Official Study Title: A Phase I and Expansion Cohort Study of Selinexor and Venetoclax in Combination with Chemotherapy in Pediatric and Young Adult Patients with Refractory or Relapsed Acute Myeloid Leukemia

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A PHASE I AND EXPANSION COHORT STUDY OF SELINEXOR AND VENETOCLAX IN COMBINATION WITH CHEMOTHERAPY IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH REFRACTORY OR RELAPSED ACUTE MYELOID LEUKEMIA

Note: When we say "you" in this informed consent document, we mean "you or your child." When we talk about research, it can be called a clinical trial, research study (study), or research protocol.

Key Information

To start, we highlight here the risks, benefits and study requirements that we think you should know before deciding if you want to take part in this research study. If you're still interested, we'll then get into more details.

A. Why are you being asked to voluntarily take part in this study?

You are being asked to take part in a research study because you have acute myeloid leukemia (AML) or acute leukemia of ambiguous lineage (ALAL) that did not go into remission after treatment (refractory) or has come back after treatment (relapsed). This is a research study to find out if two new drugs called venetoclax and selinexor are safe and if they have beneficial effects in children, adolescents and young adults when given with chemotherapy.

B. What is the usual approach to this type of leukemia?

We are asking if you want to take part in this study because there is not a standard of care treatment for your leukemia at this point.

C. Why is this study being done?

The purpose of this study is to learn more about the effects (good and bad) that occur with venetoclax and selinexor in combination with chemotherapy.

D. What will happen if you decide to take part in this study?

You will take the study drugs, venetoclax and selinexor, by mouth, in combination with intravenous (IV) cytarabine and fludarabine. G-CSF may be given to help your bone marrow recover faster.

E. What are the research risks and benefits of taking part in this study?

Common side effects of cancer treatment include nausea, vomiting, hair loss, and fatigue (tiredness).

Drugs may be given to try to prevent or decrease nausea and vomiting. Hair loss is usually temporary but very rarely it may be permanent. Chemotherapy may make you permanently unable to have children. On rare occasions, leukemia treatment can cause a second cancer to develop, usually years after the treatment is finished.

The most common serious side effect from cancer treatment is lowering of the number of normal blood cells that may result in anemia, increased chance of infection, and/or a bleeding tendency.

The side effects of venetoclax and selinexor, as well as the other chemotherapy drugs used in this study are described later in this consent under “what are the risks and benefits of taking part in this study?”

The potential benefit of this study this therapy is that it may cause your leukemia to go into remission for a period of time, but it is possible that your disease will not respond to the study treatment. The information learned from this study may help future children or young adults with relapsed cancers of the blood.

F. How many people will take part in this study?

Up to 42 children and young adults will take part in this study at St. Jude and other hospitals collaborating on this study. Up to 30 participants will take part at St. Jude.

G. What are your options?

- You may choose to have other treatment for leukemia that is generally accepted,
- You may choose to take part in a different study, if one is available
- Taking part in this research study is completely your choice.
- If you decide to take part in this study, you can change your mind and stop at any time.
- If you decide not to take part in this study, you may still be able to receive care at St. Jude.
- You may choose no treatment or to seek treatment somewhere else.

If you are still interested in taking part in this research study, SELCLAX, more detail is provided below in the following pages.

Study Contact Details and Further Information

You are encouraged to ask any questions you wish, before, during or after your treatment. If you have any questions about the study, please speak to your doctor, who will be able to provide you with the up-to-date information about the drugs and procedures involved. If there is anything that you do not understand, or if you have any other questions, please contact any of the people below.

Who to talk to for…	You can contact…	At…
• Any new or unexpected symptoms, side effects or discomforts • General study questions • Research related injuries • Any research concerns or complaints • Any medical or surgical treatments done outside of St. Jude such as with your local doctor or another hospital during this study	**Seth Karol, MD or your St. Jude Doctor** 262 Danny Thomas Place Memphis, TN 38105	901-595-3300 (Main Hospital Number)
• Your rights as a research participant • Any research concerns or complaints	**Institutional Review Board (IRB)/Research Participant Advocate** • IRB is a group of scientists and community members who make sure research meets legal and ethical standards • Research Participant Advocates are individuals who are not part of the research study team and are available to you to discuss problems, concerns and questions. The Advocate can help you obtain information and can relay any input you may have concerning the research to the research study team and the IRB.	901-595-4644 or 901-595-1139

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1. Why are you being asked to voluntarily take part in this research study?

You are being asked to take part in a research study because you have acute myeloid leukemia (AML) or acute leukemia of ambiguous lineage (ALAL) that did not go into remission after treatment (refractory) or has come back after treatment (relapsed). This is a research study to find out if two new drugs called venetoclax and selinexor are safe and if they have beneficial effects in children, adolescents and young adults when combined with standard chemotherapy for AML.

The study drug, venetoclax (also called Venclexta®), is approved by the U.S. Food and Drug Administration (FDA) to treat certain types of leukemia, including AML, in adults. Venetoclax is not approved by the FDA for treating childhood AML.

The study drug, selinexor (also called XPOVIO®), is approved by the FDA to treat certain types of lymphoma and multiple myeloma in adults. In a randomized, open label, phase 2 study (called SOPRA) of single-agent selinexor versus specified physician's choice in older adults (median age, 73.2 years) with relapsed or refractory AML, there was no difference in overall survival between the two study groups. The median overall survival was 94 days for patients treated on the selinexor arm, compared to 170 days for patients treated on the physician's choice arm (P=0.42). The overall response rates were similar (13.6% on the selinexor arm and 8.8% on the physician's choice arm), as were the rates of death from any cause (26% on the selinexor arm and 19% on the physician's choice arm). Patients treated with selinexor had several high-risk features that may have made them more difficult to treat and increased their risk of death compared to the physician's choice group. Patients in the selinexor group had a higher rate of TP53 mutations (a mutation that helps prevent the development of tumors) (16.7% vs 8.6%), a higher incidence of prior myelodysplastic syndrome (a cancer that makes AML behave more aggressively) (11% vs. 5.3%), a higher incidence of baseline neutropenia (higher risk of infection) (44.7% vs. 33.3%), and a greater percentage of smokers (38.1% vs. 29.8%). Selinexor is not approved by the FDA for treating childhood AML.

