occurring in more than 20% of patients)

• fatigue • fever • sleepiness • dizziness • nausea	• diarrhea • vomiting • constipation • low blood cell counts (red, white, platelets)	• nerve damage (possible numbness, pain, and/or loss of motor function) • cough

Occasional (occurring in 3-20% of patients)

• swelling • low blood pressure (possible dizziness/fainting) • fast heartbeat • chest pain • headache • numbness • difficulty walking • confusion • difficulty sleeping • shivering • loss of consciousness and slowing of the heart and breathing rate • depression • uncontrolled movements • memory loss	• low blood sugar • 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) • dehydration • abdominal pain • loss of appetite • abnormal taste • mouth blisters/sores (possible difficulty swallowing) • abdominal swelling	• abnormal liver tests (possible yellowing of the skin and/or eyes, or possible liver damage) • weakness • pain • abnormal sensation (such as pins and needles) • muscle weakness • tremor • blurry vision • abnormal kidney test (possible kidney damage) • difficulty breathing • build-up of fluid around the lungs • nosebleed • wheezing

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

• seizure • nerve damage (loss of motor or sensory function) • inability to speak / speech problems / difficulty forming or speaking words	• spinal fluid build-up in the brain (possible headache, mental status changes, and/or coma) • mental difficulty • mental status change	• loss of coordination • trouble with balance • breakdown of muscle tissue (possible kidney failure) • stopped breathing

• bleeding in or around the brain • decreased brain function (possible paralysis and/or coma) • weakness on one side of the body	• nerve paralysis • sensory disturbance • immune system damage to the nervous system (causing numbness and/or paralysis) • muscle tightness	• collapsed lung (possibly difficulty breathing) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

Pegasparaginase Side Effects

Pegasparaginase may **commonly (in more than 20% of patients)** cause an allergic reaction. In 3-20% of patients, the allergic reaction may be life-threatening (such as difficulty breathing, low blood pressure, and/or organ failure).

Occasional (occurring in 3-20% of patients)

• abnormal blood clotting • blood clots in a vein (possible pain, swelling, and/or redness)	• blood clots in the brain • high blood sugar (possible diabetes)	• abnormal liver tests (possible liver damage)

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

• high blood pressure • chest pain • heart valve damage • fast heartbeat • swelling (face) • seizure • fever • dizziness • inflammation of the pancreas (possible abdominal pain)	• low blood sugar • abnormal blood acid/base balance (possible organ damage) • fluid in the abdomen • blood in the urine • bladder inflammation (possible pain, bleeding, and/or urge to urinate) • bacteria in the blood • low blood counts (red, platelets, white) • increased risk of bleeding	• enlarged liver • jaundice (yellowing of skin and/or eyes) • abnormal sensation (such as pins and needles) • high blood levels of uric acid (possible painful joints and/or kidney failure) • kidney failure • difficulty breathing (possibly due to narrowing of the airways)

• 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)	• anemia due to destruction of red blood cells • liver failure	• severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Prednisone Side Effects

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

• heart failure • high blood pressure • swelling • headache • increased pressure between the skull and brain (possible swelling of the eye nerve, vision changes, and/or headaches) • mental health disturbances (including euphoria [unusual feelings of happiness or well-being]) • difficulty sleeping • mood swings • personality changes • severe depression • seizure • fatigue and anxiety • dizziness • bruising • facial skin redness • tiny dots on the skin • thin fragile skin • hives • sweating • wound healing problems	• failure of hormone-producing organs • decreased ability to process carbohydrates • high level of steroid in the body (possible mood changes and diabetes) • decreased production of adrenal hormones (possible weakness and/or low blood pressure) • diabetes • abnormal blood acid/base balance (possible organ damage) • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • body-wide loss of proteins (possible weakness and/or swelling) • low blood levels of potassium (possible muscle cramps)	• stomach ulcer (with possible hole and bleeding) • esophagus sore • abnormal liver or bone tests (possible liver damage) • pain or loss of function of the hips and/or shoulders due to bone death • loss of muscle • muscle weakness (possibly caused by muscle damage) • loss of bone strength (possible broken bones) • brittle/broken bones • tendon tear (particularly Achilles tendon) • collapse of bones in the spine • bulging eye • increased pressure in the eye (possible vision loss, pain, and/or blurry vision) • cataracts (clouding of the lens of the eye)

• Cushing's syndrome (possible weakness, diabetes, and/or bone weakness)	• high blood levels of sodium (possible weakness and/or swelling) • abdominal swelling • inflammation of the pancreas (possible abdominal pain)	• allergic reactions that are possibly 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).

