SUMMARY OF CHANGES – phase 2 consent

NCI Protocol #: 10417
Local Protocol #: VICCNCIHEM10417
Protocol Version Date: March 11, 2025

Protocol Title: Clinical Evaluation of ASTX727 in Combination with Venetoclax All-Oral Therapy vs Standard of Care Cytarabine and Anthracycline Induction Chemotherapy for Younger ELN High Risk FLT3WT Patients with Acute Myeloid Leukemia

Informed Consent Version Date: March 11, 2025

I. Additional Changes initiated by Principal Investigator:

#	Section	Comments
1.	Overview and Key Information	**PI Response:** The duration of follow-up if they choose to participate was reduced from 5 years to 2 years.
2.	Global	**PI Response:** The version date was changed to match the amended protocol. No additional changes to the ICD were made.

Research Study Informed Consent Document (Phase 2 study)

Study Title for Participants: Testing Oral Decitabine and Cedazuridine (ASTX727) in Combination with Venetoclax *vs.* Standard of Care Chemotherapy for Acute Myeloid Leukemia Patients

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10417, "Clinical Evaluation of ASTX727 in Combination with Venetoclax All-Oral Therapy *vs*. Standard of Care Cytarabine and Anthracycline Induction Chemotherapy for Younger $FLT3^{WT}$ Patients with ELN High- Risk Acute Myeloid Leukemia (NCT# NCT04817241)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have high-risk acute myeloid leukemia (AML) and you do not have a change in the gene called fms-like tyrosine kinase 3 (FLT3).

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Will venetoclax given in combination with ASTX727 help your AML stay in remission longer than patients with your cancer that receive the usual treatment?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your AML. The usual approach is defined as care most people get for AML.

What is the usual approach to my Acute Myeloid Leukemia (AML)?

The usual approach for patients who are not in a study is treatment with a combination of two chemotherapy drugs cytarabine and daunorubicin or idarubicin (referred to as the "7+3" regimen), and followed by either chemotherapy or allogenic transplant and/or maintenance therapy. The combination of standard dose cytarabine and daunorubicin is Food and Drug Administration (FDA) approved and has been the standard treatment for AML for over 40 years. For patients younger than 60 years who get the usual approach for this cancer, about 60 out of 100 people achieve a complete remission and about 35 out of 100 are free of cancer after 5 years. Among older patients and those with adverse genetic risk disease, about 35 out of 100 people achieve a complete remission and only about 10 out of 100 people are cancer free at 5 years.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get:

1) Experimental study drugs **venetoclax and ASTX727** (ASTX727 is an oral combination of decitabine and cedazuridine) for up to 12 cycles (each cycle is 28 days), until your disease gets worse, the side effects become too severe, you move on to stem cell transplantation, or you no longer want to be on the study for any other reason;

or

2) **Chemotherapy (cytarabine and daunorubicin)** for up to 2 cycles (each cycle is 28 days), until your disease gets worse, the side effects become too severe, you no longer want to be on the study for any other reason, or you move on to stem cell transplantation

At any point during your treatment, you and your physician may elect to proceed to stem cell transplantation which is the standard of care therapy for eligible patients with higher risk AML. If this occurs, your study drug will be discontinued.
After you finish receiving therapy, your doctor and study team will continue to follow your condition through clinic visits, chart review, study team investigations, or by telephone every 3 months for up to 2 years.

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

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the combination of venetoclax and ASTX727 may not be as good as the usual approach for your cancer at putting your AML in remission.

There is also a risk that you could have side effects from the study drugs, ventetoclax and ASTX727. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects of Venetoclax and ASTX727 that the study doctors know about are:

- Infection, especially when white blood cell count is low
- Anemia which may require blood transfusion
- Thrombocytopenia (low platelets) and risk of bleeding. Due to the risk of thrombocytopenia, your doctor may need to give you platelet transfusions.
- Bone marrow aplasia (loss of blood making capacity)
- Tiredness
- Tumor lysis syndrome (a condition that occurs when a large number of cancer cells die within a short period, releasing their contents into the blood). Signs and symptoms of tumor lysis syndrome include: nausea with or without vomiting, lack of appetite and fatigue, dark urine, reduced urine output, or flank pain, numbness, seizures, or hallucinations, muscle cramps and spasms, heart palpitations.