This consent form gives you information about the study that will be discussed with you. Please take your time making a decision and feel free to discuss it with your friends, family and St. Jude staff. Before agreeing to take part in this research study, it is important that you read this consent form that describes the study. After you understand the study, and if you agree to take part, you will be asked to sign this consent form. You will be given a signed copy to keep.

2. Who is sponsoring this study?

This study is being sponsored by St. Jude Children's Research Hospital.

The drug manufacturer, Karyopharm, is supplying selinexor and AbbVie is supplying venetoclax at no charge to St. Jude for conducting this study.

Unrelated to this study, St. Jude has received a charitable contribution from AbbVie, Inc. The charitable contribution is not being used for clinical or research activities, including any activities related to this study. The Institution has checks and balances in place to ensure that this charitable donation does not influence the conduct of the study. The outcome of this study will not impact how the charitable contribution is spent or whether St. Jude receives additional charitable funds from AbbVie, Inc. in the future. Your enrolling in this study will not cause any money from this charitable contribution to go to Dr. Karol, the St. Jude Principal Investigator.

3. What is the purpose of this study?

The purpose of this study is to test the safety of the two study drugs, venetoclax and selinexor, and to find the highest dose of venetoclax and selinexor that can be given safely when it is combined with chemotherapy drugs (cytarabine and fludarabine). This study tests different doses of venetoclax and selinexor to see which dose is safer in children with leukemia.

This study will be done in two parts: Part 1: Dose Escalation and Part 2: Dose Expansion. The goal of Part 1 of the study is to find the highest tolerable combination of venetoclax, selinexor and chemotherapy that we can give to patients with leukemia. Once those doses are determined, we will enroll patients on Part 2: Dose Expansion, to look at the effects of the venetoclax and selinexor in combination with chemotherapy.

Part 1 of this study has been completed and the highest tolerable doses have been determined. You are being asked to participate in Part 2 of this study.

With this part of the research study, we plan to meet the following goals:

- To learn more about the effects (good and bad) that occur with venetoclax and selinexor in combination with chemotherapy;
- To learn more about the biologic effects of venetoclax and selinexor on the cells in your body; and
- To find out how treatment with venetoclax and selinexor affect the quality of life of patients on this study.

Up to 42 participants will take part at St. Jude and several collaborating institutions. About 30 will take part at St. Jude.

4. What will be done in this study?

Before you start treatment …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- History and physical exam
- Blood and urine tests
- Electrocardiogram (ECG) to measure the electrical activity of your heart
- Echocardiogram to measure the function of your heart
- Pregnancy test (if you are a female who could have children)
- Bone marrow aspirate and biopsy to check the status of your leukemia
- Lumbar puncture (spinal tap) to check the fluid surrounding your brain and spinal cord

If the test results show that you do not meet the study eligibility, you cannot start the study treatment and your study doctor will talk to you about other treatment options.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, you can start treatment. You will take the study drugs, venetoclax and selinexor, by mouth, in combination with intravenous (IV) cytarabine and fludarabine. G-CSF may be given to help your bone marrow recover faster.

Drug	How the drug will be given	No. of doses	Days
Venetoclax	By mouth, daily	21	1-21
Selinexor	By mouth, six times	6	1, 3, 8, 10, 15 and 17
Cytarabine	IV	5	16-20
Fludarabine	IV	5	16-20
G-CSF	SubQ (a shot just under the skin) or IV	5	16-20

Exceptional responders

Your doctor may perform a bone marrow on Day 15. If you have an exceptional response to this treatment, your doctor may decide to continue venetoclax and selinexor without chemotherapy, starting Day 16. You will also have a bone marrow exam at the end of the chemotherapy cycle) to evaluate the status of your leukemia.

Taking venetoclax and selinexor

You will take venetoclax and selinexor tablets or suspension by mouth on scheduled days. You should take venetoclax within an hour of eating a meal, but you may take selinexor with or without food.

You should not drink grapefruit juice, and you should not eat grapefruit, Seville oranges or marmalades, or starfruit while you are taking venetoclax. These foods and drinks may increase the amount of venetoclax in your blood.

Do not stop taking venetoclax or selinexor unless your study doctor tells you to. If you miss a dose of venetoclax and selinexor:

- If the missed dose is by less than 8 hours, take the missed dose right away and take your next dose the following day as usual.
- If the missed dose is by more than 8 hours, do not take the dose that day and take the next dose at your usual time the next day.

If a venetoclax or selinexor dose is vomited within one hour of ingestion, you should take it again. If vomiting occurs more than 1 hour after dosing, you should not take an additional dose that day.

Intrathecal (IT) chemotherapy to prevent or treat leukemia in the spinal fluid

You may be familiar with spinal taps if they were done during your initial therapy for leukemia. Whether you decide to take part in this study or not, you will need additional spinal taps to give medicines that are necessary to prevent the leukemia from spreading to your spinal fluid, or to treat the spinal fluid if leukemia cells are present.

