

**STANFORD UNIVERSITY Research Consent Form**

Protocol Director: Steven E. Coutre, MD

*IRB Use Only*

Approval Date: November 14, 2018

Expiration Date: [REDACTED]

Protocol Title: An Open-Label Trial of Venetoclax with Ibrutinib in Relapsed and Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia

Are you participating in any other research studies?  Yes  No**INTRODUCTION TO RESEARCH STUDIES**

You are invited to voluntarily participate in a research study of venetoclax (Venclexta or ABT-199, formerly GDC-0199) and ibrutinib (Imbruvica, also known as PCI-32765), an experimental (“investigational”) combination treatment for leukemia, being conducted by Steven E. Coutre, MD, at the Stanford Cancer Center. You were selected as a possible participant in this study because you have either chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL), and your leukemia is relapsed or refractory to currently available treatments.

This document is to be used as a guide for a discussion between you and your Study Doctor and the study team. This form, called an informed consent document, was designed to help you understand why this study is being done; what part of the study is “research” or “experimental;” what will be asked of you if you choose to participate; possible risks; any inconveniences or discomforts you may experience; and other important information. This form may also be helpful as a reference if you choose to participate, as a reminder of what your role in the study is, and who to contact if you have questions at any time during your participation. You are urged to discuss any and all questions you have about this study with members of the study team. If you wish, you can also discuss this study and your role with your family doctor or medical provider.

**PURPOSE OF RESEARCH**

The proposed study investigates the use of venetoclax in combination with a standard dose of ibrutinib, as a treatment for CLL or SLL.

The proposed study is called a “Phase 2” study. The study team hopes to learn if the combination of venetoclax and ibrutinib is safe and effective to treat CLL or SLL.

Venetoclax, as Venclexta, has been approved by FDA for the treatment of patients with CLL who have a genetic mutation called “17p deletion;” after at least one prior therapy. Ibrutinib, as Imbruvica, has been approved by FDA for the treatment of CLL regardless of the presence or absence of the 17p deletion, and also to treat mantle cell lymphoma (MCL) after one prior therapy; relapsed or refractory marginal zone lymphoma (MZL); chronic graft-vs-host disease (GvHD); or Waldenström’s macroglobulinemia (WM). Both drugs are being studied in other various disease settings.

The combination of venetoclax + ibrutinib is being used in this study under a study protocol submitted to FDA, in an Investigational New Drug application (IND). Although both drugs are approved by FDA, the drugs continue to be studied in several cancer settings, including both CLL and SLL.

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Your normal medical care, or the “Standard of Care,” for CLL or SLL could include ibrutinib alone, or venetoclax if you have the 17p deletion, as well as allogeneic stem cell transplantation, chemotherapeutic agents; and/or monoclonal antibodies, as well as allogeneic hematopoietic cell transplantation (eg, bone marrow transplant). Some of these alternatives may not be right for you. Your doctor will discuss the specifics of your case with you. Your normal medical care would also include medical exams and blood tests, and medical scans to check the status of your cancer such as computed tomography (CT) or magnetic resonance imaging MRI scans.

The use of venetoclax in this research study is investigational (“experimental”). The word “investigational” means that venetoclax is not approved by the FDA for use in the United States to treat CLL that does not have the 17p deletion, or to treat SLL. This study is being conducted under an application submitted to FDA, called an “Investigational New Drug Application” or “IND.”

Venetoclax will be provided by the drug manufacturer AbbVie Inc. Ibrutinib will be provided by the drug manufacturer Pharmacyclics LLC.

The other parts of this study that are research (not part of your regular care) are the

- The collection of blood samples for determinations of drug levels in the blood
- Blood collection for genetic testing before treatment at Week 1 Day 1, and at the Final Study Visit or time of relapse.

If you decide to terminate your participation in this study, you should notify Dr Coutre at [REDACTED].

This research study is looking for 20 people with CLL or SLL. The study is being done at 2 research sites, Stanford University and City of Hope in Duarte, CA. Stanford University expects to enroll and treat about 15 research study participants.

This study is being paid for by Pharmacyclics LLC. Study drugs are being provided by Pharmacyclics and AbbVie, Inc.

**VOLUNTARY PARTICIPATION**

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

You will be informed of any significant new information about this study or the study drugs venetoclax and ibrutinib that might affect your willingness to participate in this research study.

You will be told the results of tests that are part of your medical care, but you may not be told the results of the research tests, including any future research tests.

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**DURATION OF STUDY INVOLVEMENT**

Your treatment in this research study is initially expected to take up to about 117 weeks, followed by continued treatment with ibrutinib alone if you are benefitting.

After 117 weeks, you may be able to continue treatment with ibrutinib only until you withdraw from the study, your cancer gets worse (disease progression), or death.

Your treatment in this study can continue until one of the following occurs:

- You withdraw your agreement to continue to take part in this research study
- You become “lost-to-follow-up”
- Your cancer becomes worse (disease or tumor progression)
- You need a treatment that is not allowed in this study
- You have a different illness that prevents further administration of study drugs
- You or your doctor decide that the side effects are too severe
- You are a woman and have become pregnant
- The study is terminated or
- You are removed from the research study for any of the following reasons:
  - You do not follow the study team’s instructions for the study.
  - Your Study Doctor determines it is in your best interest.
  - Other unanticipated; appropriate; and/or administrative reasons as determined by your doctor or the study sponsor.

When your participation in this study ends, you may be asked to return for a final visit to have some end-of-study evaluations or tests, or to allow medical information to be collected about your health after the trial treatment is stopped. After you finish the study, or stop taking the study drug for any other reason, you may continue to be checked regularly (physical exams; blood tests; tumor measurements; X-rays; other scans, etc) if you continue to have significant side effects from the treatment. This is called follow-up. Your Study Doctor will follow your progress, in accordance with good medical care, for as long as it is felt to be necessary by both you and the doctor, unless you ask otherwise. Many, if not all, of these procedures will be part of your regular continued medical care.

**PROCEDURES**

It may be harmful to enter this study while receiving some medications, therefore, you may need to stop taking certain medications. Your Study Doctor will review your medications and provide you with specific instructions.

Before you begin the study, you will need to have certain medical examinations, tests, or procedures to find out if you can be in the study. This is called “screening.” Some of

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these examinations, tests, or procedures may be part of your regular medical care, and/or 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.

Before you join this study, the Protocol Director Steven E. Coutre, MD and/or the research study staff will review this document with you, and ask you to sign this informed consent document. After you have signed this document, and received a signed copy, the study will begin with a screening visit.

**Screening Visit**

If you choose to participate, the first activity will be Screening. During the Screening Visit, you will be asked to have the following tests and activities or assessments. These evaluations need to be conducted within 28 days of the 1<sup>st</sup> day of treatment on this study.

**General information:** Information about you, such as date of birth; gender (sex); and ethnic origin (“demographic information”).

**Medical history:** Your complete medical history will be reviewed, including:

- Review of all medicines and/or supplements you are taking or have been taking
- Questions about any symptoms you are having
- Surgery and cancer history
- Tobacco and alcohol use
- Reproductive status

**Physical examination:** A complete physical exam will be performed, including:

- Your vital signs, including blood pressure; heart rate; temperature; breathing rate; height; weight; and other measurements
- General examination of your body systems, such as heart and lungs; ear, nose, and throat; skin; muscles and joints; stomach and gastrointestinal tract; and nervous system
- You will be asked how well you are able to perform normal daily living activities (such as bathing, driving, shopping, working, etc), according to the Eastern Cooperative Oncology Group (ECOG) performance evaluation
- You will be asked about your symptoms

**Blood collection:** Blood collection will typically be from a vein in your arm, using a blood collection needle. This is called venipuncture. If you have an implanted venous access port, this may be used for blood collection. Standard aseptic (clean) techniques will be used. A total of about 2 tablespoons (30 mL) of blood will be collected for:

- **Complete blood count (CBC) with differential**, including red blood cells (RBC, oxygen-carrying cells); white blood cells (WBC, infection-fighting cells); platelets; and other blood components.