Pegfilgrastim product 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-sndz 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 • swelling (arm/leg) • dizziness • headache • difficulty sleeping • skin rash • hair loss (partial/total) • abnormal blood test • vomiting • loss of appetite	• high levels of uric acid (possible painful joints and/or kidney failure) • low red blood cell counts • abnormal liver tests (possible liver damage) • pain (muscle/joint/limb) • weakness • muscle spasm • numbness • lung inflammation	• cough • difficulty breathing • nosebleed • allergic reaction • reaction to blood transfusion • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

The drug may occasionally cause an increased risk of infection, such as pneumonia and/or urinary tract infection. 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 • blood vessel inflammation (possible bleeding and/or bruising) • swelling (face) • bleeding in the brain • painful skin bumps	• skin condition with fever and skin lesions • leakage of fluids from blood vessels into surrounding tissue (possible difficulty breathing) • diarrhea • blood in the urine • enlarged liver • sickle cell crisis in patients with sickle cell disease	• loss of bone strength (possible broken bones) • decreased kidney function (possible kidney failure) • coughing up blood • bleeding in the lungs and/or airways

• worsening of an existing skin disease (psoriasis)	• ruptured spleen	• life-threatening allergic reaction (such as difficulty breathing, low blood pressure, and/or organ failure) • immune reaction

Drugs similar to pegfilgrastim product and filgrastim-sndz may have similar 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.

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.

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.

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.

EKGs/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. Only designated study staff will have access to study data.

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 at least 4 months after the last dose of study drug if you are sexually active.

Birth Control Specifications: If you can become pregnant or father a child, you must use acceptable birth control methods 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).

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

Optional Procedure #1: If you agree, and if you did not have a bone marrow biopsy and/or aspirate during screening, you will have a bone marrow biopsy and/or aspirate for biomarker testing during screening.

There are no benefits to you for taking part in the optional procedures. You may stop taking part at any time. There will be no cost to you for taking part in the optional procedure.

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

Optional Procedure Risks:
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.

Genetic research may result in the development of beneficial treatments, devices, new drugs, or patentable procedures. If this happens, there are no plans to compensate you. The results of any genetic tests will not be put in your health records. If this information were released, it could be misused. Such misuse could be distressing, and it could cause you or your family members to have difficulty getting insurance coverage and/or a job.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES

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

Optional Procedure #1: If you are asked, do you agree to have a bone marrow biopsy/aspirate for biomarker testing during screening?

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 AbbVie (Supporter) 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. Elias Jabbour, at 713-792-4764) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson. If you decide to withdraw, tell the study doctor so they can help you safely stop study treatment. It may be dangerous to suddenly stop.

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

study without your consent include:

- Adverse events that are not manageable with dose adjustments and/or optimal medical management, or that, in the opinion of the investigator, pose an unacceptable risk for the patient
- Non-compliance by the patient with protocol requirements
- Failure to achieve CR, CRi or PR after at least 2 cycles, unless the patient is thought to have derived clinical benefit, after discussion with the Principal Investigator
- Disease progression.
- Patient death
- Patient decision (e.g., withdrawal of consent)
- Investigator decision, if it is deemed in the best interest of the patient.

If the research performed shows information that may be needed for your safety, you will be provided with these results.

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: AbbVie (Supporter).

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

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

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.

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

In some cases, all of your identifying information may not be removed before your data or samples are used for future research. If this research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB

is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

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

Genetic Research

Samples collected from you as part of this study will be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you.

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

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

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

Conflict of Interest

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:

- Dr. Elias Jabbour (Study Chair)
- Dr. Nitin Jain (Co-investigator)
- Dr. Hagop Kantarjian (Co-investigator)
- Dr. Courtney DiNardo (Co-investigator)
- Dr. Guillermo Garcia-Manero (Co-investigator)
- Dr. Naveen Pemmaraju (Co-investigator)
- Dr. William Wierda (Co-Investigator)

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s).

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
- AbbVie (Supporter), who is a sponsor or supporter of this study, and/or 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 study dataset and key will be stored for as long as they are needed for the purposes of this study, and will be accessible by the study doctor.

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