All patients will get one IT chemotherapy before starting the first cycle. Then, if you do not have leukemia cells in your spinal fluid, you will not get any more IT chemotherapy during cycle one. If you do have leukemia cells in your spinal fluid, IT chemotherapy will be given weekly until your spinal fluid is negative for leukemia. Your doctor will decide if you get additional IT chemotherapy before additional cycles. You will also receive a vitamin supplement called leucovorin, which will help prevent or lessen side effects of the IT chemotherapy.

You will get some form of sedation or anesthesia (medicine to make you sleep) during this procedure. Spinal taps are painful and may cause headaches. The skin at the site of needle insertion is usually numbed with an anesthetic cream or lidocaine before the procedure is performed. About 1 teaspoon of spinal fluid will be withdrawn before injecting the chemotherapy.

Recovery and leukemia evaluation after treatment

You may need to be in the hospital for the administration of venetoclax and cytarabine. It will take 3-6 weeks for your blood counts to fully recover from this treatment. After you recover, a bone marrow exam will be done to evaluate the status of your leukemia.

If your leukemia responds well to this treatment, you may receive up to 3 additional cycles of selinexor and venetoclax in combination with chemotherapy.

Standard of care tests and procedures during treatment

During treatment on this study, you will have the following tests and procedures that are part of standard of care for leukemia:

- Physical exam and vital signs
- Blood tests to check your blood counts and blood chemistry
- Bone marrow exams to evaluate clinical genomics and minimal residual disease (MRD) and your leukemia's response to treatment
    - Day 15 (±2 days) unless there are leukemia cells present in your blood
    - Once between Day 35 and 42
- Blood to evaluate minimal residual disease (MRD) and your leukemia's response to treatment
    - Days 1, 8, 15 and at the end of Cycle 1

Required research studies

The following tests will be done because you are part of this study. If you were not in the study you would probably not have these tests. The information learned would not change the way you are treated, and the results of these tests will not be given to you. You and your insurance company will not be charged for the costs of the required research study tests listed below.

- Bone marrow for biomarker and proteomic studies

  Extra bone marrow will be collected during the bone marrow procedure you will have before you start treatment on this study. The pre-treatment bone marrow procedure is part of standard of care, but an extra sample will be collected for research studies.

  This bone marrow sample will be studied in St. Jude research labs with these goals:

  a) To help predict which participants may respond to treatment
  b) To find out which participants may be at increased risk for leukemia relapse
  c) To learn which participants are at risk for more side effects from treatment
  d) To find out if certain genetic mutations are present in the leukemia cells

- Blood for cell-free DNA
    - Less than ½ teaspoon of blood will be drawn at the same time you will have blood drawn for MRD studies listed above: Days 1, 8, 15 and at end of Cycle 1

- Blood for BCL2
    - Blood will be drawn on Day 8 if you had leukemia blasts in your blood at the beginning of this study.

  Any labs or assessments after Cycle 1 will be done only as clinically needed.
  There are also optional research tests that you can choose to take part in or not. They are listed later in this consent form.

5. What are the risks and benefits of taking part in this study?

a. Risks

If you choose to take part in this study, there is a risk that you may:

- Lose time at school, work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss

The chemotherapy drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. There is also a risk that you could have side effects.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

Infection: There is a serious risk of developing an infection while being treated on this research study, including serious infections that may require hospitalization. To reduce the risk of developing an infection, you will be required to take antibiotics and antifungal medication. You may be required to be in the hospital for most of the treatment so that your doctors and nurses can monitor you very carefully for any signs or symptoms of infection.

If you experience any of the following signs or symptoms while you are being treated on this research study, it is very important to call your doctor or nurse right away.

- Fever
- Pain (earache, sore throat, headache, pain with urination or having a stool)
- Redness, swelling, pain, or pus at the site of your central catheter

Risks of the study

Harmful reactions or side effects may occur in patients taking part in clinical trials. Some of these will be due to the patient's disease or prior therapy and some may be due to the drug being studied. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. In general, side effects can range from mild to serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop treatment. Although numerous measures are established to protect your health, it is possible that in some cases, side effects can be serious, long lasting, or may never go away.

Patients with leukemia may have a risk of death due to their underlying cancer or as a complication of their cancer treatment. The risk of side effects or death related to this treatment will be closely monitored.

Risks and side effects related to VENETOCLAX (Venclexta®) include:

VERY COMMON may affect more than 1 in 10 people	
• Upper respiratory tract infection (including runny nose, sore throat, or cough • Low number of white blood cells • High blood levels of phosphorous • Diarrhea • Fever with low number of white blood cells • Sepsis • Increased blood levels of bilirubin • Decreased appetite • Arthralgia (joint pain) • Low blood pressure • Hemorrhages (bleeding)	• Nausea • Vomiting • Constipation • Anemia • Feeling tired • Pneumonia • Abdominal pain • Weight loss • Decreased blood levels of potassium • Headache • Dizziness/syncope (fainting) • Low platelet count

COMMON may affect from 1 in 100 to 1 in 10 people
• Urinary tract infection • Tumor lysis syndrome (described below in detail; may experience fever, chills, nausea, vomiting, diarrhea, confusion, shortness of breath, irregular heartbeat, unusual tiredness, muscle pain, joint discomfort and/or seizure) • High blood levels of urea, phosphorous, potassium, and creatine, which could mean problems with your kidneys • Low blood levels of calcium • Stomatitis (sores in mouth) • Cholecystitis/cholelithiasis (inflammation of the gall bladder/gallstones)

Problems and side effects may occur with the use of venetoclax that are not expected or are unknown at this time. You or your legal representative will be informed in writing in a timely manner of any new information or findings that become available that may affect your choice to continue to take part in this study.

Treatment with venetoclax has been associated with nausea, diarrhea, decreases in lymphocytes and neutrophils (two different types of white blood cells), tumor lysis syndrome (TLS) and infections.

Tumor lysis syndrome (TLS)

TLS is a problem that can happen when cancer/leukemia 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 the blood, such as salts and acids, can rise. This can happen especially in people with large tumors or a high number of cancerous white cells in the blood. TLS is most likely to occur in the first 5 weeks of starting venetoclax.

Tumor lysis syndrome can lead to serious problems such as effects on the kidneys and heart (including abnormal heart rhythms) or seizures. These side effects can result in needing kidney dialysis (a special machine to remove toxins from the blood) or lead to death. If you develop TLS, your study doctor will closely monitor and treat you as needed to try to prevent these complications.

Blood tests have shown TLS in some people after receiving the initial dose of venetoclax or after receiving a higher dose of venetoclax than previously received. Two deaths in patients with chronic lymphocytic leukemia (CLL) who experienced TLS have been reported after receiving venetoclax and one CLL patient with TLS has needed dialysis.

Before starting treatment, your study doctor may ask you to drink plenty of fluids. He/she may also give you medications to help the body get rid of the salts or chemicals or broken up cell parts from your leukemia. Your doctor may hospitalize you before you start venetoclax to give fluids into your vein, do blood tests, and check for TLS. If you develop TLS, your urine may look dark, thick, or cloudy.

You may also experience fever, chills, nausea (feeling sick to your stomach), vomiting, diarrhea, confusion, shortness of breath, irregular heartbeat, unusual tiredness, muscle pain, joint discomfort and/or seizure. If you notice any of these, notify your study doctor or nurse right away.

Your study doctor will closely monitor and treat you as needed to decrease the risk of any serious changes in your blood or other complications of TLS. If blood tests suggesting TLS are seen, extra blood tests or monitoring of your heart rhythm may be recommended by your study doctor.

Second cancer

Some patients with CLL who have been treated with venetoclax and who also had received several previous chemotherapy treatments have developed an aggressive form of lymphoma (cancer of the lymph node) at the time their CLL became worse. It is unknown if venetoclax has contributed to these cases since this type of cancer can happen in people with CLL who have not received venetoclax.

Risks and side effects related to SELINEXOR (XPOVIO®) include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving selinexor, more than 20 and up to 100 may have:	
• Weight loss, loss of appetite • Nausea, vomiting, diarrhea, constipation • Tiredness, weakness • Bruising, bleeding	• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Shortness of breath

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving selinexor, from 4 to 20 may have:	
• Changes in taste • Fever • Blurred vision • Dizziness, headache • Dehydration • Severe blood infection	• Confusion • Difficulty sleeping • Swelling of arms, legs • Pain • Cough

RARE, AND SERIOUS In 100 people receiving selinexor, 3 or fewer may have:	
• Cloudiness of the eye, visual disturbances • Acute cerebellar syndrome which may cause sudden loss of coordination, balance, slurred speech, difficulty walking or talking • Change in thinking patterns • Fainting	• Sleepiness • Inflammation of the pancreas which may cause pain in belly • Blood clot which may cause swelling, pain, shortness of breath • Nosebleed

Possible side effects of CYTARABINE include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving cytarabine, more than 20 and up to 100 may have:
• Blood clot • Swelling in the rectum which may cause rectal pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth and GI tract which may cause difficulty swallowing or pain • Rash • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cytarabine, from 4 to 20 may have:	
• Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • Chest pain • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Damage to the lungs which may cause shortness of breath • Infection, especially when white blood cell count is low • Anemia which may cause tiredness, or may require blood transfusions • Bruising, bleeding	• Severe blood infection • Liver damage which may cause yellowing of skin or eyes • Kidney damage which may cause swelling, may require dialysis • Numbness and tingling of the arms and legs • Muscle pain • Dizziness • Headache • Flu-like syndrome with fever, bone pain, rash, redness of eyes, or chest pain • Swelling and redness of the eye • Hair loss

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness • Difficulty speaking, trouble standing or walking

Possible side effects of FLUDARABINE include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving Fludarabine, more than 20 and up to 100 may have:
• Cough • Infection, especially when white blood cell count is low • Bruising, bleeding • Increased risk of unusual infections lasting more than 6 months • Vomiting, loss of appetite • Tiredness, fever • Pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Fludarabine, from 4 to 20 may have:
• Damage to organs (brain, lungs, others) which may cause tiredness, changes in thinking or shortness of breath • Anemia, kidney problems which may cause tiredness, bruising, or swelling • Visual disturbances • Nausea, chills • Feeling of "pins and needles" in arms and legs • Confusion

RARE, AND SERIOUS In 100 people receiving Fludarabine, 3 or fewer may have:
• Coma, seizures (with high doses) • Blindness • Kidney damage which may require dialysis

Possible side effects of FILGRASTIM (G-CSF) include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving filgrastim, more than 20 and up to 100 may have:	
• Nosebleed • Anemia which may require transfusion • Diarrhea • Bone pain	• Fever • Tiredness • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving filgrastim, from 4 to 20 may have:
• Fluid in the body which may cause low blood pressure, shortness of breath, swelling of ankles • Damage to the lungs which may cause shortness of breath • Cough • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Kidney problems which may require dialysis • Swelling or tenderness of vessels • Headache • Rash

RARE, AND SERIOUS In 100 people receiving filgrastim, 3 or fewer may have:
• Chest pain, shortness of breath • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Rupture of the spleen causing sudden or severe pain in the left side of abdomen spreading up to your shoulder

Some drugs or supplements may interact with your treatment plan. Talk to your doctor, pharmacist, or study team before starting any new prescription or over-the-counter drugs, herbals, or supplements and before making a significant change in your diet. Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.