Some of the most common side effects of cytarabine and daunorubicin are:

- Fever or infection, especially when white blood cell count is low
- Anemia which may require blood transfusion
- Thrombocytopenia (low platelets) and risk of bleeding
- Bone marrow aplasia (loss of blood making capacity)
- Sores in mouth and GI tract which may cause difficulty swallowing or pain

There may be some risks that the study doctors do not yet know about.

Benefits

It is not known if the combination of venetoclax with ASTX727 is better tolerated or will extend your life compared to the usual approach, "7+3" chemotherapy. This study may help the study doctors learn things that may help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (National Cancer Institute [NCI]) the study sponsor. The study sponsor is the organization who oversees the study.

If you receive a bone marrow/stem cell transplantation after the study therapy, you will no longer receive the study therapy, but you will be followed to monitor your health, unless you no longer want to be followed and you remove your consent to participate.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment, "7+3" chemotherapy, to the combination of venetoclax and ASTX727. The combination of venetoclax and ASTX727 could stabilize your cancer, but it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better, the same or worse than the usual approach. To decide if it is better, the study doctors will be looking to see if the Venetoclax plus ASTX727 extends the life of patients without cancer for at least 3 months longer than the usual approach. There will be up to 86 people taking part in this portion of the study.

What are the study groups?

The study has 2 study groups which will be randomly assigned:

Group 1 (Venetoclax + ASTX727)

If you are in this group, you will get the combination of venetoclax and ASTX727. At least two days before you begin treatment you will receive medication to prevent possible known side-effects of ASTX727 and venetoclax. This includes medication to prevent nausea that will be taken starting at least one hour before the first dose of ASTX727. This will also include medication that will begin two to three days before the start of treatment with the study drugs to prevent uric acid accumulation caused by tumor lysis syndrome. In addition, it is important that for you to drink 6-8 glasses of water a day for at least two days before you begin taking venetoclax and ASTX727 to prevent some of these side-effects.

You will get ASTX727 by mouth once a day on either Days 1-5 or Days 1-4 of each cycle. ASTX727 should be taken approximately at the same time on an empty stomach in the morning before breakfast. Do not eat, drink milk or alcohol 2 hours before and 2 hours after taking ASTX727. Clear liquids such as water, black coffee, or tea are allowed. Take whole tablets with 8 oz. (240 mL) of water; do not crush, cut, or chew the tablet. A missed dose within 12 hours of the scheduled time can be made up. Take the dose as soon as possible and resume the next day on schedule. If you do not make up the dose within 12 hours, the dose should be resumed at the scheduled time the next day. You will take venetoclax by mouth once a day on either Days 1-28 or Days 1-21 of each cycle. Venetoclax should be taken with food and water at the same time each day (within 30 minutes of a meal) and at least 2 hours following ASTX727 if both study drugs scheduled that day. Your doctor will tell you how often you should take the study medication. Each cycle lasts 28 days. This study has up to 12 cycles. See the study calendar for more information. You will also be required to keep a pill diary so that drug compliance can be monitored.

You will continue ASTX727 and venetoclax for up to 12 cycles, as long as you appear to be benefiting. As an alternative, your physician may recommend you receive a stem cell transplant

as part of standard of care therapy for acute leukemia in younger and fit patients. You will be able to continue ASTX727 and venetoclax after completing 12 cycles if you are responding well to the treatment. This combination of drugs is not approved by the FDA for treatment of your disease.

There will be about 27 people in this group.

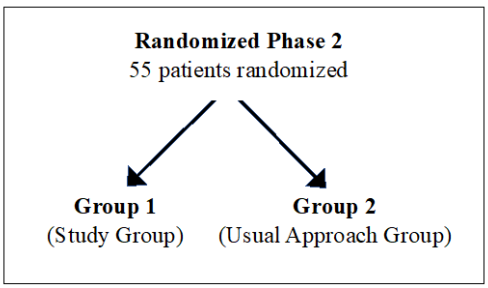
Group 2 (7+3 Chemotherapy Arm)

