Research Study Informed Consent Document

Study Title for Participants: Assessing the Ability of Combination Treatment with Venetoclax to Permit Time Limited Therapy in CLL

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: EA9161, "**A Randomized Phase III Study of the addition of Venetoclax to Ibrutinib and Obinutuzumab versus Ibrutinib and Obinutuzumab in Untreated Younger Patients with Chronic Lymphocytic Leukemia (CLL),"** (NCT03701282)

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 untreated chronic lymphocytic leukemia (CLL).

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 additional 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:

What are the good and bad effects of a time limited administration of a targeted three drug treatment combination when compared with the more standard two drug treatment

combination, which requires long-term, indefinite drug administration? Time limited administration means that you will only receive treatment for a specified period of time, rather than receiving treatment indefinitely.

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

What is the usual approach to my chronic lymphocytic leukemia (CLL)?

People who are not in a research study are usually treated with chemotherapy, monoclonal antibodies or targeted therapies that kill leukemia cells. There are several Food and Drug Administration (FDA)-approved chemotherapy, monoclonal antibodies, and non-chemotherapy drugs that are commonly used. Although these treatments are effective and typically can control the CLL for a number of years, they are not curative and many of these standard approaches require chronic, indefinite treatment.

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

- You may choose to have one of the usual approaches 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 the usual therapy drugs used for this type of cancer, ibrutinib and obinutuzumab, plus a third drug used to treat CLL called venetoclax for up to 19 months or you will get usual therapy drugs used for this type of cancer, ibrutinib and obinutuzumab, until your doctor decides your disease is getting worse or the side effects become too severe. Ibrutinib, obinutuzumab, and venetoclax are all FDA approved drugs to treat CLL, but the combination of these drugs is considered investigational.

After you finish study treatment, your doctor will continue to follow your condition for 10 years and watch you for side effects. They will check you every 3 months for 2 years after treatment. After that, they will check you every 6 months for 3 years. After that, they will check you every 12 months for 5 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 study treatment of ibrutinib, obinutuzumab, and venetoclax may not be as good as ibrutinib and obinutuzumab at treating your cancer and preventing it from coming back.

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.

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

- Easy bruising/minor bleeding
- Infusion reactions to obinutuzumab (chills, decreased blood pressure, shortness of breath)
- Fatigue
- Diarrhea
- Increased blood pressure
- Fever/risk of infection
- Decreased white blood cell count

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

Benefits

Although all the treatments being evaluated in the study are proven therapies for CLL, taking part in this study may or may not make your health better. While doctors hope that the experimental treatment in this study will lessen the side effects of your cancer and shorten the total length of cancer therapy compared to the usual treatment, there is no proof of this yet. There is evidence that the venetoclax is effective in shrinking your type of cancer. However, it is not possible to know now if the study drugs will extend your time without disease compared to the usual approach.

This study may help the study doctors understand how these study drugs work together as treatments for CLL. This study may also help the study doctors learn things that may help other 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. This may mean slowly stopping the study drugs, so that there is not a sudden unsafe change or risk to your health. 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: if you become pregnant while on this study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor, the National Cancer Institute (NCI). 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 of ibrutinib and obinutuzumab to a combination treatment of ibrutinib and obinutuzumab plus the study drug, venetoclax. The addition of venetoclax to the usual treatment may or may not help shrink your cancer. But, it could also cause side effects, which are described in the risks section below. This study will also compare the usual treatment of indefinite ibrutinib therapy to a time limited therapy schedule of approximately 18 months to better understand their effects on your quality of life and the costs of your care.

This study will help the study doctors find out if these different approaches are equally effective to the usual approaches while requiring a shorter duration of treatment. To decide if they are better, the study doctors will be looking to see if the study drugs do no worse in terms of time to progression and overall survival compared to the usual approach, even though they require a shorter duration of treatment. Ibrutinib, obinutuzumab, and venetoclax are all FDA approved drugs to treat CLL, but they will be considered investigational in the setting of this trial. There will be about 720 people taking part in this study.

What are the study groups?

This study has 2 study groups.