If your red blood cell count is low, the cells that carry oxygen around the body you may feel tired. If your red blood cell count drops very low you may need a blood transfusion.

If you have a decrease in the white blood cell count, the cells that fight infection, you may be more likely to get an infection, including a serious infection that spreads through the blood stream (sepsis). If this happens, you will have to come to the hospital to be treated with antibiotics. If your white blood cell count is very low and you get a fever, you may have to come to the hospital to get treated with antibiotics.

If you have a low platelet count, particles in the blood that help with clotting, you may have easy bruising or bleeding. If the count is very low and there is bleeding, you might need platelet transfusions to help stop the bleeding.

Possible side effects of INTRATHECAL THERAPY (spinal injection of methotrexate, cytarabine and hydrocortisone, or cytarabine alone) include:

COMMON, SOME MAY BE SERIOUS	
• Nausea and/or vomiting • Fever	• Headache

OCCASIONAL, SOME MAY BE SERIOUS	
• Swelling of the brain, which may cause stiff neck, sensitivity to light, headache, vomiting • Major change in thinking patterns • Difficulty learning	• Confusion • Tiredness • Seizure

RARE, AND SERIOUS	
• Rash • Bleeding in the brain • Paralysis, weakness	• Dizziness • Damage to the brain, which may cause changes in thinking, blindness • Infection

Other risks of study

Unknown risks

The drug combination is experimental and still being tested. There may be other risks, including death, which are not known now.

Loss of privacy

Very rarely, personal information from your records could be given out by accident. This might make you upset, embarrass you, or affect your ability to get insurance. To stop this from happening, we:

- Store records apart from names or other personal information
- Only allow members of the study team to see the records
- Store electronic data only on computers protected with a password and encryption software
- Report study results on the whole group and never identify one single person in any reports

b. Benefits

The treatment on this study will not cure your relapsed leukemia. Based on experience with the drugs used in the treatment plan, researchers believe this therapy may cause your leukemia to go into remission for a period of time, but it is possible that your disease will not respond to the study treatment. The information learned from this study may help future children or young adults with relapsed cancers of the blood.

6. What are the risks to pregnancy, to an unborn child, and to the ability to have children (fertility) when taking part in this study?

You should not become pregnant or father a baby while you are taking part in this study. You should not nurse a baby while taking study drugs because it is unknown if this could affect the baby. Both males and females who are able to have children must use a highly effective means of birth control approved by your study doctor.

Some examples of acceptable birth control for heterosexual partners include the following:

- Surgical sterilization:
  - For females: tubal ligation at least 1 month before study participation, ovaries removed, or uterus removed
  - For males: vasectomy at least 3 month before study participation
- Intrauterine device (IUD)
- Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or cream AND a condom);
- Hormonal contraceptives (examples include birth control pills, vaginal rings, or patches), associated with inhibition of ovulation for at least 1 month prior to taking study drug.
- Total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable.

Your study doctor will explain what specific hormonal contraceptive methods you can use.

You must continue the use of birth control during the entire time of your study participation and for at least 30 days after the last dose of study drugs. Your study doctor will discuss the need for birth control with you.

If you become pregnant, you must stop taking study drugs at once and notify your doctor immediately. You will not be allowed to continue in the study. You may be asked questions about the outcome of your pregnancy and the baby.

If you are a male, you are responsible for informing your partner(s) that the effects of the study drugs on an unborn fetus or embryo in humans are unknown. You and your partner(s) are responsible for using acceptable birth control as described above. If your partner becomes pregnant while you are on study, you must notify your doctor immediately. You and your partner may be asked questions about the outcome of the pregnancy and the baby. Written informed consent for release of medical information from your partner will be obtained prior to collecting any information about the pregnancy and baby.

7. Can you stop taking part in this study?

a. Can you change your mind about participating in this research study?

You may change your mind about taking part in this research study and stop at any time. If available, you may continue to receive routine medical care at St. Jude or participate in another study. This decision will not affect your relationship with your doctor at St. Jude.

If you change your mind about participating in this study, samples or related information that have already been used by researchers will not be returned or removed.

b. Can you be taken out of this study without your consent?

Your St. Jude doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest,
- If new information becomes available,
- If you do not follow the study rules,
- If the study is stopped by the sponsor, St. Jude

8. What are you other options and can you have other treatments while taking part in this study?

a. Other Treatment Options

If you decide not to take part in this study, you have choices. For example:

- you may choose to receive other chemotherapy, not part of a research study
- you may choose to take part in a different study, if one is available
- or you could decide not to be treated

b. Can you participate in other research studies at the same time?

Please check with your study doctor before thinking about taking part in any other research.

c. Other medications, vitamins, and supplements

While in this study, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture, or other alternative treatments.

Tell your study doctor about any changes to these during your participation in the research study. Your study doctor will explain to you which treatments or medications need to be stopped for the time you are involved in the research study.

9. How much will it cost you to take part in this study?

If you have health care coverage, we will bill your health care insurer for all standard of care services, tests, and procedures, as applicable. Billing your health care insurer impacts your annual deductible and life-time maximum, if any. This may affect your health care coverage to some extent if you go to another health care provider or institution in the future.

At St. Jude, you will not be responsible for or receive bills for co-pays, co-insurance, deductibles, or similar patient-liability amounts, or for the cost of medical care related to your disease or this study not covered by your health insurer. This includes research-only costs. Research-only tests and procedures (such as optional biopsy or blood samples for biomarker testing) will not be billed to you or your health care insurer.

10. Will you be paid for your time or expenses while taking part in this study?

You will not be paid for your time or expenses.