If you are in this group, you will get the usual drugs used to treat this type of cancer, cytarabine plus daunorubicin. Before you begin treatment, you will be given medicine to prevent nausea, vomiting and infections (fungal, viral and/or bacterial infections), which are possible side effects of 7+3 chemotherapy. In the first cycle, you will receive cytarabine as a continuous infusion through a vein in your arm on Days 1-7 of each cycle. You will also receive daunorubicin through a vein in your arm on Days 1,2, and 3. To determine if this therapy was effective, your physician may perform a bone marrow biopsy after 2-3 weeks. If there is need for more therapy, you may receive a second cycle of this therapy. In this case, you will receive cytarabine as a continuous infusion through a vein in your arm on Days 1-5. Likewise, you will also receive daunorubicin through a vein in your arm on Days 1 and 2. Each cycle is 28 days. This study has up to 2 cycles of treatment. After completion of these 2 cycles of daunorubicin and cytarabine, your physician may recommend you receive a stem cell transplant as part of standard of care therapy for acute leukemia in younger and fit patients. You will be able to continue ASTX727 and venetoclax after completing 12 cycles if you are responding well to the treatment. See the study calendar for more information.

There will be about 27 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading from the top and read to the bottom, following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Blood collections done before you begin your study, on Days 2, 3, 4, 5, 8, 15, 22, of Cycle 1, on Day 1 of every cycle thereafter, and at the end of the study. Approximately 30 mL of blood will be collected at each collection time.
- If you are taking venetoclax and ASTX727: Bone marrow aspiration or biopsy done to check the status of your disease before you begin study treatment, on Day 8 of Cycle 1, on Day 1 of Cycle 2, Cycle 5 and Cycle 8, when you finish study treatment or come off study for any reason, and if your doctor is concerned that the leukemia has returned.. Approximately 30mL of bone marrow will be collected at each collection time.
- If you are taking 7+3 Chemotherapy: A bone marrow aspiration or biopsy done to check the status of your disease before you begin study treatment, approximately 14 days into your therapy to determine if the therapy is working, upon recovery of your cell counts between D28-D57, when you finish study treatment, come off study for any reason, or if your doctor is concerned that the leukemia has returned.
- Physical exams done weekly during the first cycle and on the first day of every cycle thereafter.
- Electrocardiogram before you begin your study and at the end of the study

This study will use genetic tests that may identify changes in the genes in your tumor DNA. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. If the changes in your genes were inherited, the changes could also affect the health of your family members.

Certain genetic changes may affect your future treatments or procedures after completion of this study.

Some exams, tests, and procedures are a necessary part of the research study but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

You will have mandatory bone marrow aspiration samples taken for the study. The first will be before you begin treatment. The bone marrow samples for research will be collected during the bone marrow aspiration that you have to check the status of your disease. Approximately 30mL of bone marrow will be collected at each collection time point including 15mL for research studies. You will not have to have a separate procedure for this collection, and the additional amount taken for research does not put you at greater risk. If you are taking venetoclax and ASTX727, you will have a second mandatory bone marrow aspiration on Day 8 of the first cycle of treatment. These samples will be used for research purposes to look at other features of your leukemia cells that may help determine how to better kill leukemia cells with treatment for future patients with AML. You and your study doctor will not get the results of this testing. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

Blood samples will also be taken for the study. Blood samples will only be collected if you are receiving venetoclax and ASTX727 to check the levels of venetoclax in your blood. The mandatory blood collections will be on Days 5 and 22 of Cycle 1 before you take your dose of venetoclax and 1 hour, 2 hours, 4 hours, and 7 hours after taking venetoclax.

A patient study calendar is attached at the end of this document. It shows how often these procedures will be done.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the combination of venetoclax with ASTX727 may not be as good as the usual approach for your AML at getting it into remission.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

Venetoclax in combination with ASTX727 used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 3 months for men and 6 months for women after you have completed the study.

Genetic Testing Risks

The genetic test used in this study will test your tumor for genetic changes in commonly mutated genes in AML. Rarely, these genetic changes may also be present in your normal tissue and

passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. If you want to find out if the change is in your normal tissue, then you will need to get other tests done outside of this study.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your doctor will talk with you about what testing your normal tissue may mean for you and your family. He or she also may suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for any genetic tests and visits to a genetic counselor done outside of this study.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, tenderness, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection or significant bleeding can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Blood Draw Risks

Some of the risks from drawing blood from your arm may include pain, bruising, light-headedness, and rarely, infection. For most people, needle punctures to get blood samples do not cause any serious harm. Let your study doctor know of any questions you have about possible side effects. The multiple, and frequent blood draws taken from your arm for research testing may be burdensome and inconvenient given the time you need to stay in the hospital. In addition, the frequent needle sticks may be uncomfortable as your infusion line cannot be used. You can ask the study doctor questions about side effects at any time.