- **Group 1 (Arm A)**

  If you are in this group, you will get a study drug called venetoclax plus the usual therapy drugs used to treat this type of cancer, ibrutinib and obinutuzumab. You will get both ibrutinib and venetoclax as capsules and tablets you take by mouth and you will get obinutuzumab through a vein in the arm, as described in the table below. Each cycle last 28 days. If you are in this group, you will have 19 cycles.

  There will be about 360 people in this group.

  Another way to know when you will receive each study drug is to follow the table below.

Cycle	**Which treatments you will receive:**
1	• Ibrutinib, daily • Obinutuzumab, on days 1, 2, 8, and 15
2	• Ibrutinib, daily • Obinutuzumab, on day 1
3-6	• Ibrutinib, daily • Obinutuzumab, on day 1 • Venetoclax, daily
7-14	• Ibrutinib, daily • Venetoclax, daily
15-19	• Ibrutinib, daily

- **Group 2 (Arm B)**

  If you are in this group, you will get the usual therapy drugs used to treat this type of cancer, ibrutinib and obinutuzumab. You will get ibrutinib as a capsule you take by mouth and you will get obinutuzumab through a vein in the arm, as described in the table below. Each cycle has 28 days. If you are in this group, you will continue to receive treatment until your disease gets worse or the side effects become too severe.

  There will be about 360 people in this group.

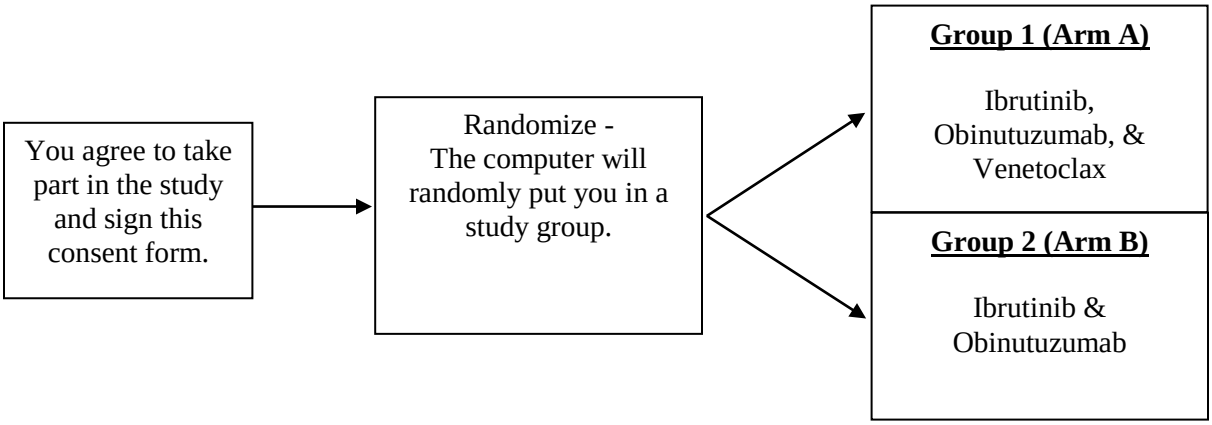
  Another way to know when you will receive each study drug is to follow the table below.

Cycle	**Which treatments you will receive:**
1	• Ibrutinib, daily • Obinutuzumab, on days 1, 2, 8, and 15
2-6	• Ibrutinib, daily • Obinutuzumab, on day 1

7-19	• Ibrutinib, daily
19 and beyond	• Ibrutinib, daily

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 (Arm A) or Group 2 (Arm B).

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, 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.

However, some of these tests may be done more frequently during the study to monitor your safety and health. Listed below are exams, tests, and procedures that we will use 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 tests to monitor your health throughout, as necessary.
- CT scan of chest, abdomen, and pelvis at 1-2 times, depending on when you register to the study and which arm you are randomized to:
  - You will have CT scan before beginning study treatment and after cycle 19. If you are on arm A, you will also have a CT scan on day 1 of cycle 3.
- Bone marrow aspirate and biopsy before beginning study treatment and after cycle 19.