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- **Serum chemistry**, consisting of tests for blood chemicals that indicate how well your body and organs are working, and if you have any significant diseases.  
**NOTE:** You may be asked to not drink or eat anything (“fast”) for several hours before the test.
- **Coagulation tests** to determine how well your blood clots.
- **CLL Blood test**, if your 17p deletion status is not known. A little less than 1 teaspoon (4 mL) of blood will be collected. If not collected at Screening, this sample will be collected before treatment on the 1<sup>st</sup> day of treatment.
- **Serum pregnancy test** (if you are a woman who can become pregnant. A urine pregnancy test may also be required. The pregnancy test(s) must be negative within 7 days before the 1<sup>st</sup> dose of the Study Drug.
- **Blood test for certain types of viral infections**, including hepatitis viruses. These tests are required to participate in this study.
  - **Notice pursuant to California Senate Bill 699** (April 2006): Health care providers and laboratories such as those involved in this study are required to confidentially report positive HIV or hepatitis B or C test results by *patient name* to the San Mateo County Dept of Public Health and to the California Dept of Health Services. You have the right to refuse the test for these viruses, but you will not be able to be in this study. Additional important information is provided below.
    - There are numerous treatment options available to the patient who tests positive.
    - There is a risk of false negatives (a false negative is a test result that indicates a person does not have a condition, but they really do).
    - There is a need for routine testing.
    - For more information, see California Health and Safety Code 120990.

**Electrocardiogram (ECG):** This non-radiation test measures and records the electrical activity of your heart. The procedure is called a 12-lead ECG because 12 wires will be attached to your chest near your heart, and at your wrists/arms and ankles/legs with adhesive pads. You will be asked to lie still during the procedure. A computer will make a recording of your heart’s electrical activity, which will tell doctors information about how well your heart is working.

**Bone marrow biopsy**, consisting of a standard collection of a sample of the marrow from within a large bone, typically the hip (pelvis). The complete tissue sample, called a “biopsy,” usually has a small piece of bone and a sample of the pulpy marrow material from within the bone, called the “aspirate.” The doctor will give you a local painkiller, and make an incision over the bone to be sampled, and a large needle will be used to collect the sample. Tell the doctor if you think this will make you very uncomfortable.

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The biopsy will be used for a type of microscopic evaluation called “cytogenetics” and other testing to determine or confirm your diagnosis.

**Disease Status / Cancer Assessment:** The extent and severity of your tumor will be assessed during the physical exam above, and by a radiologic evaluation (an “X-ray”) within 28 days of starting study treatment. These scans look at the blood flow and the extent and activity of your cancer, and are a part of your regular medical care (Standard-of-Care, SOC). The radiologic evaluation may be computed tomography (CT) scan; or a magnetic resonance imaging (MRI); or an alternate scan as medically necessary. Regardless of which scan will be conducted, these scans are part of your regular medical care. These procedures are described below:

**CT scan (an “X-ray”)** with or without contrast may be performed according to standard practice. The CT scan will be used to look at the blood flow and the extent and activity of your cancer. This scan is part of your normal medical care. You may be asked to not drink or eat anything (“fast”) for several hours before the scan. The scan will take about 30 to 60 minutes. You will need to remove all jewelry, piercings, and other metal items. A tourniquet will be applied to your arm or leg to help find a vein, and a contrast agent will be injected into a vein. For some patients, the contrast agent may be given orally. The entire scan procedure will take about 30 to 60 minutes. You will be asked to lie still on a long narrow bench, or scanner bed, for up to 45 minutes. You will be asked not to move during the scan and to relax and breathe normally. A strap and/or pillows may be placed across your body to prevent movement. You may experience some discomfort or anxiety from being in the confined space. If this bothers you too much, the study team may provide you with a medication to help you stay calm. During the CT scan procedure, the scanner will rotate around you, and make clicking sounds, which is normal. Tell the CT technician immediately if you have any breathing difficulties; sweating; numbness; or heart palpitations.

**IT IS VERY IMPORTANT THAT YOU IMMEDIATELY TELL THE INVESTIGATOR AND THE CT TECHNICIAN** if any of the following apply to you:

- You are or could be pregnant.
- You have, or previously had, kidney problems.
- You are taking Glucophage (metformin).
- You have any allergies to medications, contrast agents, iodine, or shellfish, or have a history or severe allergies.
- You have recently taken or received barium (“barium study”) or bismuth, or have recently taken Pepto-Bismol; Kaopectate; Maalox; Bismatrol; or other digestive aids.
- You have a cardiac pacemaker or any other biomedical device, such as surgical clips, pins; screws; or metal plates in or on your body.

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- You have any body piercings in or near the area of the scan;
- In some cases, these could mean you should not have a CT scan performed.

**Magnetic Resonance Imaging (MRI):** An MRI, which does not require radiation exposure, may be used in place of a CT “X-ray” scan. The MRI will be performed according to standard practice, and will take about 30 to 60 minutes. MRI machines use a powerful magnet and radiofrequency fields to make images of the body interior, and to evaluate blood flow and the extent of the cancer. An MRI scanner is a large, tunnel-shaped machine, and uses a strong magnet and radiofrequency magnetic fields to make images of the body interior. This magnet is very strong, and will attract or pull on some metals and affect some electronic devices, including magnetic access cards, and the magnetic strip on credit / debit / ID cards. Do not bring any metal objects into the magnet room. Any metal objects that you are carrying or have in your body could be a hazard to you or others. Watches; hearing aids or other removable medical devices; jewelry / rings; credit / debit / ID / access cards should be removed. You will be provided a way to secure these items. Because the magnetic field is so strong, tell the study team now, and also tell the MRI operator before entering the MRI room, if any of the following apply to you.

**IT IS VERY IMPORTANT THAT YOU IMMEDIATELY TELL THE INVESTIGATOR AND THE MRI OPERATOR** if you have a cardiac pacemaker or any other biomedical device in or on your body.

- You have any other metal objects in or on your body, such as:
  - Metal plates; pins; screws; surgical clips
  - Medical devices, including hearing aids
  - Other implants
  - Metal fragments in your body, such as bullet fragments or shrapnel fragments
  - Piercings
- You have ever had a head or eye injury involving metal fragments
- You have ever worked in a metal or fabrication shop
- You have a history of severe allergies, or have previously had a reaction to a Gadolinium-based contrast agents
- You have, or previously had, kidney problems
- You are or could be pregnant
- In some cases, these could mean you should not have an MRI scan performed

The scanning procedure is very much like an X-ray, but uses a strong magnetic field instead of X-rays. You will not be able to feel the magnetic field. You will be asked to lie on a long narrow bench for up to 45 minutes while the machine performs the scan. You will be asked not to move during the scan and to relax and breathe normally. During this time, you will not be exposed to X-rays, but rather the magnetic field. During the

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scan, the bench you are lying on will move into a narrow space in the scanner. Many steps have been taken to make the procedure comfortable, but you may still experience some discomfort or anxiety ("claustrophobia") from being in this confined space. If this bothers you too much, the study team may provide you with a medication to help you stay calm. The scanner will make repetitive tapping noises, which can seem very loud inside the scanner. You may be provided with earplugs or headphones to wear.

**IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.**

**Women of Childbearing Potential**

If you are pregnant or currently breast-feeding, you may not participate in this study. It is not known whether the Study Drug is safe for fetuses or breast-fed babies. A pregnancy test, as described above, will be conducted.

**Location:** The location of the Screening Visit will be in the Stanford Cancer Center Clinics at 875 Blake Wilbur Dr, or as otherwise directed by study staff.

Medical imaging may be performed at the following clinic locations. The Study Team will let you know which locations you need to go to:

Stanford Hospital  
MRI department, ground floor  
300 Pasteur Dr  
Stanford, CA 94305  
Phone [REDACTED]

Stanford Cancer Center,  
Blake Wilbur Building  
Radiology, ground floor  
900 Blake Wilbur Dr  
Palo Alto, CA 94306  
Phone [REDACTED]

Stanford Medicine Outpatient Center  
Pavilion B  
450 Broadway St  
Redwood City, CA 94063  
Phone [REDACTED]

Stanford Medicine Imaging Center  
451 Sherman Ave  
Palo Alto, CA 94306  
Phone [REDACTED]

**Study Treatment**

All participants in this study will receive the anti-cancer study drugs ibrutinib and venetoclax. You may know ibrutinib by the tradename Imbruvica, and venetoclax by the tradename Venclexta. This study tests whether adding venetoclax to ibrutinib therapy improves the overall anti-cancer effect for people with CLL or SLL, independent of mutation status.

