Update #12

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO A041702

A RANDOMIZED PHASE III STUDY OF IBRUTINIB PLUS OBINUTUZUMAB VERSUS IBRUTINIB PLUS VENETOCLAX AND OBINUTUZUMAB IN UNTREATED OLDER PATIENTS (≥ 65 YEARS OF AGE) WITH CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

[X]	**Update:**	[ ]	**Status Change:**
[X]	Editorial/Administrative changes	[ ]	Activation
[ ]	Eligibility changes	[ ]	Closure
[ ]	Therapy/Dose Modifications/Study Calendar changes	[ ]	Suspension
[ ]	Scientific/Statistical Considerations changes	[ ]	Reactivation
[ ]	Correlative Science/BioMS changes		
[X]	Informed Consent changes		
[X]	Other: Updated CAEPR for Venetoclax		

The changes included in this update to A041702 have been made in response to the NCI Action Letter from Dr. Steven Gore (steven.gore@nih.gov). This Action Letter is posted on the A041702 study page on the CTSU website. A revised CAEPR for Venetoclax drug with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate the new risks, consistent with the NCI Model Consent Template instructions.

No recommended level of IRB review is provided by the Alliance as the CIRB is the IRB of record for this trial. This amendment must be implemented within 30 days after posting.

A consent form addendum will need to be signed by all patients currently receiving treatment or having treatment held with Venetoclax. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Title Page

- The Protocol Coordinator contact has been updated.
- The Data Manager contact has been updated.

Section 9.4.3 (Comprehensive Adverse Events and Potential Risks list (CAEPR) for Venetoclax (ABT-199, NSC 766270))

This section has been revised to include the updated venetoclax CAEPR (Version 2.2, July 22, 2025) provided by CTEP. Changes from Version 2.1 to Version 2.2 include the following:

- The SPEER grades have been updated.

- Added New Risk:
  - Rare but Serious: Hepatobiliary disorders - Other (drug-induced liver injury)
  - Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution: Alanine aminotransferase increased; Cataract; Colitis; Creatinine increased; Delirium; Esophageal pain; Esophageal ulcer; Fall; Generalized muscle weakness; Leukemia secondary to oncology chemotherapy; Metabolism and nutrition disorders - Other (hypervolemia); Mucositis oral; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Richter's syndrome); Pain in extremity; Pneumonitis

- Increase in Risk Attribution:
  - Changed to Less Likely from Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution: Back pain; Hyperphosphatemia

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Anemia; Fatigue
  - Changed to Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution from Less Likely: Hypertension; Hypophosphatemia

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UPDATES TO THE MODEL CONSENT:

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

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for venetoclax:

- Added New Risk:
  - Rare: Damage to the liver which may cause yellowing of eyes and skin, swelling

- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Anemia which may require blood transfusion; Tiredness

- Changed to Also Reported on Venetoclax Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): High blood pressure which may cause headaches, dizziness, blurred vision

- Provided Further Clarification:
  - Pain in joints (under Occasional) is now reported as Pain (under Occasional)

INFORMED CONSENT ADDENDUM:

A new informed consent addendum has been added to reflect the new or additional information for Venetoclax with this update. This addendum is intended to be signed by all patients currently receiving treatment or having treatment held with Venetoclax.

A replacement protocol document, model consent, and informed consent addendum have been issued.

This study remains closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of a new anti-cancer drug, Venetoclax, to the usual treatment (Ibrutinib and Obinutuzumab) in untreated, older patients with Chronic Lymphocytic Leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol A041702, "A Randomized Phase III Study of Ibrutinib Plus Obinutuzumab Versus Ibrutinib plus Venetoclax and Obinutuzumab in Untreated Older Patients (≥ 65 Years of Age) with Chronic Lymphocytic Leukemia (CLL)" (NCT # NCT03737981)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. 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 intermediate or high-risk chronic lymphocytic leukemia that has not been treated before.

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. 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. 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 questions:

1. Is adding a new anti-cancer drug (venetoclax) to the usual treatment (ibrutinib plus obinutuzumab) better, the same as, or worse than the usual treatment alone for untreated older patients with CLL/SLL?
2. Can patients who have no detectable CLL after a year of receiving the usual treatment plus the new anti-cancer drug discontinue therapy?

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

What is the usual approach to my chronic lymphocytic leukemia?

The usual approach for older patients who have not yet been treated and are not in a study would be treated with one or two Food and Drug Administration (FDA) approved drugs. One treatment option is a chemotherapy drug combined with a CD20 monoclonal antibody (for example, chlorambucil plus obinutuzumab or bendamustine plus rituximab). With this approach, over 80% of patients are expected to respond. At 2 years after treatment, about 74% of patients are expected to be in remission. Another approach is to treat with the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib, given alone or in combination with a CD20 monoclonal antibody (like obinutuzumab or rituximab). With this approach, over 90% of patients are expected to respond. At 2 years of treatment, about 88% of patients are expected to be in remission.

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 initially either get the drugs ibrutinib plus obinutuzumab (IO), or you will get the drugs ibrutinib plus obinutuzumab plus study drug venetoclax (IVO). Obinutuzumab will be given for 6 cycles (28 days) and ibrutinib will be given for about 1 year (in both groups). If randomized to the IVO arm, venetoclax will be given for about 1 year. You will have to complete a medication diary for ibrutinib and venetoclax for the duration of treatment. After this time, you will have CT scans and a bone marrow biopsy to determine whether any detectable chronic lymphocytic leukemia remains.

If you were initially treated with ibrutinib plus obinutuzumab, you will continue ibrutinib until your disease gets worse or the side effects become too severe.

If you were initially treated with ibrutinib plus obinutuzumab plus venetoclax and you have detectable chronic lymphocytic leukemia, you will continue ibrutinib until your disease gets worse or the side effects become too severe. If you have no detectable chronic lymphocytic leukemia, you will stop ibrutinib and be closely monitored by your doctor.

After you finish your study treatment, your doctor will continue to follow your condition for 10 years to watch for side effects and to see if your disease gets worse. You will have a clinic visit with your doctor every 3 months for 6 years. Then, you will have a clinic visit with your doctor every 6 months for the remaining 4 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

There is evidence that both the regimens of (1) ibrutinib plus obinutuzumab, and (2) ibrutinib plus obinutuzumab plus venetoclax are effective in the treatment of chronic lymphocytic leukemia. 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 the study, there is a risk that the study drugs may not be as good as the usual approach for your cancer and your chronic lymphocytic leukemia might get worse. If this happens, your doctor will take you off of the study and discuss other treatment options with you.

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

The medications 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 18 months after you have completed obinutuzumab treatment

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

- Some common side effects seen with ibrutinib are bruising, joint pain, diarrhea, heartburn, and rash. Ibrutinib can also cause atrial fibrillation (an abnormal heart rhythm). These risks are the same whether you receive ibrutinib as part of a clinical trial or as standard of care.
- Obinutuzumab can cause infusion reactions during the first infusion, which can cause fever, chills, shortness of breath, nausea, chest pain, or low blood pressure. This risk might be lower when you receive the drug in combination with ibrutinib.
- Venetoclax can cause tumor lysis syndrome, where the cancer cells break down quickly and can release toxins into the bloodstream. Giving venetoclax after treatment with ibrutinib and obinutuzumab, as is done in this trial, may reduce this risk.
- All three drugs can cause lowering of the neutrophil count, which can lead to infection. This risk might be more common when these drugs are given in combination.

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

Benefits

There is evidence that both the regimens of ibrutinib plus obinutuzumab and ibrutinib plus obinutuzumab plus venetoclax are effective in the treatment of chronic lymphocytic leukemia. It is not possible to know now whether ibrutinib plus obinutuzumab plus venetoclax is better than the usual approach of ibrutinib plus obinutuzumab or ibrutinib alone in terms of taking longer for

chronic lymphocytic leukemia to return. This study will help the study doctors learn things that will 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.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (the National Cancer Institute). The study sponsor is the organization who oversees the study.

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 alone (ibrutinib plus obinutuzumab) to using venetoclax plus the usual treatment. The addition of venetoclax to the usual treatment could prevent your chronic lymphocytic leukemia from returning. But, it could also cause side effects, which are described in the risks section. The study will also see if patients who receive ibrutinib plus obinutuzumab plus venetoclax and have no detectable chronic lymphocytic leukemia after 1 year of treatment, can stop taking ibrutinib.

This study will help the study doctors find out if this different approach is better than the usual approach. To do this, the study doctors will look at how long remissions last in patients treated with the usual approach versus those treated with the three-drug combination. In the group of patients receiving the three-drug combination (ibrutinib, obinutuzumab, venetoclax), those patients who have no detectable CLL will stop ibrutinib after about a year, and those who still have evidence of CLL/SLL will continue ibrutinib.

All of these therapies are already approved by the FDA for use in chronic lymphocytic leukemia. There will be about 418 people taking part in this study.

What are the study groups?

This study has a screening step. The purpose of this step is to test your blood to find out if it has a specific chromosome abnormality called deletion 17p. We will review Fluorescence in Situ Hybridization (FISH) that you have already had. This does not affect your eligibility to the study, but we will try to assign the same number of patients with this abnormality to each treatment group.

This study has 2 main study groups.

- **Group 1 (ibrutinib plus obinutuzumab)**

  If you are in this group, you will get the usual drugs used to treat this type of cancer (ibrutinib and obinutuzumab). You will take ibrutinib pills by mouth once a day for 15 cycles. You will receive an intravenous infusion of obinutuzumab on days 1, 2, 8, and 15 during Cycle 1, and then on day 1 of cycles 2-6. Each cycle lasts 28 days. At the beginning or Cycle 15, CT scans will be performed, and a bone marrow aspirate and blood will be collected from you. These will be sent to researchers to see if you have detectable amounts of chronic lymphocytic leukemia.

  You will then go on to take ibrutinib pills by mouth once a day until your disease gets worse or your side effects become severe.

  There will be about 209 people in this group.

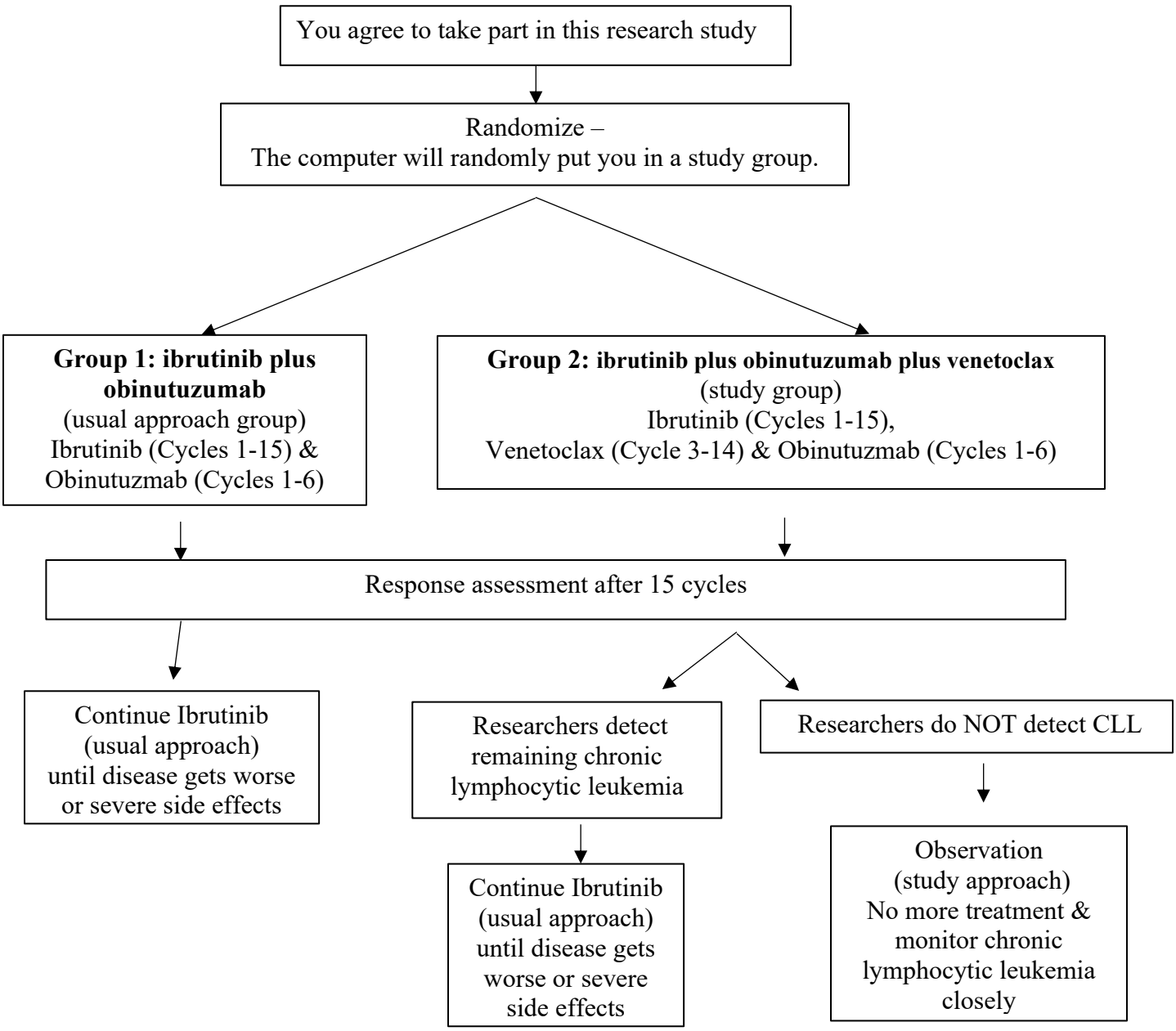
- **Group 2 (ibrutinib plus obinutuzumab plus venetoclax)**

  If you are in this group, you will get a study drug called venetoclax plus the usual drugs (ibrutinib and obinutuzumab) used to treat this type of cancer. You will receive an intravenous infusion of obinutuzumab on days 1, 2, 8, and 15 during Cycle 1, and then on day 1 of cycles 2-6. You will take ibrutinib pills by mouth once a day for 15 cycles. You will take venetoclax by mouth once a day starting on Cycle 3 Day 1 until the end of Cycle 14. Each cycle lasts 28 days. At the beginning of Cycle 15, CT scans will be performed and a bone marrow aspirate and blood will be collected from you to see if you have detectable amounts of chronic lymphocytic leukemia. If you still have detectable chronic lymphocytic leukemia, you will then go on to take ibrutinib pills by mouth once a day until your disease gets worse or your side effects become severe. If you no longer have detectable chronic lymphocytic leukemia, then you will stop taking the drugs and you will be monitored closely by your doctor.

  There will be about 209 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 on the following page. 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.

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 need to have a bone marrow sample, a blood sample, and a buccal cell (inside of the mouth) sample taken for the study. The bone marrow will be taken before starting the treatment, on the first day of the fifteenth cycle of treatment, and when stopping treatment. First, you may receive a small amount of anesthetic to reduce the pain. Then a special wide needle with a syringe attached will be pushed into the center of the bone. A sample of liquid bone marrow (soft, spongy tissue in the center of the bone) will be removed with the syringe. The bone marrow will be used to determine whether any chronic lymphocytic leukemia is left in the bone marrow after fourteen cycles of therapy. It is standard of care to perform bone marrow biopsies to assess response. In this study, however, if you are in the ibrutinib plus obinutuzumab plus venetoclax group (Group 2), we will use the bone marrow sample in addition to the CT scan and blood work, to determine whether you should continue ibrutinib or not. This is part of the research study.

A blood sample will be taken before starting treatment, then on the first day of the fifteenth cycle of treatment, then every six cycles of treatment until the eightieth cycle of treatment, then every twelve cycles, at relapse/progression, and when stopping treatment. The blood will be taken from a vein in your arm. The blood will be used to determine whether certain abnormalities in chronic lymphocytic leukemia cells will predict responses to these medications. The blood obtained on the first day of the fifteenth cycle of treatment will also be used to help determine response and, like the bone marrow, will help decide whether you will continue ibrutinib if randomized to the ibrutinib plus obinutuzumab plus venetoclax group. The blood taken later on in the study will be stored to determine whether there is detectable chronic lymphocytic leukemia and also whether certain abnormalities are present that would predict future relapse.

The buccal cell sample will be taken before you start treatment. The inside of your cheek will be scraped to collect the cells or you might be asked to rinse with mouthwash and spit into a tube. The buccal cell sample will be used to obtain a baseline gene samples with which to compare cancer cells.

Leftover bone marrow, blood and buccal samples may be stored for biobanking. This will be discussed in the section under “Optional studies.”

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 study drugs may not be as good as the usual approach for your chronic lymphocytic leukemia at preventing the cancer from coming back.

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.

Genetic Testing Risks

As part of the study, genetic tests will be performed on your leukemia cells. Any abnormalities in the leukemia cells will be compared with normal cells from your mouth to determine whether abnormalities are specific to the leukemia cells or found in normal cells too. Changes found in your normal cells may be passed down in families. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

While it is not expected that abnormalities will be found in your normal cells, if abnormalities are found in your normal cells that have an impact on your health or the health of your family, these results will be shared with your doctor. . Your doctor will talk with you about what the tests results may mean for you and your family. He or she also may suggest you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for visits to a genetic counselor.

Bone Marrow Aspirate & Biopsy Risks

There may be some temporary pain or discomfort associated with bone marrow aspirations and biopsies at the site where the needle is inserted. The side effects associated with obtaining bone marrow samples include pain at the site of the procedure, as well as possible bleeding, bruising or swelling. There is also a very small chance that you could develop an infection at the site of the procedure.

Blood collection risks

There can be mild pain, or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but may only last a few minutes after blood is drawn.

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

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.

Study Group 1 and Group 2 – Possible side effects of Ibrutinib and Obinutuzumab are listed in the tables below. This drug is part of the usual approach for treating this type of cancer:

Possible Side Effects of Ibrutinib (PCI-32765)
Table Version 2.9, April 10, 2025

COMMON, SOME MAY BE SERIOUS In 100 people receiving ibrutinib (PCI-32765), more than 20 and up to 100 may have:
• Fever • Infection, especially when white blood cell count is low • Pain

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ibrutinib (PCI-32765), from 4 to 20 may have:
• Anemia which may require blood transfusion • Abnormal heartbeat which may cause fainting • Constipation, diarrhea, heartburn, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Swelling of arms, legs • Tiredness • Bruising, bleeding • Loss of appetite, dehydration • A new skin growth that is not cancerous

- Headache
- Muscle weakness
- Numbness, tingling or pain of the arms and legs
- Cough, shortness of breath
- Rash
- High blood pressure which may cause headache, dizziness, blurred vision

RARE, AND SERIOUS

In 100 people receiving ibrutinib (PCI-32765), 3 or fewer may have:

- Blood clot which may cause swelling
- Death
- Liver damage which may cause yellowing of eyes and skin, swelling
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Prior liver infection that returns which may cause yellowing of eyes and skin, tiredness
- Fungal infection of the lungs or central nervous system which may cause cough, shortness of breath, fever, confusion, headache or stiff neck
- Hepatitis
- Kidney damage which may require dialysis
- A new cancer resulting from treatment of earlier cancer
- Stroke which may cause paralysis, weakness
- Damage to the lungs which may cause shortness of breath
- Rash or skin nodules related to underlying disease
- Swelling and redness of the skin
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body
- Low blood pressure
- Swelling or tenderness of blood vessels in the skin

Possible Side Effects of Obinutuzumab

Table Version 2.4, January 15, 2025

COMMON, SOME MAY BE SERIOUS

In 100 people receiving obinutuzumab (Gazyva), more than 20 and up to 100 may have:

- Nausea
- Tiredness, fever
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving obinutuzumab (Gazyva), from 4 to 20 may have:

- Anemia which may require blood transfusion

• Pain • Constipation, diarrhea, vomiting • A tear or hole in the bowels that may require surgery which may cause difficulty swallowing • Chills • Infection, especially when white blood cell count is low • Bruising, bleeding • Dizziness, headache • Painful urination • Inability to control urine • Cough, shortness of breath • Runny nose • Hair loss, itching, rash, hives • Flushing • High blood pressure which may cause headaches, dizziness, blurred vision • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving obinutuzumab (Gazyva), 3 or fewer may have:
• Blood clot • Abnormal heartbeat which may cause fainting • Chest pain • Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness • Prior liver infection that returns which may cause yellow eyes and skin, tiredness • Kidney damage which may require dialysis • A type of skin cancer • A new skin cancer resulting from treatment of earlier cancer • Damage to the brain which may cause changes in thinking and may be life-threatening

Study Group 2 - In addition to side effects listed above, people who are in Group 2 may also have some side effects from venetoclax. These side effects are listed in the table below.

Possible Side Effects of Venetoclax
Table Version Date July 22, 2025

COMMON, SOME MAY BE SERIOUS In 100 people receiving venetoclax (ABT-199), more than 20 and up to 100 may have:
• Diarrhea, nausea • 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:
• Anemia which may require blood transfusion • Constipation, vomiting • Tiredness, fever • Bruising, bleeding • Pain • Headache • Cough

RARE, AND SERIOUS In 100 people receiving venetoclax (ABT-199), 3 or fewer may have:
• Damage to the liver which may cause yellowing of eyes and skin, swelling • Kidney damage which may require dialysis

Additional Drug Risks
You should avoid a specific class of drugs that called CYP3A inhibitors. These types of drugs decrease the metabolism of the study drugs, which can cause side effects. You should also avoid grapefruit products, Seville oranges, and starfruit.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

COVID 19 Risks
Patients with CLL are at higher risks for complications from COVID 19. Vaccines, including the COVID 19 vaccine, are less effective in patients with CLL, and it is likely that treatment of any kind further decreases the effectiveness of the vaccine. It is recommended that trial participants continue COVID 19 precautions including mask wearing.

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, the date and time when you take the study drug (venetoclax) and you take the drug ibrutinib.

For men: Do not father a baby while taking part in this study. Tell your study doctor right away if you think that your partner has become pregnant during the study or within 180 days after your last dose of drug and study drug.

For women: If you are of reproductive potential, you should use an appropriate method of birth control throughout your participation in this study. Tell your study doctor right away if you think that you are pregnant during the study or within 18 months after your last dose of drug and study drug.

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 chronic lymphocytic leukemia. 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. This includes doctor visits, CT scans, most blood tests, and standard testing on bone marrow biopsies.
- the costs of getting the obinutuzumab ready and giving it to you.
- the cost of preparing venetoclax and ibrutinib for dispensing
- your insurance co-pays and deductibles.

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 analysis of the blood and bone marrow sample taken after 14 cycles to determine if any CLL remains (minimal residual disease analysis).
- Central fluorescence in situ hybridization (FISH) testing prior to treatment
- Analysis of buccal cell sample

You or your insurance provider will not have to pay for the ibrutinib, obinutuzumab, or venetoclax 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 NCI, 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, Alliance, and any company supporting the study now or in the future.
- The 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.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct 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.

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.

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

Optional sample 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.

Unknown future studies

If you choose to take part in this optional study, leftover blood marrow aspirate, blood and saliva that were collected under the study will be stored for future use. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance for Clinical Trials in Oncology and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

We don't know what research may be done in the future using your bone marrow aspirate, blood and saliva 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.
- Future research studies may include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems.
- 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 be 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.

What is involved in this optional sample storage?

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

1. Leftover samples of blood, bone marrow and saliva 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.
2. 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.
3. 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 storage?

- 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 sample 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 storage?

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 storage?

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 storage?

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 storage?

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 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