These exams, tests and procedures are part of regular cancer care and may be done even if

you do not join the study. If you have had some of them recently, they may not need to be repeated. Many of these tests will be repeated throughout the study.

You will need to have a bone marrow biopsy before you begin the study; you will also need a bone marrow biopsy after 19 cycles of treatment at the time of response evaluation. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. These samples will be sent to a central laboratory for review of how your cancer is affected by the treatment. You and your study doctor will not get the results of this central review. 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. If there are any leftover samples that will possibly be stored for bio-banking, we will ask to keep it for future unspecified research. This will be discussed in the section under "Optional Studies."

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.

Quality of life study

If you are an English speaker you will be required to fill out a form with questions about your physical and emotional well-being. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out this form at 11 times in person:

- before beginning study treatment
- on day 1 of cycles 3, 7, and 15
- at the end of cycle 19,
- during follow up (once every 6 months for 2 years and 48 months after beginning study treatment)
- if your cancer gets worse

Each form will take about 5-15 minutes to complete. The forms will ask about things like tiredness, pain, emotional support, and relationships. You don't have to answer any question that makes you feel uncomfortable.

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 cancer at shrinking or stabilizing your cancer.

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.

The study drugs 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 a certain amount of time after you have completed the study depending on what study drugs you have taken (specifics are below in the 'What are my responsibilities in this study?' section.

Biopsy Risks

Common side effects of a biopsy 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 can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

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.
4. Some side effects may make it hard for you to have children.

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 (Arm A) and Group 2 (Arm B) – Possible side effects of ibrutinib and obinutuzumab are listed in the tables below. These drugs are part of the usual approach for treating this type of cancer:

Possible Side Effects of Ibrutinib (PCI-32765):

(Table Version Date: January 29, 2018)

COMMON, SOME MAY BE SERIOUS In 100 people receiving ibrutinib (PCI-32765), more than 20 and up to 100 may have:
• Diarrhea

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving ibrutinib (PCI-32765), from 4 to 20 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Abnormal heartbeat which may cause fainting • Blurred vision • Pain • Constipation, nausea, vomiting • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Tiredness, fever • Bruising, bleeding • Loss of appetite, dehydration • A new skin growth that is not cancerous • Dizziness, headache • Cough, shortness of breath • Rash • High blood pressure

RARE, AND SERIOUS In 100 people receiving ibrutinib (PCI-32765), 3 or fewer may have:
• Blood clot • 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 • Fungal infection of the lungs or central nervous system which may cause cough, shortness of breath, fever, confusion, headache or stiff neck • Kidney damage which may require dialysis • A new cancer resulting from treatment of earlier cancer • Numbness, tingling or pain of the arms and legs • Damage to lungs which may cause shortness of breath • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Low blood pressure

Possible Side Effects of Obinutuzumab:

(Table Version Date: January 7, 2019)

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 • Low blood pressure which may cause feeling faint

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving obinutuzumab (gazyva), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Diarrhea, vomiting • A tear or hole in internal organs that may require surgery which may cause difficulty swallowing

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving obinutuzumab (gazyva), from 4 to 20 may have:
• 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

RARE, AND SERIOUS In 100 people receiving obinutuzumab (gazyva), 3 or fewer may have:
• Chest pain • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Abnormal heartbeat • Prior liver infection that returns which may cause yellow eyes and skin, tiredness • Kidney damage which may require dialysis • A new skin cancer resulting from treatment of earlier cancer

Study Group 1 (Arm A) - In addition to side effects listed above, people who are in Group 1 (Arm A) may also have some side effects from venetoclax. These side effects are listed below.

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

Additional Drug Risks

The study drug could interact with other drugs and food. Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body process the study drugs. Supplements such as fish oil, vitamin E preparations, or other vitamins should be avoided. Your study doctor will give you information about these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

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

Lymphocytosis and leukostasis

You may experience an increase in the number of lymphocytes, a type of white blood cell, in your blood. This may occur in the first few weeks of treatment and you should not assume that this increase in white blood cells means progression of your disease. This increase may last for several weeks to months. Increased number of white blood cells in your bloodstream may decrease blood flow resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in patients treated with Ibrutinib. Your doctor will monitor your blood counts and may administer additional therapy as needed. Talk to your doctor about what your test results mean.