All participants will receive ibrutinib 420 mg PO daily, or until your CLL / SLL gets worse (disease progression). Venetoclax treatment will start at Week 9 at 20 mg/day, increasing each week to 50 mg/day; 100 mg/day; 200 mg/day; and finally 400 mg/day, as shown in the following table.

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Your Study Doctor will give you a prescription for a medication such as allopurinol to reduce your blood levels of uric acid before beginning treatment with venetoclax. This is to help minimize the occurrence of a specific type of adverse reaction (tumor lysis syndrome, TLS, discussed later in this document). Treatment with allopurinol or similar may need to be continued for up to 5 weeks.

Week	Venetoclax (mg/day)	Ibrutinib (mg/day)
1	0	420
9	20	420
10	50	420
11	100	420
12	200	420
13	400	420
14 to 61	MTD dose	420
62+	0	420

This dose escalation is the same way venetoclax is normally used, except venetoclax and ibrutinib are not normally used together. On Weeks 14 to 117 of treatment, participants will take either 400 mg/day venetoclax, or the highest dose they could take without having serious side effects.

You will receive the study drugs venetoclax and ibrutinib in childproof bottles. Tell the study team if childproof bottles are a difficulty for you.

**Study Treatment Period Evaluations**

During the treatment period, you will take the study treatments ibrutinib and venetoclax, provided as daily tablets or capsules. Your Study Doctor will provide the study treatments and instructions for days in-between scheduled Study Visits. You will receive a study diary to help you keep track of each study treatment and any adverse effects that you experience. You will also need to record any information related to any symptoms/side effects that you experience while taking the study treatments. You will need to bring this diary back to the clinic for review by the study personnel at every clinic visit. The study team will provide instructions for the completion of the study diary.

Study Visits will be on Treatment Day 1; then Week 5; then weekly for Weeks 9 to 13 (this is when you will be receiving venetoclax); on Weeks 14; 18; 22; 26; 30; 38; 50; and 62, and then every 12 weeks thereafter. The Study Team will tell you how flexible the Study Visit Days are. You will also have to come into the study clinic to provide blood samples ONLY on the day after (ie, 24 hours) your first treatment with venetoclax at Week 9, and on the day after you start a higher dose of venetoclax, ie, Day 2 of Weeks 10, 11, 12, and 13. You will also be asked to come in for a Study Visit if the

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doctor suspects that your cancer has returned (relapsed). The following tests and evaluations will be conducted.

**Medical history:** Your medical information as described above will be reviewed and updated, including any side effects that you have experienced since the previous visit.

**Physical examination:** A physical exam with vital signs and ECOG performance status, as described above, will be conducted.

**Blood collection:** Blood will be collected as described above. Except for the samples to test for blood levels of the study drugs and for cancer mutation testing, the amount of blood collected will be about 1 tablespoon (15 mL).

- CBC with differential (hematology)
- Serum chemistry
- CLL blood test, as described above, if not collected during Screening.
- Blood for tumor burden testing (ClonoSEQ). Less than 1 tablespoon (10 mL) of blood will be collected to evaluate the extent of your cancer. These samples will be collected on Study Day 1 before your first treatment.
- Blood for cancer mutation testing. About 2 tablespoons (30 mL) of blood will be collected to evaluate your cancer for genetic mutations. These samples will be collected on Study Day 1 before your first treatment, and at the Final Study Visit or time of relapse. More information about this type of testing is provided below under “Your Genetic Data / Tissue Sampling for Research and Genetic Testing.”
- Blood to test for study drug levels in your blood (pharmacokinetics, pK). pK samples will be collected on Treatment Day 1, and at study Weeks 9 to 13, and at Weeks 14; 18; 22; 26; and 30. On Treatment Day 1, and Day 1 of Weeks 9 to 13, blood samples will be collected before study treatment, and at about 1 hour; 2 hours; 4 hours; 6 hours; and 8 hours after study treatment (about 2 tablespoons (30 mL) will be collected). On Day 2 of Weeks 9 to 13, you will also have to come into the study clinic for a blood sample collection [about 1 teaspoon (5 mL)]. For Weeks 14; 18; 22; 26; and 30, only a single sample [about 1 teaspoon (5 mL)] will be collected before study treatment for that week.

**Electrocardiogram (ECG):** As described above, if the Study Doctor feels it is necessary to evaluate your current medical condition.

**Bone marrow biopsy:** As described above, if / when the Study Doctor suspects that your cancer may have gotten worse (disease progression).

**Disease Status / Cancer Assessment:** As described above. These assessments will occur at the Study Visit that you start venetoclax (Week 9) and continue weekly through Week 14, and then at Weeks 18; 22; 26; 30; 38; 50; and 62, and then every 12 weeks thereafter. This will include a CT or MRI scan, as described above, at about Week 9; Week 37; and Week 61, and then every 12 weeks thereafter.

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**Adverse event monitoring:** During the treatment period, the Study Doctors will monitor you for any potential side effects. If the side effects are severe, the Study Doctors may temporarily stop study medication; change the dosage of your study medication; or withdraw your medication completely.

**Treatment Discontinuation**

At the time that it is decided you should conclude treatment in this study, you will have a final study visit, and the following tests and procedures/assessments will be performed:

**Medical history:** as described above.

**Physical examination:** as described above.

**Blood collection:** Blood will be collected as described above, for hematology; CLL blood test; and cancer mutation testing. About 1 tablespoon (15 mL) will be collected.

**Disease Status / Cancer Assessment:** As described above, with CT or MRI scan.

**Electrocardiogram (ECG):** As described above, if the Study Doctor feels it is necessary to evaluate your current medical condition.

**Adverse event monitoring:** as described above.

**Location:** The location of the Study Visits will be at the Study Clinic and the Stanford medical imaging locations, as described above.

**End-of-Treatment** (about 30 days after last dose)

When you are finished taking the Study Drugs, you will have the following tests and procedures/assessments.

**Medical history:** as described above.

**Physical examination:** as described above.

**Blood collection:** Blood will be collected as described above, for hematology; blood chemistry; and cancer mutation testing. About 3 tablespoons (45 mL) will be collected.

**Electrocardiogram (ECG):** As described above, if the Study Doctor feels it is necessary to evaluate your current medical condition.

**Location:** The location of the End-of-Treatment Visit will be at Study Clinic and the Stanford medical imaging locations, as described above.

**Study Follow-Up Procedures**

As part of your regular medical care, the study team would like to follow-up with you about every 3 months after you finish study treatment. The following tests and procedures/assessments will be conducted.

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**Medical history:** as described above.**Physical examination:** as described above.**Blood collection:** Blood will be collected as described above, for hematology; blood chemistry; and cancer mutation testing. About 3 tablespoons (45 mL) will be collected.**Adverse event monitoring:** as described above.**Disease Status / Cancer Assessment:** As described above, but without CT or MRI scan or bone marrow biopsy unless medically justified.

If necessary, the study team may ask you to return to the center for additional study tests (“follow-up tests”) to clarify or confirm data already generated in the study.

Throughout the study, you will be told the results of tests that are part of your clinical care, but you may not be told the results of the tests for research purposes only, including the genetic tests and any future research tests.

**Location:** The location of the Study Follow-Up Visit will be at the Study Clinic and the Stanford medical imaging locations, as described above.**Long-term Survival Follow-Up Procedures**

Long-term, the study team may follow-up with you to obtain medical history information, as described above.

**Your Genetic Data / Tissue Sampling for Research and Genetic Testing**

Research using tissues, such as from your research blood sample for cancer mutation testing, is an important way to try to understand human disease. Sometimes, research may include the testing and study of genes, also known as DNA, and related materials called proteins. This type of testing is also called “genetic analysis” or called “pharmacogenomic research.” You are being given this information because the investigators want to include your blood sample in a research project and because they want to save the samples for future research.

There are several things you should know before participating in this study and allowing your blood to be studied in this way. This subject is complicated, and there are many considerations. Ask for more information if you do not understand any part of this information.

Genes are in every cell of your body. Your genes were inherited from your biological parents and carry instructions for the body to grow, develop, and survive. Genes are made of a substance called DNA. Most genes and DNA are identical among human beings, but there are small variations between different people. These small genetic differences are why people have their own unique characteristics, such as hair color, eye color, height, and other characteristics. Some traits affected by genetics are not visible, such as why different people have different responses, including

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side effects, to the same drug. The proteins in your body were determined by your genes, and control how your body works. Differences in genes and therefore proteins can affect the way a disease develops, the way drugs act against the disease, or the way your body uses the drugs.

The purpose of this type of research is to understand the cause of disease or the bodily response to the treatments (such as safety findings or drug level patterns). In this study, the genetic research is being done to see if the treatment reduces the detectable levels of genetic material associated with your kind of cancer.

Agreeing to provide this blood sample is required to participate in this study.

The data from your sample for this genetic research project will be used for research purposes only. This genetic research sample may be used for additional research including: additional studies of CLL or other types of cancer; as a comparison sample ("control sample") in other cancer studies or in a group of other patients' samples to determine the natural difference in genes and proteins in groups of people with cancer; or to develop new gene research techniques. The sample and/or data generated from them will be held by the study team; Stanford; and/or Pharmacyclics LLC (and its affiliates and collaborators, eg, Janssen Biotech, Inc.) for many years. These samples and data generated from them may be used for any purpose including research, which may lead to the development of medical products such as devices, or new drugs or patentable processes and procedures; shared with other researchers; or entered into databases, provided confidentiality is upheld. The information in these databases may be kept forever, however, information that could directly identify you will not be included in these databases.

Although you will be told the results of study tests that are part of your regular medical care, the genetic testing described here will not be used for decisions about your medical care, and there may be no results from this genetic research for many years, therefore the results of the genetic testing may not be given to you, your doctor, or any other staff at the study center.

**Providing genetic information to others**

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

Be aware that that GINA 2008 does not specifically protect you against genetic discrimination by companies that sell life insurance; disability insurance; or long-term care insurance.

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**PARTICIPANT RESPONSIBILITIES**

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Drinks lots of water while receiving treatment, especially when taking venetoclax, to help reduce the chance of a specific type of adverse event (tumor lysis syndrome, TLS, discussed later in this document).
- Be sure to tell the study staff all your present and past diseases, allergies and any drugs or medications you are taking. This is for your safety. Other drugs or medications includes all prescription drugs; over-the-counter (OTC) drugs; herbal preparations; and nutritional supplements. These may interact with the study drugs. If any other medical provider prescribes new medications for you while you are on this study, please contact the study staff before taking the new medicine, or have that medical provider contact the study staff before prescribing it to you. You should not take any new non-prescription medicine while you are on this study unless you first check with the study staff. See the following precautions. The Study Team will give you more information.

**Venetoclax should not be taken with CYP3A inhibitors or potent CYP3A inducers such as warfarin or rifampin.**

**Venetoclax should be taken with caution when using weak or moderate CYP3A inducers, or CYP2C8 and CYP2C9 substrates.**

**Also, do not eat grapefruit or grapefruit products; Seville oranges or products such as marmalade containing Seville oranges; or star fruit from 3 days before your first dose of venetoclax through the last day of venetoclax treatment, completed due to possible metabolic interactions between the fruit and venetoclax .**

- Come to the Study Visits as scheduled.
- Take the Study Drugs as instructed.
- Maintain control of the Study Drugs, and keep them in a safe place where children cannot access them. Follow any additional storage instructions that you are provided with.
- Ask questions as you think of them.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or study team if you change your mind about staying in the study.
- Tell the Protocol Director or study team about any side effects, doctor visits, or hospitalizations that you may have.

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- Tell the Protocol Director or study team if you believe you might be pregnant or gotten your partner pregnant.
- Do not breast-feed an infant. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, breast-feeding should be discontinued during ibrutinib treatment.
- You must use a medically-approved method of birth control, preferably a barrier method, for the duration of the treatment period and for at least 1 month after the last day you receive the Study Drug.
- Keep, complete, and return your study diaries as instructed.

**About Pregnancy**

To participate in this study, you must agree to avoid sexual intercourse or use a highly-effective birth-control method(s). Acceptable methods of birth control are listed below. If you do not use the required birth-control method(s), you may be discontinued from this study. Please ask the Study Doctor or study team if you have any questions.

- Abstinence
- Not able to have children / sterilization (eg, tubal ligation / hysterectomy or vasectomy for the participant or the partner of a monogamous participant)
- Hormonal contraceptive, such as birth control pills (must have 2 hormones) or approved injected or implanted hormonal methods of contraception
  - Hormonal contraceptive must only be used in combination with a barrier method of contraception (eg, condoms or diaphragm)
- Some IUDs (intrauterine devices) or an intrauterine system (IUS)

Any or both methods must be judged by the investigator to be effective, and to not interfere with the study. In particular, use of a hormonal contraception must be approved by the Study Doctor before you begin taking the Study Drug. There is a risk that pregnancy could still result despite the responsible use of a reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

**Women of Childbearing Potential:** If you are a woman capable of having children and choose to have sex, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk, for 12 weeks after your last dose of study drug. The only certain way to be 100% certain you will not get pregnant is to not have sex. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you; the fetus (unborn child); or the child may be exposed to unknown risks. To confirm that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.

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During the study, if you become pregnant, or you think you may be, you must immediately stop taking the Study Drug and tell your Study Doctor. If you become pregnant during the study, the Study Drug may involve unforeseeable risks to the unborn baby, and your pregnancy will be followed to determine the outcome. The Information about you; your pregnancy; and the birth of your child will continue to be collected even after study treatment is stopped.

**Men:** Venetoclax treatment may reduce the ability of a man to produce sperm. In dogs, this effect was not reversible after 4 weeks of dosing. If you are a male and may wish to have children, you should consider sperm banking before treatment with venetoclax. The study team can provide you with more information.

If you are a man, while you are on study treatment and for 12 weeks after your last dose of study drug, you must:

- Prevent pregnancy in your female partners
- Prevent the possible exposure of a pregnant female to the Study Drug from your semen
- You should inform your female partners of the potential for harm to her or a fetus. They should know that if pregnancy occurs, they should promptly notify their doctors
- Not donate sperm
- If your partner becomes pregnant, you need to tell both the Study Team and her physician immediately

Your doctor will discuss with you whether your preference for birth control is considered adequate.

**WITHDRAWAL FROM THE STUDY**

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify [REDACTED]. To help you safely finish your participation in the study, the Study Doctors may ask you to have more tests and you will be asked to come into the clinic for an End-of-Treatment Visit after stopping the Study Drug. The Study Doctor will discuss your treatment options with you at this time. If your participation in the study is ended, you must return all study-related supplies, including unused Study Drug.

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If you withdraw from the study, or the study medication is stopped for any reason,

- Your cancer may get worse.
- To help you leave the study safely, the Study Doctors may ask you to have more tests.
- The Study Doctors may also ask if you wish to take part in the follow-up portion of the study. If you agree to continue with the follow-up portion of the study, information about your health will continue to be collected as described above in the Follow-up Procedures section.
- The Study Doctor will discuss with you the different withdrawal decisions, including your options for continued treatment.
- If your participation in the study ends, you must return all study-related supplies, including unused Study Drug.
- Data and information from your participation may not be removed from the research study database and may continue to be used to complete the research analysis. This is discussed in more detail under the heading “Authorization To Use Your Health Information For Research Purposes” on the following pages.

The Protocol Director may also withdraw you from the study and the study medications may be stopped, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- If your tumor worsens (tumor progression).
- If you have serious side effects during treatment with Study Drug.
- You have become pregnant.
- You need treatment not allowed in the study.
- The study is stopped by the drug manufacturer; the Study Doctor; the Stanford Institutional Review Board (the IRB, a group of people who review the research to protect your rights), or by a regulatory agency such as the US FDA.
- Other administrative reasons.
- Unanticipated circumstances.

**POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES**

There are risks, discomforts, and inconveniences associated with any research study. This section describes the reasonably foreseeable risks; discomforts; and inconveniences that you may experience. In addition, because this is a research study, there may be risks that are not yet known (“unforeseeable”), including a risk of death due to unknown risks. These deserve careful thought.

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You should talk with the Study Doctor if you have any questions. If you do not understand what any of the words in this section or elsewhere mean, please ask the Study Doctor or study staff to explain these terms to you.

You must tell the Study Doctor or Study Team about all side effects that you have. If you experience serious problems, you may be asked to return to the study center for more tests. Furthermore, due to the risk of side effects resulting from different combinations of drugs (called drug-drug interactions), you must inform the Study Team of any medications you are taking, including over-the-counter medicines or herbal remedies, during the course of the study, and you must also notify the Study Doctor of any other medical treatments or procedures that may be necessary for you to undergo. If you are not honest about your side effects and other medications and procedures, it may not be safe for you to stay in the study. All patients in the study will be monitored for side effects. Your Study Doctor may give you medications or stop the study drug(s) for a short time or reduce their dose to try to help lessen some of the side effects.

Each person's reaction to the study drug may be different. You may experience a side effect that could not be predicted by the Study Doctor. Please review the side effects known to be related to the study drug being evaluated in this study. You may experience many, some, or none of the side effects described below. Side effects may be mild, moderate, or severe, and although they usually subside, they could also be permanent. It is possible that a side effect could be fatal.

If you experience serious problems, you may be asked to return to the study center for more tests. If you experience the following symptoms of an allergic reaction, contact the Study Doctor or the Study Team **immediately**. If you are in distress, **CALL 911 immediately**.

- Allergic reaction, including rash, hives and/or itching of the skin, or blisters; increased heart rate (a fast pulse or tachycardia); and/or abnormal or increased sweating
- Swelling of the face, mouth, lips, gums, tongue and/or neck
- Wheezing; shortness of breath; or difficulty breathing
- Dizziness; confusion; feeling light-headed; pounding or racing heart; and/or fainting
- Fever; chills; weakness; confusion; body aches; cold or flu symptoms; and/or feeling tired
- Easy bruising and/or bleeding
- Sudden severe headaches; weakness in the arms or legs; difficulty speaking or understanding speech; and/or loss of balance
- Yellowing of the eyes and skin (jaundice), dark-colored urine; and/or gray- or clay-colored bowel movement (stools);

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- Upset stomach (nausea), loss of appetite; tiredness (fatigue); and/r diarrhea
- Severe skin reactions and/or rash with blisters and peeling skin or spreads quickly, which may include open ulcers or sores in the mouth and other areas of the body

**Venetoclax** has been administered to at least 567 people with cancer. The following side effects (adverse events) were reported to be related to treatment with venetoclax.

**Most Common Side Effects of the Study Drug Venetoclax [these side effects occurred in more than 1 in 10 people taking venetoclax (more than 10%)]**

- Decreased levels of neutrophils in the blood (cells that help fight infection, neutropenia)
- Decreased levels of red blood cells and/or hemoglobin (anemia)
- Decreased levels of platelets in the blood (thrombocytopenia). May cause bruises or even bleeding
- Upset stomach (nausea)
- Diarrhea
- Upper respiratory tract infection (URI)

**Less-likely Side Effects of the Study Drug Venetoclax [these side effects occurred in more than 1 in 100 people taking venetoclax (1% to 10%)]**

- Low white blood cell count (WBC, blood cells that help fight infection) with fever (febrile neutropenia)
- Persistent cough with lung inflammation (bronchitis)
- Lung infection (pneumonia or similar)
- Respiratory tract infection
- Viral upper respiratory tract infection
- Lower respiratory tract infection
- Flu (influenza)
- Common cold (nasopharyngitis)
- Herpes infection (Herpes zoster)
- Oral herpes
- Yeast infection of mouth (oral candidiasis)
- Other Candida infection (candidiasis)
- Urinary tract infection (UTI)
- Bacterial skin infection, may become serious (cellulitis)
- Bacterial infection of the blood (sepsis), a serious condition
- Reduced levels of calcium in the blood (hypocalcaemia)

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- Increased levels of phosphate in the blood (hyperphosphatemia)
- Increased levels of potassium in the blood (hyperkalemia)
- Increased levels of uric acid in the blood (hyperuricemia)
- Tumor lysis syndrome (additional information below)

Following are specific safety warnings and precautions when taking venetoclax.

**Food Effects**

When you eat your meals relative to when you take your venetoclax can change the effects, or the amount of the effect, of venetoclax. Follow the directions of the study team, and try to eat and take your venetoclax at the same time every day.

**Tumor Lysis Syndrome (TLS)**

Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells has occurred with venetoclax treatment, most often right after starting treatment, or if the patient has a large or extensive cancer. The levels of breakdown products in your blood may cause changes in kidney function, abnormal heartbeat, or seizures. This is called tumor lysis syndrome (TLS). Your Study Doctor will give you a medication to reduce the chance of TLS, but may still do blood tests to check for TLS.

**Reduced blood levels of infection-fighting cells (neutropenia)**

Venetoclax treatment may reduce your blood levels of a certain type of white blood cell (WBC), called neutrophils (neutropenia), or in general (leukopenia) in your blood. These types of cells help fight infections, and reduced numbers may mean a greater risk of infection. There may be an increased risk of infection, which can be serious. You may receive an additional medication to help boost the levels of these type of cells.

**Other Blood Effects**

Venetoclax treatment may reduce your levels of red blood cells (RBC), which is called anemia. This may make you feel weak or tired, or worsen how weak or tired you feel due to other causes.

Venetoclax treatment may reduce your blood levels of platelets. This may cause bruises or even bleeding, or worsen how easily you bruise or bleed due to other causes.

**Reproductive Effects**

Venetoclax treatment may reduce the ability of a man to produce sperm. In dogs, this effect was not reversible after 4 weeks of dosing. If you are a male and may want to have children, you should consider sperm banking before treatment with venetoclax. The study team can provide you with more information.

**Second Cancer**

At least 10 people receiving venetoclax have developed a second, new cancer (a different cancer not the same as the first disease). This number does not include

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instances of skin cancer that was not melanoma. Most patients had one or more other risk factors, such as being elderly or having received multiple prior therapies. No pattern was apparent, and no instances of 2<sup>nd</sup> cancer were considered to be related to venetoclax.

**Use with Other Medications, including Vaccines**

There may be risks if venetoclax is used with other medications. Consult your Study Team before taking any additional medications during this study. Talk with your doctor before getting any vaccines during this study. Use of venetoclax may raise the chances of an infection or make the vaccine not work as well.

**Ibrutinib.** The following side effects (adverse events) were reported in people receiving ibrutinib.

**Most Common Side Effects of the Study Drug Ibrutinib (these side effects occurred in at least 1 in every 5 people taking ibrutinib, 20% or more)**

- Muscle and joint pain (musculoskeletal pain)
- Low white blood cell count (WBC, blood cells that help fight infection) (neutropenia)
- Bruises
- Rash
- Upset stomach (nausea)
- Increase in frequency of diarrhea (loose or watery stools)

**Less-likely Side Effects (these side effects occurred in at least 1 in every 10 people taking ibrutinib; 10% or more)**

- Common cold (upper respiratory tract infection)
- Lung infection (pneumonia)
- Sores in the mouth (stomatitis)
- Sinus infection (sinusitis)
- Skin infection
- Fever (pyrexia)
- Low platelet count (cells that help blood to clot) (thrombocytopenia)
- High blood pressure (hypertension)
- Headache
- Joint aches (arthralgia)
- Vomiting
- Constipation

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- Swelling of the hands or feet (peripheral edema)
- Muscle spasms

**Unlikely Side Effects (these side effects occurred in at least 1 in every 100 people taking ibrutinib; 1% or more)**

- Non-melanoma skin cancer, such as basal cell carcinoma (BCC) or squamous cell carcinoma
- Severe infection throughout the body (sepsis)
- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Abnormal heart rhythm (atrial fibrillation)
- Urinary tract infection (UTI)
- Increased level of uric acid in the blood (hyperuricemia)
- Dizziness
- Nose bleed (epistaxis)
- Small red or purple spots caused by bleeding under the skin (petechiae)
- Low white blood cell count (WBC, blood cells that help fight infection) with fever (febrile neutropenia)
- Increase in WBC counts (leukocytosis)
- Increase in lymphocyte (a type of WBC) count (lymphocytosis)
- Blurry vision
- Skin redness (erythema)
- Fingernails or toenails breaking (onychoclasia)