Side Effect Risks

The 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 test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at the usual drugs used to treat this type of cancer vs. a combination of study drugs. This different combination of drugs may increase your side effects or may cause new side effects.

You should notify your doctor immediately at the first sign of poorly formed or loose stools or an increased frequency of bowel movements. Loperamide (Imodium) should be kept on hand and should be taken as recommended by your doctor.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of ASTX727
(Table Version Date: June 27, 2022)**:**

COMMON, SOME MAY BE SERIOUS In 100 people receiving ASTX727 (cedazuridine, decitabine), more than 20 and up to 100 may have:
• Anemia, which may require blood transfusion • Tiredness • Bruising, bleeding

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ASTX727 (cedazuridine, decitabine), from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Constipation, diarrhea, nausea, vomiting • Sores in the mouth, which may cause difficulty swallowing • Loss of appetite • Dizziness, headache

Possible Side Effects of Venetoclax (ABT-199)
(Table Version Date: May 8, 2019)**:**

COMMON, SOME MAY BE SERIOUS In 100 people receiving venetoclax (ABT-199), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea • Tiredness • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving venetoclax (ABT-199), from 4 to 20 may have:
• Constipation, vomiting • Fever • Bruising, bleeding • Pain in joints • Headache • Cough • High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS In 100 people receiving venetoclax (ABT-199), 3 or fewer may have:
• Kidney damage which may require dialysis

Possible Side Effects of Cytarabine
(Table Version Date: August 30, 2019)

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

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• 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 Daunorubicin
(Table Version Date: October 10, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, more than 20 and up to 100 may have:
• Pink or red colored urine, sweat, or saliva • Nausea, vomiting • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, from 4 to 20 may have:
• Damage to the heart which may cause shortness of breath, tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may require transfusion • Pain and sores in mouth and throat • Diarrhea • Redness and pain at the site of previous radiation • Swelling and redness at the site of injection • Loss of nails • Dark discoloration of the nail, skin

RARE, AND SERIOUS In 100 people receiving Daunorubicin, 3 or fewer may have:
• Cancer of the bone marrow (leukemia) caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Additional Drug Risks

The study drugs could interact with other drugs and food. Venetoclax is broken down in your body by the enzyme CYP3A. Therefore, taking venetoclax along with other drugs that may inhibit CYP3A could increase the amount of venetoclax you will be exposed to. Drugs you should not take during Cycle 1 Day 1 through Cycle 1 Day 14 include strong CYP3A inhibitors such as ketoconazole, itraconazole, posaconazole, voriconazole, ritonavir, and clarithromycin, or moderate CYP3A inhibitors such as erythromycin, ciprofloxacin, diltiazem, fluconazole, and verapamil. Grapefruit products, Seville oranges, and starfruit should be avoided during treatment. Your study doctor will give you a clinical trial wallet card that lists the study drugs that you are taking. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the usual treatments (daunorubicin and cytarabine) or the study drugs (venetoclax and ASTX727). If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects

  - any doctors' visits or hospital stays outside of this study
  - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 3 months for men and 6 months for women after your last day of study treatment.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the venetoclax and ASTX727 or cytarabine and daunorubicin ready and giving it to you.
- the costs of the cytarabine and daunorubicin
- your insurance co-pays and deductibles.
- If you are taking venetoclax and ASTX727: Bone marrow aspiration or biopsy done to check the status of your disease before you begin study treatment, on Day 1 of Cycle 2, Cycle 5 and Cycle 8, when you finish study treatment, or come off study for any reason, and if your doctor is concerned that the leukemia has returned.
- If you are taking 7+3 Chemoterapy: Bone marrow aspiration or biopsy done to check the status of your disease before you begin study treatment and possibly between the middle of Cycle 1, upon recovery of your cell counts between D28-D57, and when you finish study treatment, come off study for any reason, or if your doctor is concerned that the leukemia has returned.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The bone marrow aspirations on Day 8 of Cycle 1.
- If you are taking venetoclax and ASTX727: The blood collection to check the level of venetoclax in your blood on Day 5 and Day 22 of Cycle 1.