11. What if there is a problem while taking part in this study?

If you are injured from being in this research study, please notify your St. Jude Doctor or the study doctor, Dr. Seth Karol. St. Jude will offer you reasonable and necessary medical treatment for that injury. If you need more care than St. Jude can provide or if you prefer to seek treatment elsewhere, we will help you find medical care somewhere else. St. Jude may bill your insurance company or other third parties, if appropriate.

It is not the hospital's policy to provide payment for other types of costs, such as lost wages, disability, or discomfort if you are injured from being in this study. You are not giving up any of your rights by signing this consent form.

12. How will new findings related to your participation in this study be shared with you?

You will receive results from all the standard of care tests and procedures, including genetic testing. You will not receive results from the research studies, since they will not impact your care.

The researcher will tell you of any new information learned during your study participation which might cause you to change your mind about continuing the study.

13. How will you find out the results of this study?

St. Jude researchers share information with people in studies in many ways including:

- Articles on www.stjude.org
- In newsletters
- In medical or scientific journals
- In the media
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by the U.S. Law. This website will not include information that can identify you. At most the website will include a summary of the results. You can search this website at any time.

Published research results will only describe groups of people who took part in the study. Information that points out a single person will not be in research journals or other reports.

14. Will any genetic tests be done and what are the risks of genetic testing?

This study involves reading through all your genetic material to find certain changes that may explain information about you and/or your health condition (like how your health condition relates to other conditions, how certain drugs affect you or your health condition, etc.). The genetic material, or genes, are stored in your cells. The genetic material will be obtained from your sample (i.e., tumor, blood, skin, etc.). Information obtained from reading through your genes, as well as information about your health condition, will be entered into one or more scientific repositories or databases maintained by St. Jude Children's Research Hospital, the Federal Government, the European Genome-phenome Archive, or others.

Risks of Somatic Genetic/Genomic Testing

From the tumor testing alone, it may not be possible to tell if a genetic change is likely inherited or inheritable, or if it is only present in the tumor/cancer cells. To find out if a genetic change is inherited or able to be passed on to your children, your normal tissue sample would need to be tested. If you want to have your normal tissue tested, you should talk to your doctor to learn how this can be done.

It is possible that testing your tumor/cancer tissue will not help us better understand or find a cause of your disease or help us recommend a treatment. Most tests are not perfectly correct. There is also a chance that there could be an error in the testing or analysis.

After learning your results, you might feel anxious, upset or frustrated. Your doctor can discuss these concerns with you and arrange for needed follow-up, such as with the Genetics Service or other support services (social work, spiritual care, or psychology).

The genomic test report will be placed into your electronic medical record and may be seen by your other doctors and health care workers at St. Jude or other facilities that obtain your medical record with your permission or legal authority.

Risks of Germline Genetic/Genomic Testing

There is a chance that the genomic test results of your normal tissue will show that you have an inherited health condition, or a condition that can be passed down to any children you have. The condition discovered might show that you and possibly other family members are at risk of developing tumors or at risk of developing other health problems unrelated to cancer. It is also possible that testing your normal tissue sample will not find any genetic changes that will affect your current management or future health risks. Sometimes, genetic testing can find gene changes that we do not completely understand. This uncertainty may lead to anxiety or confusion.

After learning your results, you might feel anxious, upset or frustrated. Your doctor will discuss these concerns with you and arrange for needed follow-up, such as with the Genetics Service or other support services (social work, spiritual care, or psychology).

When the genomic test report comes from a CLIA certified laboratory, the results will be placed into your electronic medical record and may be seen by your other doctors and health care workers at St. Jude or other facilities that obtain your medical record with your permission or legal authority.

Currently, the U.S. law known as the “Genetic Information Nondiscrimination Act” (GINA) prohibits discrimination based on genetic findings in some circumstances:

a. GINA prohibits health care insurers from requesting or requiring genetic information of an individual or an individual’s family members or using genetic information for decisions about health insurance coverage or rates, or to exclude preexisting conditions.
b. In companies of 15 or more employees, GINA prohibits employment and employee-related decisions from being made on the basis of genetic information of an individual or an individual’s family members.

GINA protections do not apply to:

a. the presence of disease or a health disorder,
b. life insurance, long-term care insurance, or disability insurance. These insurance companies consider may this information in making insurance decisions affecting you,
c. both health care plans and employment from companies employing fewer than 15 people, and
d. people in the military.
e. There are other health plans that GINA does not apply. Please ask your study doctor if you have any questions.

15. What about identifiable private information and identifiable biospecimens (blood, tissue, urine, cells, and any type of data and/or samples) obtained from you during the study?

If you choose to take part in this study, your data and/or specimens will be used to answer the research question(s) and to publish the findings of this study. Published research results will only describe groups of people who took part in the study. Information that points out a single person will not be in research journals or other reports. You will not own your research data and/or specimens. If researchers use your data and/or specimens to create a new product or idea, including those that may have commercial value, you will not benefit financially. There is no plan to share any money with you.

St. Jude's researchers and their collaborators will store the data and specimens collected in this study in electronic databases and other locations and will store specimens in the biorepository or other locations. They may use the data and/or specimens collected in this study for future research purposes and may share some of the data or specimens with others without seeking further consent from you. You may not receive results from that future research.

Sharing data and/or specimens is part of research. It may increase what can be learned from this study and future studies. Often data sharing is required as a condition of funding or for publishing study results. It is also needed to allow other researchers to validate study findings and to come up with new ideas.

Your data and/or specimens may be shared with government agencies, research collaborators, and other researchers and organizations conducting research that may not be related to this study. Your data may also be put in government or other databases/repositories as mentioned in the section above "Will any genetic tests be done and what are the risks of genetic testing?"