**Rare Side Effects (these side effects occurred in less than 1 in every 100 people taking ibrutinib; less than 1%)**

- High levels of cancer cell breakdown products, which may lead to changes in kidney function, abnormal heartbeat, or seizures (tumor lysis syndrome)
- Bleeding around the brain (subdural hematoma)
- Liver failure (hepatic failure)
- High WBC count with abnormal clumping that can lead to bleeding (leukostasis syndrome)
- Inflammation of the fatty tissue underneath the skin (panniculitis)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- Swollen face, lip, mouth, tongue or throat (angioedema)
- Itchy rash (urticaria)

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- Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachyarrhythmia)

**Serious Side Effects of Ibrutinib – Contact your Study Doctor IMMEDIATELY.**

Most of these side effects listed above have been mild to moderate in severity; however severe side effects have occurred. Some side effects have been severe enough to lead to study drug discontinuation, dose modification or reduction, hospitalization, disability, and sometimes death. If any of the events below happen, contact your Study Doctor **immediately** to help prevent the event from getting worse. If the event gets worse or you are in distress, **CALL 911**. Your study doctor may also choose to stop ibrutinib for a short time or reduce its dose to allow you to recover from any side effects.

**Effects on the heart**

Abnormal heartbeats (atrial fibrillation; atrial flutter; and/or ventricular tachyarrhythmia) have been reported in patients treated with ibrutinib especially when they also have had heart conditions; increased blood pressure; infections; or an abnormal heartbeat in the past. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart; chest discomfort; shortness of breath; dizziness; fainting; feeling light-headed; and/or weakness. You should seek medical attention and notify your Study Doctor **immediately** if you develop any of these symptoms while receiving the study drug.

**Interstitial lung disease (ILD)**

Interstitial lung disease is a group of lung disorders in which the tissues become inflamed and may become damaged. Interstitial lung disease is not associated with infections (eg, bacteria, viruses, fungi) and has been reported in patients treated with ibrutinib. You should report to your physician if you have cough; or any signs of new or worsening respiratory symptoms, such as shortness of breath or difficulty breathing. Notify your Study Doctor **immediately**, as these symptoms could also be due to other events, such as heart problems (see above).

**Tumor Lysis Syndrome (TLS)**

Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your study doctor may do blood tests to check for TLS.

**Non-Melanoma Skin Cancer and Other Cancers**

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and may be related to the use of ibrutinib. Other cancers have been reported such as solid tumors and blood cancers,

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but their relationship to the use of ibrutinib is unknown. You should tell your study doctor if you develop a new cancer while in the study.

### Hypertension

Hypertension is also called high blood pressure, and has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your study doctor know if you have any of the symptoms of high blood pressure which may mean that you have developed hypertension or that your hypertension is getting worse. Your study doctor may adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

### Infections

You may experience viral, bacterial, or fungal infections during treatment with ibrutinib. Some of these infections have been associated with hospitalization and death. Contact your Study Doctor **immediately** if you have fever; chills; weakness; confusion; body aches; cold or flu symptoms; vomiting; jaundice; feel tired; or feel short of breath. These could be signs of a serious infection. Your study doctor may start or continue medication to help prevent or treat an infection.

A rare and usually fatal viral disease in the brain, progressive multifocal leukoencephalopathy (PML), has been reported in patients treated with ibrutinib in combination with rituximab and in patients who were previously treated with rituximab. If you experience symptoms such as weakness, paralysis, vision loss and/or impaired speech, you should seek medical attention **immediately** and also tell your Study Doctor.

### Bleeding effects

You may experience bruising or bleeding during treatment with ibrutinib. Rarely, serious or fatal internal bleeding may occur, such as bleeding in your stomach, in your intestine, or in or around your brain, sometimes resulting in death. 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. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided while taking ibrutinib.

Seek medical attention **immediately** and also call your Study Doctor if you have signs or symptoms of severe bleeding in or around the brain such as sudden severe headaches; weakness in the arms or legs; difficulty speaking or understanding speech; or loss of balance. You should also seek medical attention **immediately** and notify your Study Doctor if you have signs or symptoms of serious

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bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.

**Lymphocytosis and leukostasis**

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

**Decreased blood counts**

Severe decreases in white blood cells, red blood cells, and platelets (neutropenia, anemia, and thrombocytopenia) were reported in subjects treated with ibrutinib. If you experience symptoms such as fever; weakness; or easy bruising and/or bleeding; you should tell your Study Doctor **immediately** and seek medical attention.

**Liver Failure**

Rare cases of liver failure have been reported in patients treated with ibrutinib. Symptoms of liver failure include yellowing of the eyes and skin (jaundice), itching of the skin, dark-colored urine; gray- or clay-colored bowel movement (stools); confusion; upset stomach (nausea), loss of appetite; tiredness (fatigue); or diarrhea. You should tell your Study Doctor **immediately** if you have any of these symptoms which may suggest liver disease. Your Study Doctor may be able to diagnose and provide you required medical care.

**Allergic reactions**

Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction to the study drugs, you might develop a rash; difficulty breathing; wheezing when you breathe; sudden low blood pressure with light-headedness; swelling around the mouth, throat or eyes; a racing heartbeat; and/or abnormal or increased sweating. Before starting the study drug, you must tell your Study Doctor about any drug allergies. You should tell the Study Doctor **immediately** if you have any allergy symptoms listed above.

**Rash**

A maculopapular rash (flat, red areas on the skin with small bumps) has been commonly reported in patients treated with ibrutinib alone or in combination with other drugs. Most rashes are mild to moderate in severity and begin 2 to 3 weeks or longer after starting ibrutinib.

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There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction or “SCAR,” involving more than 50% of the body), and/or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas of the body (Stevens-Johnson Syndrome). These skin rashes could be life-threatening. You should notify your Study Doctor **immediately** if you develop a rash that spreads quickly, or if you notice peeling of your skin, with or without ulcers or sores in your mouth.

**Interference with other drugs**

Some juices or foods like grapefruit 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, including fish oil, Vitamin E, or other vitamins, may change how your regular medications, or your regular supplements, work. It is very important that you avoid grapefruit juice and Seville oranges and tell the Study Doctor about all medications, supplements, or herbal medicine like St John’s wort that you are taking during the study. You should notify your Study Doctor **immediately** about any side effects to avoid possible harm.

**Other Serious Side Effects of Ibrutinib****Lymphocytosis and leukostasis (increases in WBC)**

You may experience an increase in the number of lymphocytes, which is a type of white blood cell, in your blood (lymphocytosis). This may occur in the first few weeks of treatment and you should not assume that this increase in white blood cells means that your disease is worsening. This increase may last for several weeks to months. Increased number of white blood cells in your bloodstream may change the blood flow resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in patients treated with ibrutinib. It is not clear whether ibrutinib will increase the number of total white blood cells in the blood, not just the lymphocytes. This is something the Study Team will be looking out for. Your Study Doctor will monitor your blood counts and may administer additional therapy as needed. Talk to your Study Doctor about what your test results mean.

**Tumor Lysis Syndrome (TLS)**

Tumor lysis syndrome (TLS), discussed above, may occur with ibrutinib treatment, and may cause changes in kidney function, abnormal heartbeat, or seizures. Your Study Doctor may do blood tests to check for TLS.

**High blood pressure (hypertension)**

High blood pressure, also called hypertension, has been commonly-reported in subjects treated with ibrutinib. Sometimes people with high blood pressure may have headaches; dizziness; nervousness; sweating; difficulty in sleeping; facial flushing or

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nosebleeds; but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your Study Doctor know if you have any of the symptoms of high blood pressure, which may mean that you have developed hypertension or that your hypertension is getting worse. Your Study Doctor may adjust existing anti-hypertensive medications and/or start anti-hypertensive therapy as appropriate.