You or your insurance provider will not have to pay for the venetoclax and ASTX727 while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study or the study agent/treatment now or in the future. This would include any organization helping the company with the study.

- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- TheNCI and the groups it works with to review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this study. There is no penalty for saying "no." You and your insurance company will not be billed for this optional study. If you sign up for, but cannot complete this study for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for the following study.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

If you choose to take part in this optional study, researchers will collect bone marrow for research before you begin treatment and if your disease gets worse. This study will test your cells to try to understand if your specific cells would have or have not responded to the usual treatment given for your disease instead of the study drugs. This optional study will also try to understand if your cells collected at the time that your disease got worse might still respond to the usual treatment given for your disease.

Unknown future studies

If you choose to take part in this optional study, a sample of your bone marrow will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Experimental Therapeutics Clinical Trials Network and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your bone marrow samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. Additional marrow will be drawn during your mandatory bone marrow aspirates to check your disease status that occur before you begin study treatment and if your disease gets worse and will be sent to the biobank.
2. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to a bone marrow aspirate are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection or significant bleeding can occur. It is

important to remember that there will be no additional procedure, and these additional bone marrow samples will be taken at the time of bone marrow biopsies done to manage your clinical care on the study and will not cause any additional risk, pain, or inconvenience.

- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory study described above.

YES NO

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Patient Study Calendar

Patient Friendly Calendar for Phase 2 Venetoclax+ASTX727 Combination

Cycle = 28-days	Before you begin study treatment	CYCLE 1									CYCLES 2+									Post-Treatment		
		D1	D2	D3	D4	D5	D8 +/- 2 days	D15	D22	D28	D1	D2	D3	D4	D5	D8 +/- 2 days	D15	D22	D28	When you finish study treatment	Follow-Up 3 months after you finish study treatment	Long term Follow-Up every 3 months for up to 2 years after you finish study treatment
Venetoclax[a]		X----------X									X----------X											
ASTX727[b]		X	X	X	X	X					X	X	X	X	X							
Pre-study [Before you begin study treatment] procedures including Informed Consent, Demographics, Medical History, and Height	X																					
Check of all medications you are taking and side effects evaluation	X	X	X	X	X	X	X	X	X		X									X	X	
Physical exam	X	X					X	X	X		X									X	X	
Assessment of how you perform everyday tasks and activities	X	X									X									X	X	
Vital signs	X	X	X	X	X	X	X	X	X		X									X	X	
Weight	X	X					X	X	X		X					X	X	X		X	X	
Survival Status																						X
Medication to prevent infections[f]		X----------X									X----------X											
Medication to reduce nausea caused by study drugs		X	X	X	X	X																
Medication to reduce	X	X----------X									X----------X											

Cycle = 28-days	Before you begin study treatment	CYCLE 1									CYCLES 2+									Post-Treatment		
		D1	D2	D3	D4	D5	D8 +/- 2 days	D15	D22	D28	D1	D2	D3	D4	D5	D8 +/- 2 days	D15	D22	D28	When you finish study treatment	Follow-Up 3 months after you finish study treatment	Long term Follow-Up every 3 months for up to 2 years after you finish study treatment
uric acid caused by tumor lysis syndrome[g]																						
Blood draws for complete blood count and general health status	X	X	X	X	X	X	X	X	X		X									X	X	
Blood test to check the level of Magnesium, phosphorous, electrolytes, uric acid and cholesterol in your blood	X	X	X	X	X	X	X	X	X		X[e]											
Blood test to see how well your blood clots	X																			X		
ECG (Assessment will be taken as your doctor indicates it is necessary)	X																			X		
Blood or urine collection for pregnancy test	X	X																		X		
Urine Tests (Assessment will be taken as your doctor indicates it is necessary)	X																			X		
Chest X-ray or CT scan	X																			X		
Bone marrow aspiration or biopsy to check the status of your disease	X										X[e]									X		
Mandatory Bone marrow aspiration for	X						X															