Future research using your samples and data is likely to include studies that look at genomic and genetic information to understand causes and cures for health conditions. Because science constantly advances, we do not yet know what other future uses of research data and/or specimens may include. There is no time-limit on sharing of information.

This future research may be unrelated to the current study and may include outside researchers and organizations from around the world. These organizations may include for-profit companies conducting medical research. We or others who distribute data or samples may be paid for data or samples, including yours. You will not receive payment if this happens.

St. Jude will do its best to protect and maintain your data and/or specimens in a safe way. One of the ways we protect your data and/or specimens is by limiting the uses of the information and the type of information that is shared, especially your personal information. This may occur through data sharing agreements and review by oversight groups within St Jude. Often the data and specimens may be coded to protect your identity before they are shared, and we will keep the key to the code in a secure way.

If data and/or specimens are used or shared with any information that may be likely to identify you, such as your name, address, or medical record number, further institutional review and approval would be required. In these cases, we will review whether additional consent from you is required.

Generally, if your data and/or specimens are used and shared without any personal identifiers or only with information that is less likely to identify you (such as the date of a procedure), further review and approval is not needed, and you will not be contacted.

Data sharing could change over time and may continue after the study ends.

The use and sharing of your data and/or specimens is required for participation in this research study. The purpose of research is to learn and discover new information to make improvements to patient care and/or treatments. To make these improvements, research results must be shared with others. By agreeing to take part in research studies, you are agreeing for your information or data to be used and shared with others. If you are generally not comfortable with the use and sharing of your data and/or specimens in future research as explained this consent, you should talk with your doctor before agreeing to take part in this study.

16. What about permission to use your data/information (HIPAA Privacy Rule), privacy and confidentiality?

Permission to Use Your Data/Information- HIPAA Privacy Rule and Privacy

The HIPAA Privacy Rule defines the situations in which PHI (protected health information) may be used or given to someone outside of the hospital to be used or released for research and other purposes. PHI includes information such as your name, MRN, date of birth, or other identifying information, including research information placed in your medical record.

To do this research, St. Jude Children's Research Hospital (St. Jude) will need to collect, use, and share your private health information. St. Jude is required by law to protect your health information. By signing this consent form, you give St. Jude permission to use and/or release (share) your private health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it

and may share your information with others without your permission, if permitted by laws governing them.

If you sign this consent form, you give permission to all researchers and their staff involved in the study at St. Jude to use or release (share) your health information that identifies you for the research study described in this document.

The health information that we may use or release includes things learned from the procedures and treatments describes in this consent form, as well as all information from your medical record (which may include information such as HIV status, drug, alcohol, or STD treatment, genetic test results, or mental health condition and/or treatment, physical examinations, and lab tests). This may include, for example, all information in a medical record, results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition.

If you sign this consent form, you give St. Jude permission to share your information for future research studies about disease or advancing science and for future unspecified research. You also give permission for us to place this information on databases as described below under Privacy and Confidentiality.

Information from research testing will be analyzed in a CLIA-certified (medical) laboratory or a research-only laboratory. By signing, you give St. Jude permission to put your research information obtained from a CLIA-certified laboratory into your medical record. Results from research-only laboratories will not be put into your medical record and will not generally be available to you or your doctor.

Any information placed in the medical record becomes a permanent part of your record, is kept indefinitely, It is protected like any other part of your medical record as described in the Notice of Privacy Practices. You have the right to see, copy, and ask for changes to your PHI that will be used or shared. However, research information may not be available until after the end of the study.

When you first registered at St. Jude, you received a copy of the St. Jude Notice of Privacy Practices. It tells how your PHI, including research information placed in your medical record, may be used or given to someone outside of St. Jude. You have the right to read the Notice of Privacy Practices before you sign this consent form. It may have changes since you first registered at St. Jude. You can find it at the bottom of every page on the St. Jude internet website: www.stjude.org

The people who may view, request, receive, or use your private health information include St. Jude researchers and their staff, and other doctors, nurses, and staff members. Additionally, St. Jude may share your information with other people or groups of people. These include:

- Food and Drug Administration (FDA)
- Office of Human Research Protections (OHRP)
- National Institutes of Health (NIH)
- Other government agencies
- Your insurance company and other health benefits plan, including government coverage such as Medicaid

- Accrediting agencies like the Joint Commission and the College of American Pathologists
- St. Jude Children's Research Hospital Institutional Review Board (IRB)Other committees or people involved in overseeing research studies
- AbbVie Pharmaceuticals (the drug manufacturer of venetoclax)
- Karyopharm Therapeutics (the drug manufacturer of selinexor)
- Gateway for Cancer Research Foundation
- Others who have access to your medical record by authorization or law
- Other approved health care providers

You do not have to sign this consent form which gives your permission, but if you do not, you may not receive research-related treatment.

Please note that you may change your mind and take back (revoke) this permission at any time. Even if you take back this permission, St. Jude Children's Research Hospital may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. To take back this consent form/permission, you must write to:

HIPAA Privacy Officer
St. Jude Children's Research Hospital
262 Danny Thomas Place, Mail Stop 280
Memphis, TN 38105

This permission does not have an expiration date.

Confidentiality

We will protect the confidentiality of your information to the extent reasonably possible.

Researchers and study staff are required by law to report suspected child abuse, threat of harm to self or others, and certain diseases that spread from person to person.

If you consent to take part in this study, information obtained from this study, as well as information about disease signs and symptoms, will be entered into one or more scientific databases maintained by St. Jude Children's Research Hospital and the Federal Government. The information will be held securely electronically at St. Jude Children's Research Hospital. Your name will not be passed on to anyone else outside the research team who is not involved in the study. You will be allocated a study number, which will be used as a code to identify you on all study forms. Any research-related information about you that leaves the hospital will have your name and address removed so that you cannot be recognized.