**Non-Melanoma Skin Cancer and Other Cancers**

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and maybe related to the use of ibrutinib. Other cancers have been reported such as solid tumors and blood cancers, the relationship to the use of ibrutinib is unknown. You should tell your Study Doctor if you develop a new cancer while in the study.

**Drug interruption for any surgical procedures**

Ibrutinib may increase the risk of bleeding with any surgical procedure. Ibrutinib should be held at least 3 to 7 days before and after surgery depending upon the type of surgery and the risk of bleeding. For emergency surgical procedures, ibrutinib should be discontinued (stopped) after the procedure until the surgical site is reasonably healed (not oozing fluid).

Please contact your Study Doctor if you have any surgical procedures and your Study Doctor will tell you when to stop ibrutinib and when to restart it following a surgical procedure.

**Use with Other Medications, including Vaccines**

There may be risks if ibrutinib is used with other medications. Consult your Study Team before taking any additional medications during this study. Talk with your doctor before getting any vaccines during this study. Use of ibrutinib may raise the chances of an infection or make the vaccine not work as well.

**Risks of Ibrutinib during the Maintenance Phase**

The effects and safety of ibrutinib as maintenance therapy is unknown.

You may have all, some, or none of the listed side effects of ibrutinib. Please tell the Study Doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think they are related to the study drug. Your Study Doctors and nurses will check you closely for side effects. You may receive medicines or other treatments to prevent or reduce some of these effects. In addition to the risks listed above, there could be unknown or unexpected side effects associated with the use of ibrutinib. You will be told in a timely manner, verbally and in writing, of any new information, findings, or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

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You should get medical help and contact the Study Doctor or study staff if you have any of these or any other side effects during the study.

In addition, there are other risks and possible discomforts you might experience from the study procedures. The following discusses procedure risks related only to the research, and does not include risks of procedures that should be discussed as part of your regular medical care.

- Blood draws: A blood draw may cause fainting; inflammation of the vein; stinging, discomfort, or pain; bruising; discomfort; redness; burning; or bleeding at the site where the needle is placed to draw the blood. There is a slight chance of infection. You may feel dizzy or you may faint. If you feel faint, you should immediately lie down to avoid falling
- ECG: Risks from an ECG can include skin irritation and/or a rash from the gel, or from wearing or removing the patches.
- MRI: The very strong magnetic fields of the MRI machine do not cause generally cause harmful effects at the levels used in the machine. However, there are some important considerations. The magnet will attract or even move some metals and affect or damage some electronic devices. Exposure of the following to MRI magnetic fields may cause harm to you or others.
  - Artificial heart valve; a pacemaker; or any other biomedical device in or on your body. These devices could malfunction when exposed to the very strong magnetic field.
  - Metal plate; pin; screws; surgical clips; metallic fragments; or any other metallic implant in your body. These pieces of metal could move while in your body, causing possible serious injury or death.

In addition, when you are in the MRI scanner, you may experience discomfort or anxiety due to the small amount of space inside the machine, or from the loud noises the MRI scanner makes. You may receive a medication to calm you if you need help with this.

If you have a history of severe allergies (eg, bee-sting reaction, food, shellfish, or nut reactions), or have previously had a reaction to medications or contrast agents, in particular, Gadolinium-based contrast agents, you may be at risk of a serious reaction, which can be severe and/or life-threatening, including breathing difficulty; sweating; numbness; or heart palpitations. Tell the study team or technician **immediately if you experience these.**

- Radiologic imaging: X-ray / CT scans. A CT scan exposes you to radiation (discussed below). When you are in the scanner, you may experience discomfort or anxiety due to be in the small amount of space inside the machine, or from the loud noises the scanner makes. If you become anxious or concerned in tight spaces, or from loud noises, tell the study team or technician before the scan. You may receive a medication to calm you if you need help with this.

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- Bone marrow biopsy: The most common side effects, which are usually minor, include pain; discomfort; bleeding; swelling; scarring; bruising; infection; and fever. In extremely rare cases, an allergic reaction to the local anesthetic used to numb the biopsy site can occur. This is a routine procedure, and established institutional procedures will be followed.
- Pregnancy / Reproductive Risk: There may be known or unknown risks to a fetus (unborn child) or the pregnant woman, even if it is the man participating in this study. The effects of ibrutinib on a developing fetus or a child are also unknown; therefore women who are pregnant or nursing are not allowed to be in this study. Nobody knows what these risks are right now. Some of these drugs cause women to have premature (early) delivery, or to have a child with birth defects. There is a risk that pregnancy could still result despite the responsible use of reliable method of birth control. Detailed information about preventing pregnancy is given elsewhere in this document.
- Women of childbearing potential: If you believe you might be pregnant, or even if you experience a menses cycle (“have your period”), you must inform the Protocol Director or study team immediately.
- Breast-feeding: It is not known whether ibrutinib or its metabolites are excreted in human milk. Nobody knows what these risks are right now. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ibrutinib, breast-feeding should be discontinued during ibrutinib treatment.
- Genetic research risks: This research involves genetic studies and information. Procedures have been put into place that are designed to make it very difficult for the results from genetic research to be linked to you. However, even without your name or other identifiers, your genetic information is unique to you, and there is a remote possibility that someone could trace the information in a central database back, and identify you. There is a remote possibility information from your participation in this study could adversely affect you or your family in some way if a genetic disorder were discovered.
- Personal anxiety: Following are some common concerns that research subjects may have.
  - You may be asked sensitive or private questions which you normally do not discuss. It may be necessary to answer some of these questions related to your health and medical status.
  - You may feel embarrassed during the physical exam. You may request that the physical exam be done by a clinician of the same gender.
  - You may be concerned about your personal information being revealed. Although the Study Team; the IRB; and FDA do their best to protect your personal information, this cannot be absolutely guaranteed.

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- Other risks: Since venetoclax and ibrutinib are investigational when taken in combination, there may be other risks that are unknown (“unforeseeable”) at this time.
- You may experience some inconvenience due to the schedule and length of Study Visits. Your doctor may require that you remain in the clinic until very late in the day or that you even stay overnight in order to comply with the requested blood sampling schedule on some of the pharmacokinetic (PK) days.

**It is important that you report all symptoms and side effects that you experience as soon as they occur, whether or not you think they are caused by the Study Drug. Contact the Study Team at [REDACTED] or via the Nurse Coordinators at [REDACTED] (24 hour number). If you are unable to reach anyone at the number(s) listed above, and you feel you may need medical attention, call 911 or go to the nearest emergency room.**

**POTENTIAL BENEFITS**

It is possible that your condition or health may improve because of your participation in this study. The use of the study treatment, venetoclax plus ibrutinib may help to treat your disease. However, there is no guarantee that you will benefit in this or any other way.

Although you may not directly benefit from participation in this study, information learned from this study may help other people in the future, including other people with cancer.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

**ALTERNATIVES**

You do not have to be in this study to receive treatment for your CLL or SLL. Possible alternative treatments and side effects of these treatments depend on the characteristics and stage of your cancer. The effectiveness and side effects of other treatments may be different for different people. Instead of taking part in this study, you may choose to:

- Receive treatment with other chemotherapy drugs, including those approved for use in the US, including fludarabine; bendamustine; rituximab; cyclophosphamide; and others, alone or in combination. There are numerous treatments that may or may not be suitable for the specifics of your cancer.
- Participate in another research study with a different study drug or procedure
- While your type of cancer may be treatable with currently approved and available medications and procedures, another alternative is to receive only comfort care,

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also called “palliative care,” like painkillers. These types of treatments do not treat your cancer (ie, are not curative), and only make you comfortable (symptom relief). If you think you might prefer comfort care, please discuss this with your family, friends, and doctor. NOTE: The Study Doctors do not recommend this decision for you at this time, although it is and will remain your decision.

The Study Doctors will discuss with you the risks and benefits of these alternatives, including which other treatments might be suitable for you.

If you decide that you do not wish to take part in this study and wish to pursue any of these, or other alternatives, this will not change your regular medical care or the other treatment choices in any way.

**PARTICIPANT’S RIGHTS**

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Study Director. You can also tell any other member of the study staff.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study. After you hear about this information, you have the right to withdraw from the program.

