THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT/AUTHORIZATION FOR PARTICIPATION IN RESEARCH WITH OPTIONAL PROCEDURES

Ponatinib as Second Line Therapy for Patients with Chronic Myeloid Leukemia in Chronic Phase Resistant Second Generation Tyrosine Kinase Inhibitors

2012-0669

Study Chair: Elias Jabbour

_____ _____
Participant's Name Medical Record Number

This is an informed consent and authorization form for a research study. It includes a summary about the study. A more detailed description of procedures and risks is provided after the summary.

This research has been reviewed and approved by the MD Anderson Institutional Review Board (IRB - a committee that reviews research studies).

STUDY SUMMARY

You are being asked to take part in this study because you have chronic myeloid leukemia (CML) that has not responded to a type of therapy called second generation Tyrosine Kinase Inhibitors (such as bosutinib, dasatinib, and nilotinib).

The goal of this clinical research study is to learn if ponatinib can help to control CML in chronic phase. The safety of this drug will also be studied.

This is an investigational study. Ponatinib is FDA approved to treat patients with certain types of leukemia. Its use in this study is investigational.

Ponatinib is designed to block the function of BCR-ABL, which is the abnormal protein responsible for causing CML. This may cause the cancer cells to die.

Taking the study drug may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. **If you take part in this study, you should know that Ponatinib may cause a blood clot to form in an artery or in a vein.** Depending on the location of the clot, this could cause a heart attack, a stroke, severe damage to other tissue, or death. A blood clot may occur within 2 weeks after you start taking the drug. About 25% (1 in 4) of patients taking the drug form an abnormal clot. Blood clots can occur in patients that do not have other known risk factors for forming clots. If you develop a blood clot, you will need to stop taking ponatinib. In some cases, emergency surgery could be needed to remove the clot and restore blood flow.

You can read a list of potential side effects below in the Possible Risks section of this consent.

You may take the study drug for up to 5 years. You will be taken off study early if intolerable side effects occur, if the disease gets worse, or if you are unable to follow study directions. Your participation on the study will be over when you have completed the follow-up visit/call (described below).

Ponatinib will be provided at no cost to you during the study.

You may choose not to take part in this study. You may choose to receive standard therapy drugs, such as continuing second generation Tyrosine Kinase Inhibitors (bosutinib, dasatinib, or nilotinib). You may choose to receive a stem cell transplant. You may choose to receive other investigational therapy, if available. The study doctor will discuss with you the possible risks and benefits of these treatments. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. You will have screening tests to help the doctor decide if you are eligible to take part in this study. The following tests and procedures will be performed within 28 days before your first dose of study drug:

- Your medical history and any drugs you are taking will be recorded.
- You will have a physical exam.
- You will be asked how well you are able to perform the normal activities of daily living (performance status).
- Blood (about 3 teaspoon) will be drawn for routine tests and to check the status of the disease.
- You will have an electrocardiogram (EKG) to check your heart function.

- If you have not had one in the last 3 months, you will have a bone marrow aspirate to check the status of the disease. To collect a bone marrow aspirate, an area of the hip or other site is numbed with anesthetic, and a small amount of bone marrow is withdrawn through a large needle.
- If you are able to become pregnant, you will have a blood (about 1 teaspoon) or urine pregnancy test. To take part in this study, you must not be pregnant.

The study doctor will discuss the screening test results with you. If the screening tests show that you are not eligible to take part in the study, you will not be enrolled. Other treatment options will be discussed with you.

Up to 50 participants will be enrolled in this study. All will be enrolled at MD Anderson.

Study Drug Administration

You will take ponatinib by mouth 1 time every day while you are on study with about a cup (8 ounces) of water. You may take ponatinib with or without food. If you vomit a dose, you should not take ponatinib again to make up for that dose. You should wait until your next scheduled dose. You should avoid taking antacids 2 hours before or after ponatinib. Your doctor will discuss other drugs that you cannot take with ponatinib.

Study Visits

The study staff will help you schedule your study visits. The following tests and procedures will be performed:

- Blood (about 1/2 tablespoon each time) will be drawn for routine tests every 1-2 weeks for the first 4 weeks, every 4-6 weeks for the first year, every 3-4 months for second year, then every 4-6 months after that. These tests can be done by your home doctor and sent to your study doctor.
- You will have an EKG every 3 months for the first year.
- You will have a physical exam and you will be asked about any drugs you may be taking and any side effects you may be having every 3 months for the first year, then every 6-12 months after that.
- Blood (about 2 teaspoons) will be drawn to check the status of the disease every 3-4 months for the first year, then every 6-12 after that.
- You will have a bone marrow aspirate for genetic testing and to check the status of the disease every 3-4 months for the first year, then every 6-12 months for the next 3 years.
- You will have an echocardiogram (ECHO) at 3 months and 12 months from the time you started the treatment.

If the disease gets worse or the disease never responds to treatment with ponatinib, blood (about 1 tablespoon) will be drawn within 30 days after your last dose of ponatinib to check for changes in the BCR-ABL protein which may explain why there was no response to the study drug.