Bleeding effects

You may experience bruising or bleeding during treatment with Ibrutinib. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain, may occur. If you take other medicines or supplements that increase your risk of bleeding, such as aspirin, non-

steroidal anti-inflammatory drugs (NSAIDs) or medicines used to prevent or treat blood clots or stroke, Ibrutinib may increase this risk. These medications should not be taken while on study. Some blood thinners such as warfarin or other vitamin K antagonists should not be taken together with Ibrutinib. Call your doctor if you have signs or symptoms of serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.

Interference with other drugs

Some foods like starfruit, grapefruit juice, and Seville oranges, as well as some medications, may interfere with the way your body processes Ibrutinib. This interference could cause the amount of Ibrutinib in your body to be higher or lower than expected. It is also possible that taking the study drug with your regular medications or supplements may change how your regular medications, or your regular supplements, work. Supplements such as fish oil, vitamin E preparations, or other vitamins should be avoided while taking Ibrutinib. It is very important that you avoid grapefruit, starfruit, and Seville oranges and tell the study doctor about all medications or supplements you are taking during the study. Be sure to tell your doctor or study staff immediately about side effects to avoid possible harm.

Drug interruption for any surgical procedures

Ibrutinib may increase the risk of bleeding with any surgical procedure. Current guidelines recommend Ibrutinib be stopped at least 3 to 7 days before and after surgery depending on the type of surgery and the risk of bleeding. Please contact your study doctor if you have any planned surgical procedures. For emergency surgical procedures, current guidelines recommend Ibrutinib be discontinued (stopped) after the procedure and stopped for at least 7 days after the procedure.

Please contact your study doctor as soon as possible and your study doctor will tell you when to stop Ibrutinib and/or venetoclax and when to restart it following a surgical procedure.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Imaging Risks

The CT scans that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called “background radiation.” No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

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 or:

- Within 18 months after the last dose of the study drug obinutuzumab,
- Within 90 days after the last dose of the study drug ibrutinib, and
- Within 30 days after the last dose of the study drug venetoclax.

For men: Do not father a baby while taking part in this study or:

- Within 18 months after the last dose of the study drug obinutuzumab,
- Within 90 days after the last dose of the study treatment ibrutinib, and
- Within 30 days after the last dose of the study drug venetoclax.

Also, men must agree not to donate sperm for 90 days after the last dose of study drug.

For all: Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 18 months after your last dose of study drug. It is important you understand that you need to use birth control while on this study and for the timeframes specified above after you stop taking study treatment.

If a woman and become pregnant while on this research study or within 18 months after the last dose of study drug, you will be asked information concerning the outcome of your pregnancy. If you are a male and your female partner becomes pregnant while you are on the study or within 18 months after the last dose of study drug, you must notify the investigator. The pregnant female partner should be advised to call her healthcare provider immediately.

If you are sexually active and able to have children, you are strongly advised to use a highly effective method of birth control while taking study treatment, as well as for timeframes specified above after you stop taking study treatment, to prevent pregnancy in either you or your partner. A **"Highly effective method of birth control"** is defined as a method that has a low failure rate (i.e. less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with two hormones, some intrauterine devices (IUDs), sexual abstinence or a sterilized partner.

If you choose to be sexually active during the study, you must accept that pregnancy could still result, exposing you or your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing fetus.

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.
- Bone marrow aspirates and biopsies done as part of the usual care for your cancer as well as 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 or your insurance provider will not have to pay for the study agents, ibrutinib, obinutuzumab, or venetoclax while you take part in this study. However, you and/or your insurance plan will need to pay for the costs of preparing these study agents and giving them to you.

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. Contact information for your study doctor is listed on the consent cover page. 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.

No funds have been set aside to compensate you in the event of injury.

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.