Research data obtained from this study from standard of care tests and procedures and research tests and procedures such as tumor and normal specimens and genetic data, are often shared with the research community using various databases, including those maintained by St. Jude, the federal government, and international collaborative databases. This is to advance scientific discovery, and to satisfy requirements of organizations that fund research, and journals that publish the results of research.

There are two types of databases used for sharing research data. One is a public, unrestricted access database and the other is a controlled access database. Each is described below.

Unrestricted access databases:

The information from research studies using your samples, genetic information, and some health information may be freely available in a public, unrestricted database that anyone can use. A public database could include information on hundreds of thousands of genetic variations in your DNA code, as well as your ethnic group and sex. Summary-level information about all participants included in a dataset, including you, but not genetic data for each individual, may be shared.

Some examples of information that may be shared includes how different genes are associated with different traits or diseases across the many participants in the dataset, or how often certain gene changes are seen across participants from many studies. However, the risk of anyone identifying you with this information is very low. This public information will not be labeled with your name or other information that could be used to easily identify you.

Controlled access databases:

Your individual genomic data and health information may be put in a controlled-access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to easily identify you.

Researchers approved to access information in the database must agree to protect the information and not to try to identify you. Examples are the St Jude Cloud, which is run by St. Jude, the database of Genotypes and Phenotypes which is run by the Federal Government, and the European Genome-Phenome archive. These are databases available to researchers to use genomic information from tumor and non-tumor samples to study genetic changes in pediatric diseases.

If you decide you would like to take part in this research study, please ask any questions you have, and read and sign this consent form. You will be given a copy of it to keep. A copy of this consent form will also be put in your patient notes, one will be put with the study records, and one may be sent to the Research Sponsor.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this informed consent document and to consider taking part in this study.

17. Optional Research Tests or Procedures

This section is about optional research studies you can choose to take part in if you participate in the main research study.

You will not get health benefits from any of these optional studies. There are no costs to you or your insurance or other payors. You will not be paid for taking part in these optional studies. If any of the research leads to new tests, drugs, or other commercial products, there is no plan to share any money with you.

The results from these optional research studies will not be added to your medical record.

You can still take part in the main study even if you say “no” to any or all of these optional studies. If you sign up for but cannot complete any of the optional studies for any reason, you can still take part in the main study. If you choose to take part in these studies later, you will be asked to sign a consent form.

The results from these optional research studies will not be added to your medical record.

You can still take part in the main study even if you say “no” to any or all of these optional studies. If you sign up for but cannot complete any of the optional studies for any reason, you can still take part in the main study. If you choose to take part in these studies later, you will be asked to sign a consent form.

Optional Quality of Life Study (Cycle 1 only)

If you are 5 years of age or older, and you choose to take part in this study, you will be asked to fill out 2 forms with questions about your physical and emotional well-being. Researchers will use this information to learn more about how cancer and cancer treatment affects people. You will be asked to fill out questionnaires three times during the normal study clinic visits:

- at baseline prior to the start of treatment
- during the second week of treatment
- after completion of one cycle of treatment

The questionnaires will take about 15-30 minu*tes* to complete. The forms will ask about things about how you perform daily actives, fatigue, pain, anxiety and depression. You can skip any question you do not want to answer.

Please circle your answer: I choose to take part in the Quality of Life study:

YES **NO**

18. Signatures

PARENT/GUARDIAN STATEMENT (Required for participants younger than 18 years): I have read this document or it was read to me. I have been encouraged to ask questions and all my questions have been answered. I give permission for my child to be in this research study.

_____ _____ _____AM/PM
Parent/Legal Guardian Signature Date Time (circle one)

ASSENT DISCUSSION (Required for participants 7-13 years old):

☐ The research was explained to the minor participant in age-appropriate terms and the minor verbally agreed to take part in the study.

☐ Minor declined to take part in the study. The minor declined for the following reason(s):

_____
_

☐ An assent discussion was not initiated with the minor for the following reason(s):

☐ Minor is under 7 years of age.
☐ Minor is incapacitated.
☐ Minor refused to take part in the discussion.
☐
Other_____

RESEARCH PARTICIPANT STATEMENT (14-17 years old and Adult Participants 18 years and older): I have read this document or it was read to me. I have been encouraged to ask questions and all my questions were answered. I agree to take part in this research study.

_____ _____ _____AM/PM
Research Participant Signature Date Time (circle one)

RESEARCHER/DESIGNEE STATEMENT: I have explained the research to the participant and his/her parent(s) or legal guardian(s). The research participant and parent(s)/guardian(s) were encouraged to ask questions and all questions were answered to their satisfaction. A copy of this form has been given to the participant or his/her representative.

_____	_____	_____AM/PM
Researcher/Designee Signature	Date	Time (circle one)

_____
Print Name

_____	_____	_____AM/PM
Interpreter (if needed) Signature	Date	Time (circle one)

RESEARCH PARTICIPANT ADVOCATE STATEMENT: I observed the informed consent process. The research study, intervention/observation, risks, benefits, and alternatives were presented to the research participant and/or legal guardian(s). They were encouraged to ask questions, and research team members answered all their questions. The participant / parent(s) indicated that they: 1) understood the information presented; and 2) voluntarily consented/agreed to take part in the research.

_____	_____	_____AM/PM
Research Participant Advocate	Date	Time (circle one)

_____	_____	_____AM/PM
Interpreter (if needed) Date		Time (circle one)

PLEASE UPLOAD COMPLETED CONSENT FORM TO EPIC.