Follow-Up
Within 30 days after you leave the study, you will be called or you will come to the clinic to learn about any side effects or symptoms you may be having. If you are called, this call will last about 2-3 minutes.

Your Responsibilities
If you take part in this research, you will be responsible for telling the study team about any symptoms or side effects you have, following study directions, and coming to all study appointments (or contacting the study team to reschedule).

2. POSSIBLE RISKS

While on this study, you are at risk for side effects. These side effects will vary from person to person. The more commonly occurring side effects are listed in this form, as are rare but serious side effects that the drug is known to cause. You should discuss these with the study doctor. You may also want to ask about other uncommon side effects that have been observed in small numbers of patients but are not listed in this form. Many side effects go away shortly after the drug is stopped but in some cases, side effects may be serious, long-lasting or permanent, and may even result in death and/or hospitalization.

Tell the study staff about any side effects you may have, even if you do not think they are related to the study drug.

Ponatinib Side Effects

Common (occurring in more than 20% of patients)

• high blood pressure • swelling (arm/leg) • heart attack • blood clots in an artery (possible organ damage such as stroke and/or heart attack) • blood clots in a vein (possible pain, swelling, and/or redness) • blood vessel disorder (possible tissue death) • fatigue • weakness • headache	• skin rash • dry skin • high blood sugar (possible diabetes) • low blood sugar • abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood pressure, organ failure, heart problems, changes in mental status, and/or seizure) • abdominal pain • constipation	• vomiting • mouth blisters/sores (possible difficulty swallowing) • digestive system bleeding • abnormal digestive blood test (possible pancreas inflammation/damage) • low blood counts (white, red, platelet) • abnormal liver tests (possible liver damage) • pain (joint/muscle)

• fever • bleeding in the brain • stroke	• nausea • loss of appetite • diarrhea	• difficulty breathing • severe life-threatening infection (possible low blood pressure, kidney failure, and/or heart failure)

Ponatinib may commonly cause low blood cell counts (white blood cells, red blood cells, and/or platelets).

- A low white blood cell count increases your risk of infection (such as pneumonia and/or severe blood infection). Infections may occur anywhere and become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.
- A low platelet count increases your risk of bleeding (such as nosebleeds, bruising, stroke, and/or digestive system bleeding). You may need a platelet transfusion.
- A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.

Occasional (occurring in 3-20% of patients)

• fast/irregular heartbeat • heart and/or lung failure • decreased blood supply to the heart • heart and/or blood vessel disease • shock caused by heart damage • build-up of fluid in the tissue around the heart • decreased supply of blood through the arteries (possible tissue death) • difficulty sleeping • dizziness • chills • sweating • flushing • itching • hair loss (partial or total)	• weight loss • abdominal swelling • upset stomach • dry mouth • problems with urination • high blood levels of uric acid (possible painful joints and/or kidney failure) • impotence • abnormal liver tests (possible yellowing of the skin and/or eyes) • blood clots in a vein to the liver (possible liver and/or digestive system damage) • pain (arm/leg/back/bone) • muscle spasms • nerve damage (possible numbness, pain, and/or loss of	• blood clot inside the eye (possible blindness) • eye irritation/pain • swelling under the central part of the retina (possible vision loss) • bleeding in the eye • dry eyes • blurry vision • blood clot inside the eye (possible blindness) • abnormal kidney test (possible kidney damage) • fluid in or around the lung (possible difficulty breathing) • blockage in the lung (possible pain, shortness of breath, and/or failure to breathe)

• high blood levels of fat (possible heart disease and/or stroke) • underactive thyroid gland (possible weight gain, heart failure, and/or constipation) • inflammation of the pancreas (possible abdominal pain)	motor function) • abnormal sensation (such as pins and needles) • muscle spasms	• cough • voice changes (possible hoarseness) • infection

Rare but serious (occurring in fewer than 3% of patients)

• slow heartbeat • reduced blood supply to the arms and legs • narrowing of the arteries (possible high blood pressure, fatigue, and/or weakness) • swelling of the brain (possible headache and/or mental status changes) • temporary stroke symptoms • painful skin bumps • fluid in the abdomen	• abnormal connections or passageways between different parts of the digestive system • hole in the intestines (possibly leaking contents into the abdomen) • nerve damage (affecting the head and neck) • blindness • cataracts (clouding of the lens of the eye) • increased pressure in the eye (possible vision loss)	• inflammation of the eye and/or inside the eye (possible sores on the eye) • narrowing of the arteries that carry blood to one or both of the kidneys • allergic reaction (such as a skin reaction) • breakdown products of the cancer cells entering the blood stream (possible weakness, low blood pressure, muscle cramps, kidney damage, and/or other organ damage)

Frequency unknown

• severe increase in blood pressure (possible stroke) • blocked blood vessel (such as an artery in the abdomen)	• decreased blood circulation • blood clots in the heart (possible heart attack) • increased sensitivity of the senses • wound healing problems	• liver failure • irritation in the tissue lining the eye • amputation due to tissue death

Ponatinib may cause reactivation of hepatitis B infection (possible liver damage and/or liver failure).