The ECOG-ACRIN Cancer Research Group is conducting this study. ECOG-ACRIN is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG-ACRIN or another group that is participating in this study.

There are organizations that may look at 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:

- Montana Cancer Consortium
- The study sponsor supporting the study now or in the future.
- The pharmaceutical collaborators who supply the study agents.
- The Institutional Review Board (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 National Cancer Institute (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

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, 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 information for your study doctor is listed on the consent cover page.

For questions about your rights while in this study, you may contact the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

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

Tobacco Use Assessment Substudy

If you agree to participate in this study you will be asked to do an online survey regarding your tobacco use. Regardless if you have used tobacco or not, the information you provide is important to us. Recent research has found that tobacco use can have a powerful effect on how patients respond to cancer treatments. The purpose of this study is to obtain information on tobacco use among clinical trial participants to examine whether tobacco use is associated with treatment outcomes, ultimately to help maximize the effectiveness of cancer treatment.

For this substudy, you will complete the survey online at 3 different timepoints (before the study treatment, 3 months after starting treatment, and 6 months after starting treatment). Each survey should take you about 6 minutes to complete. To participate, you will be asked for your email address so we can send you a link to the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO).

Up to 1500 patients will be enrolled in this study.

Optional sample collections for known laboratory studies and 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 blood and bone marrow for research to learn about how the study treatment affects your cancer

Unknown future studies

If you choose to take part in this optional study, samples of blood, and cheek cells will be collected and stored. Storing samples for future studies is called "bio-banking." The biobank is being run by ECOG-ACRIN 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 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.

What is involved in this optional sample collection?

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

1. We would like to collect blood and bone marrow for research, and additional blood and some cheek cells to be stored in the biobank.
    - Approximately one (1) teaspoon of bone marrow aspirate will be collected prior to the start of treatment and at the time of your response evaluation after cycle 19 of

therapy. The bone marrow collections are to occur at the time of those performed for clinical assessments. Additional procedures should not be required.

- Approximately six (6) tablespoons of blood will be collected prior to the start of treatment and approximately five (5) tablespoons of blood will be collected after cycle 2 of therapy, day 1 of cycle 8, day 1 of cycle 14, at the time of your response evaluation after cycle 19 of therapy, 24, 30, 36, 48, and 60 months after randomization, and if your cancer worsens.
- Cheek cells will be collected prior to the start of treatment (or any other time point during the study) by rinsing your mouth with mouthwash (Scope) or salt water.
- The above samples and your leftover bone marrow samples from the central review 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 collection?

The most common risks related to drawing blood from your arm are brief pain and maybe a bruise, bleeding, or feeling faint.

The most common risks related to bone marrow aspiration are infection, bleeding or bruising at the site of the aspiration, as well as possible inflammation of the vein and temporary pain and discomfort.

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 samples 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, who will let the biobank know. Contact information for your study doctor is listed on the consent cover page. Then, any samples that remain 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. Contact information for your study doctor is listed on the consent cover page.

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

Participation in optional quality of life study:

- **I agree to take part in the quality of life study and will fill out these forms.**

YES NO

Participation in optional Tobacco Use Assessment Substudy:

- **I agree to take part in the Tobacco Use Assessment Substudy.**

YES NO

Samples for known future studies:

May we have samples of your blood and bone marrow for laboratory research studies?

- **I agree to have my samples collected and I agree that my samples and related health information may be used for the laboratory research studies described above.**

YES NO

Samples for unknown future studies:

May we have samples of your bone marrow and blood, for future research?

- **I agree to provide additional samples for research.**

YES NO

May we keep any bone marrow and blood leftover after the laboratory research studies for future research?

- **My samples and related information may be kept in a Biobank for use in future health research.**

YES NO

This is the end of the section about optional studies.

Signature:

This study has been explained to me, and I have been told what my enrollment in the study involves. I have read all pages of this consent and have had my questions answered to my satisfaction at this time. I consent to participate in this study and any additional studies where I circled 'yes'. I understand that by signing this form I have not given up any of my legal rights. I will be given a copy of this consent form. I may also request a copy of the protocol (full study plan).

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)