**ClinicalTrials.gov**

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by US 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.

The description of this clinical trial is at <https://clinicaltrials.gov/ct2/show/NCT03045328>.

**CONFIDENTIALITY**

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.

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Patient information may be provided to Federal and other regulatory agencies as required. The US FDA, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of venetoclax and ibrutinib. The results will be provided to the drug manufacturers AbbVie Inc. and Pharmacyclics, LLC; their affiliates and collaborators (eg, Janssen Biotech, Inc.); the Food and Drug Administration (FDA); and other federal and regulatory agencies as required.

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## Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

### What is the purpose of this research study and how will my health information be utilized in the study?

This study may help the drug manufacturers and FDA determine if development of venetoclax plus ibrutinib as a combination treatment should continue. Information from this study will be submitted to the companies supporting this study (AbbVie Inc and Pharmacyclics LLC, and their affiliates and collaborators, eg, Janssen Biotech, Inc.) and international regulatory agencies including the FDA. The results from this research study are expected to be presented at scientific or medical meetings or published in scientific journals. **You will not be personally identified in the publications, although representatives of the sponsor and FDA and other international regulatory agencies may need to know who you are.**

### Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment.

Signing the form is not a condition for receiving any medical care outside the study.

### If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in

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the study, except to the extent that the law allows us to continue using your information (eg, necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to:

[REDACTED]  
875 Blake Wilbur Dr, MC 5821  
Stanford, CA 94305

**What Personal Information Will Be Obtained, Used or Disclosed?**

Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to identifiers such as your name and initials; address including ZIP code; phone numbers; dates including date of birth; age; sex; race; ethnicity; Medicare ID number; medical record number (MRN); and other numbers or codes such as your study ID number that might identify you. During the study, researchers will also obtain information about your health status, life-style choices, medical history, and medical diagnoses, including family medical history and allergies; your current and past medications or therapies; your physical examination results including height and weight, blood pressure readings, heart rate, breathing rate and temperature; your laboratory test results including blood, urine, and pregnancy tests; results of procedures, such as cancer assessments, medical scans including MRI and CT scans, bone marrow aspiration/biopsy; results of genetic and biomarker testing; and medical reports, such as the discharge summary and radiology, post-operative, and pathology reports. **The researchers will also get information from your medical record (including hospital records from the Stanford Healthcare and your referring physician’s records).**

**Who May Use or Disclose the Information?**

The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director [REDACTED]
- Research Staff
- The Stanford University Administrative Panel on Human Subjects in Medical Research; the Stanford Data and Safety Monitoring

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Committee (DSMC); and/or any other unit of Stanford University as necessary

**Who May Receive or Use the Information?**

The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- Pharmacocyclics LLC (and its affiliates, eg, Janssen Biotech Inc.), and AbbVie, Inc., or their representatives
- The Food and Drug Administration (FDA) and/or other state or international regulatory authorities
- The Office for Human Research Protections (OHRP) in the US Department of Health and Human Services (DHHS)
- The US Centers for Medicare & Medicaid Services (CMS), the agency responsible for administration of the Medicare program
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

**When will my authorization expire?**

Your authorization for the use and/or disclosure of your health information will end on 31 December 2066 or when the research project ends, whichever is earlier.

**Will access to my medical record be limited during the study?**

To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (eg, if included in your official medical record).

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\_\_\_\_\_  
Signature of Adult Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Printed Name of Adult Participant

\_\_\_\_\_  
*If needed:* Signature of Legally Authorized Representative (LAR)

\_\_\_\_\_  
Printed Name of LAR

\_\_\_\_\_  
Date

\_\_\_\_\_  
LAR's Authority to Act for Participant  
(e.g., parent, guardian, or conservator)

***NOTE:*** *If using the Short Form Consent process for informed consent in another language pursuant to an "Alteration of HIPAA Authorization," neither the participant nor their LAR should sign the HIPAA "Authorization To Use Your Health Information For Research Purposes" above.*

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**FINANCIAL CONSIDERATIONS****Payments**

You will not be paid to participate in this research study. There is no reimbursement offered for any expenses related to your participation in this study.

This study includes the collection of research samples. Any of your samples which are used in research may result in new products; tests; or discoveries. In some instances, these products may have commercial value, and may be developed and owned by the study team; Stanford University; Pharmacyclics LLC (and its affiliates and collaborators, eg, Janssen Biotech, Inc.) and/or others. However, donors of samples do not retain any property rights to the samples or data derived from them. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

**Costs**

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the Study Visits.

You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance.** Participation in this study is not a substitute for health insurance.

Some insurance companies or other 3<sup>rd</sup>-party payers may not pay for standard-of-care procedures or laboratory tests, including hospitalization, when they are done as part of a research study. You should consult with your health benefit plan to determine whether your medical costs associated with your care during this study are covered.

**Funding Source**

Pharmacyclics LLC is providing financial support and/or materials (ie, study drugs) for this study. AbbVie, Inc is providing materials (ie, study drugs) for this study.

**Consultative or Financial Relationships**

Dr. Coutre receives no direct compensation from Pharmacyclics and/or AbbVie for the conduct of this study.

**COMPENSATION for Research-Related Injury**

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop

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medical complications from participating in this study. If such complications arise, the Protocol Director and the research study team will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, **you may be responsible for these costs.** If you are unable to pay for such costs, the Protocol Director and/or the research study staff will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

You do not waive any liability rights for personal injury by signing this form.

**CONTACT INFORMATION**

**Questions, Concerns, Complaints, or to Report an Injury or Side Effect:** If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the Protocol Director, [REDACTED]. You should also contact him at any time if you feel you have been hurt by being a part of this study.

If you are unable to reach anyone at the number(s) listed above, and you feel you may need medical attention, call or go to the nearest emergency room.

**Independent Contact:** If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at ([REDACTED]) or toll-free at ([REDACTED]). You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4<sup>th</sup> Floor, Palo Alto, CA 94306.

**Alternate Contact:** If you cannot reach the Protocol Director, or if you need to change your appointment, please contact the Study Team at ([REDACTED]).

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**EXPERIMENTAL SUBJECT'S BILL OF RIGHTS**

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- Be informed of the nature and purpose of the experiment;
- Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- Be given a description of any attendant discomforts and risks reasonably expected;
- Be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- Be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- Be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- Be given an opportunity to ask questions concerning the experiment or the procedures involved;
- Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- Be given a copy of the signed and dated consent form; and
- Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

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**STANFORD UNIVERSITY Research Consent Form**

Protocol Director: Steven E. Coutre, MD

*IRB Use Only*

Approval Date: November 14, 2018

Expiration Date: [REDACTED]

Protocol Title: An Open-Label Trial of Venetoclax with Ibrutinib in Relapsed and Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia

May we contact you about future studies that may be of interest to you?      **Yes**      **No**

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

\_\_\_\_\_  
Printed Name of **Adult Participant**

\_\_\_\_\_  
Signature of Adult Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
*If needed:* Printed Name of **Legally Authorized Representative (LAR)**

\_\_\_\_\_  
Signature of LAR

\_\_\_\_\_  
Date

\_\_\_\_\_  
LAR's Authority to Act for Participant (eg, parent, guardian, or conservator)

\_\_\_\_\_  
Printed Name of **Person Obtaining Consent (POC)**

\_\_\_\_\_  
Signature of POC

\_\_\_\_\_  
Date

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short-form foreign language informed consent document.

\_\_\_\_\_  
Printed name of **witness**

\_\_\_\_\_  
Signature of witness

\_\_\_\_\_  
Date

(eg, staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

The translated short form must be signed and dated by **BOTH** the participant (or their LAR) **AND** the witness.

The English consent form ("referred to as the "Summary Form" in the regulations"):

- Must be signed by **BOTH** the witness **AND** the Person Obtaining Consent (POC).
- The non-English speaking participant / LAR does **NOT** sign the English consent.
- The non-English speaking participant / LAR should **NOT** sign the HIPAA participant line.
- If the participant / LAR is non-English speaking, the POC must ensure that:
  - 1) The LAR's Description of Authority is completed, and
  - 2) Any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process. .

Participant ID: \_\_\_\_\_