Cycle = 28-days	Before you begin study treatment	CYCLE 1									CYCLES 2+									Post-Treatment		
		D1	D2	D3	D4	D5	D8 +/- 2 days	D15	D22	D28	D1	D2	D3	D4	D5	D8 +/- 2 days	D15	D22	D28	When you finish study treatment	Follow-Up 3 months after you finish study treatment	Long term Follow-Up every 3 months for up to 2 years after you finish study treatment
research purposes																						
Optional bone marrow aspiration for research purposes																				X		
Mandatory blood collection for research[d]						X			X													

a. Venetoclax: Dose as assigned.
b. ASTX727: 1 fixed dose combination tablet on Day 1 to Day 5 every 28-day cycle.
c. Day 1 of Cycles 2, 5, and 8 and if your doctor is concerned that the leukemia has returned or you come off the study for any reason.
d. Blood collection on Day 5 and Day 22: before you take your dose of venetoclax and 1 hour, 2 hours, 4 hours, and 7 hours after taking your dose.
e. Electrolytes will be measured twice within week 1 of cycle 2
f. Antimicrobial medicine is not mandatory and will be administered if your doctor is concerned about infections.
g. Medicine to reduce uric acid will begin 2-3 days before the start of your study treatment.

Patient Friendly Calendar for Phase 2 7+3 Chemotherapy Arm

Protocol Activities Cycle = 4 weeks (28days)	Before you begin study treatment	CYCLE 1 Induction				Cycle 1 response assessments	CYCLE 2 Induction*				Cycle 2 response assessments	Post-Treatment		
		D1	D3	D4	D7	Weekly until recovery or day 57 +/- 3 days	D1	D2	D4	D5	Weekly until recovery or day 57 +/- 3 days	When you finish study treatment	Follow-Up 28 days after your last dose of study treatment	Long term Follow-Up every 3 months for up to 2 years after you finish study treatment
Cytarabine[a]		X----------X					X----------X							
Daunorubicin[b]		X----------X					X----------X							
Pre-study [Before you begin study treatment] procedures including Informed Consent, Demographics, Medical History, and Height	X													
Check of all medicatins you are taking and side effects evaluation	X	X		X		X	X			X	X	X	X	
Physical exam (as scheduled and as requested by your doctor)	X	X		X		X	X			X	X	X		
An assessment of how well you perform every-day tasks	X	X				X	X				X	X		
Vital signs	X	X		X		X	X			X	X			
Weight	X	X				X	X				X			
Survival Status														X
Blood draws for complete blood count and general health status	X	X		X		X	X			X	X	X		
ECG (Assessment will be taken as your doctor indicates it is necessary)	X													
Blood or urine collection for pregnancy test	X													
Evaluation of heart performance	X						X							
Urine tests	X											X		
Chest X-ray or CT scan	X													
Medication to prevent infections[d]		X----------X					X----------X							

Protocol Activities Cycle = 4 weeks (28days)	Before you begin study treatment	CYCLE 1 Induction				Cycle 1 response assessments	CYCLE 2 Induction*				Cycle 2 response assessments	Post-Treatment		
		D1	D3	D4	D7	Weekly until recovery or day 57 +/- 3 days	D1	D2	D4	D5	Weekly until recovery or day 57 +/- 3 days	When you finish study treatment	Follow-Up 28 days after your last dose of study treatment	Long term Follow-Up every 3 months for up to 2 years after you finish study treatment
Medication to prevent nausea caused by chemotherapy		X----------X												
Bone marrow aspiration or biopsy to check the status of your disease	X					X[c]					X[c]	X		
Mandatory Bone marrow aspiration for research purposes	X													
Optional bone marrow aspiration for research purposes												X		

*if necessary

a. Cytarabine: Dose as assigned on Day 1-6 of each cycle.
b. Daunorubicin: Dose as assigned on Day 1-3 of each cycle.
c. Upon recovery of cell counts between D28-D57. A biopsy on D14 may be taken at the discretion of the investigator/treating institution to assess for the need of re-induction. Additional bone marrow aspirations or biopsies will be done if come off study for any reason, or if your doctor is concerned that the leukemia has returned
d. Antimicrobial medicine is not mandatory and will be administered if your doctor is concerned about infections.