Other Side Effects

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

EKGs and ECHOs may cause discomfort while lying on the exam table, and the tape on the EKG pads may cause skin irritation.

Having **bone marrow aspirations** performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the aspiration. An allergic reaction to the anesthetic may occur. A scar may form at the aspiration site.

Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen, which may result in a **loss of confidentiality**. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Because taking part in this study can result in risks to an unborn or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while on this study. You must use birth control during the study if you are sexually active.

Birth Control Specifications: Women who are able to become pregnant and men who can father a child must use acceptable forms of birth control while taking the study drug and for at least 3 months after the last dose of study drug.

Males: The acceptable form of birth control is condoms.

Females: Acceptable forms of birth control are barrier methods (condom or diaphragm), birth control pills or injections, intrauterine devices (IUDs), spermicidal jelly or foam, or tubal ligation.

Males: Tell the doctor right away if your partner becomes pregnant or suspects pregnancy.

Females: If you are pregnant, you will not be enrolled on this study. If you become pregnant or suspect that you are pregnant, you must tell your doctor right away.

Getting pregnant will result in your removal from this study.

OPTIONAL PROCEDURES FOR THE STUDY

You do not have to agree to take part in the optional procedures in order to receive treatment on this study. There are no benefits to you for taking part in the optional procedures. Future patients may benefit from what is learned. There will be no cost to you for taking part in the optional procedures.

Optional Procedure #1: You are being asked to allow extra blood (about 1 teaspoon each time) to be drawn to learn more about how ponatinib may work. If you agree, this blood will be drawn before you start treatment and 3-4 times during Year 1, then 1-2 times each year after that.

Optional Procedure Risks:

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Optional Procedure Alternatives:
You may receive the study drug without taking part in the optional procedures. You may withdraw from the optional procedures at any time.

CONSENT/PERMISSION/AUTHORIZATION FOR OPTIONAL PROCEDURES
Circle your choice of "yes" or "no" for each of the following optional procedures:

Optional Procedure #1: Do you agree to have extra blood drawn to learn more about how ponatinib may work?

YES **NO**

3. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or TAKEDA for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not

giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs, including hospitalization, nausea, vomiting, low blood cell counts, and dehydration. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research.

You will receive no compensation for taking part in this study.

Additional Information

4. You may ask the study chair (Dr. Elias Jabbour, at 713-792-4764) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor who can help you safely stop study treatment. It may be dangerous to suddenly stop study treatment. The study doctor will also decide if you need to have any visits or tests to check on your health. If you withdraw from this study, you can still choose to be treated at MD Anderson.

   If you stop being in the research, already collected data may not be removed from the study database. You may be asked whether the study doctor can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, TAKEDA the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson. Possible reasons your participation in this study may be stopped include if the disease gets worse, if intolerable side effects occur, if you are

unable to follow study directions, or if the study is stopped.

7. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study, and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

8. MD Anderson may benefit from your participation and/or what is learned in this study.

9. This study is sponsored and/or supported by: TAKEDA.

10. In a medical emergency, you may be cared for by someone who has a financial interest with the study sponsor(s)/supporter. If you have any questions about this, you may call the IRB at 713-792-6477.

Future Research

Data

Your personal information is being collected as part of this study. These data may be used by researchers at MD Anderson and TAKEDA. and/or shared with other researchers and/or institutions for use in future research.

Samples

Samples (such as blood and/or tissue) are being collected from you as part of this study. Researchers at MD Anderson may use any leftover samples that are stored at MD Anderson in future research. Leftover samples stored by TAKEDA may be used in future research.

If identifiers are removed from your identifiable private information or identifiable samples that are collected during this research, that information or those samples could be used for future research studies or shared with another researcher for future research studies without your additional informed consent.
In some cases, all of your identifying information may not be removed before your data or research samples are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or research samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

If this research is not performed at MD Anderson, MD Anderson will not have oversight of any data and/or samples.

Genetic Research

Research samples collected from you as part of this study may be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when deciding to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Nor does this federal law prohibit discrimination based on an already known genetic disease or disorder.

Conflict of Interest

Dr. Elias Jabbour (Study Chair) has received compensation from TAKEDA as a Consultant. The financial interests are within the limits of the conflict of interest policy.

Dr. Hagop Kantarjian (Collaborator) has received compensation for providing services to Takeda. The financial interests are within the limits of the conflict of interest policy.

Authorization for Use and Disclosure of Protected Health Information:

A. During the course of this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson

- TAKEDA who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer at 713-745-6636. If you withdraw your authorization, you will be removed from the study and the data collected about you up to that point can be used and included in data analysis. However, no further information about you will be collected.

E. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT/AUTHORIZATION

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under this protocol.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE

A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS) and patients who are illiterate.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT