

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: CC#144525 – A Study of the Safety, Immunopharmacodynamics and Anti-tumor Activity of Ibrutinib Combined with Gemcitabine and Nab-Paclitaxel in Patients with Metastatic Pancreatic Adenocarcinoma

This is a clinical trial, a type of research study. Your study doctor, Margaret Tempero, M.D. or one of her associates from the UCSF Helen Diller Family Comprehensive Cancer Center, will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to volunteer for this study because you have metastatic pancreatic cancer. Metastatic means the cancer has spread to areas of your body outside of your pancreas.

Why is this study being done?

The main purpose of this study is to test the safety of different dose levels of the study drug ibrutinib when administered with gemcitabine and nab-paclitaxel, and to find out what effect, good and/or bad, the highest well-tolerated dose of ibrutinib has on you and your metastatic pancreatic cancer.

The study drug ibrutinib is an “investigational drug” in this study. This means ibrutinib has not been approved by the U.S. Food and Drug Administration (FDA) for pancreatic cancer. Ibrutinib is approved by the FDA for treatment of the following types of cancers of white blood cells, Chronic Lymphocytic Leukemia (CLL), Mantle Cell Lymphoma (MCL) with one prior therapy and Waldenstrom Macroglobulinemia (WM) which, is a type of non-Hodgkin lymphoma (NHL). This study will investigate the effects of using ibrutinib to treat patients with solid tumors such as pancreatic cancer, and is considered to be investigational. In animal studies and lab experiments, ibrutinib has been shown to prevent or slow the growth of cancer cells when used with other chemotherapies like gemcitabine.

In this study, ibrutinib will be administered with gemcitabine plus nab-paclitaxel. The combination of gemcitabine and nab-paclitaxel is known to be effective in treating pancreatic cancer and is widely used for treatment. Ibrutinib is a pill that is taken orally and will be given in combination with gemcitabine and nab-paclitaxel. Gemcitabine and nab-paclitaxel are approved by United States FDA-approved to treat advanced pancreatic cancer.

Funding for this study is being provided by Pharmacyclics LLC, an AbbVie Company. Pharmacyclics, the manufacturer of the study drug ibrutinib, will provide the study drug at no cost to study participants.

How many people will take part in this study?

About 25 people will take part in this study at UCSF and up to 50 people will take part among all sites.

What will happen if I take part in this research study?

You will receive chemotherapy (gemcitabine and nab-paclitaxel) and study drug (ibrutinib). There are two parts to this study. Part 1 will test 2 to 4 dose levels of ibrutinib that have already been tested in other clinical studies and have been found to be safe in people with and without cancer, and safe and effective in people with lymphoma. The first 3 subjects will receive the second highest dose of ibrutinib in combination with gemcitabine and nab-paclitaxel. If that dose is found to be well tolerated, the next 3 subjects will receive the highest dose of ibrutinib with gemcitabine and nab-paclitaxel. If the highest dose is well tolerated, then then 3 more subjects will receive the highest dose ibrutinib with gemcitabine and nab-paclitaxel to confirm the safety of this combination of therapies. If the highest dose is not well tolerated, then the next lowest dose will be tested, and so on until the best tolerated dose is found.

Once the safety of the highest tolerated dose is confirmed in at least 6 subjects, Part 2 of the study will be opened for enrollment. If you are eligible to receive therapy, you will have a biopsy before starting ibrutinib-only therapy. You will then receive ibrutinib for 7 days and have a second biopsy after completing the ibrutinib-only therapy and before starting the combination of chemotherapy. Approximately 20 patients will be enrolled in Part 2.

Before you begin the main part of the study...

You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. These exams, tests or procedures are part of regular routine cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated, your study doctor will let you know. You may have some procedures done for research purposes because you are participating in the study, they will be noted as Research Procedures in this form.

Approximately 14 days before you begin treatment, you will have the following screening tests and procedures (this will take about 8-12 hours).

- A complete medical history to review any conditions or past treatments that would prevent you from taking part in this study.
- A physical exam including measurements of your vital signs (temperature, pulse, blood pressure, weight and height). Your overall well-being will also be assessed.
- Evaluation of how well you can perform normal daily activities.
- Blood samples for: (3-4 tablespoons)
 - Routine laboratory tests (2-3 tablespoons).
 - Blood sample to test for tumor biomarkers
 - Blood samples to test for Hepatitis B and Hepatitis C
- A urine or blood serum pregnancy test (about 1 teaspoon) if you are a woman of childbearing age.

- You will have computed tomography (CT) or magnetic resonance imaging (MRI) scans at certain times to measure the size of your tumor(s).
 - CT scan: This is a test that uses special x-ray equipment to make detailed pictures of body tissues and organs. For this exam, you will need to lie still on a table inside a large doughnut-shaped machine. The table will move and the machine will make clicking and whirring noises as the pictures are taken. If necessary, an iodine dye (contrast material) will first be injected into a vein. The iodine dye makes tissue and organs more visible in the pictures. Each CT scan will take 15-30 minutes.
 - MRI scan: This is a test that uses special equipment to make detailed pictures of body tissues and organs. For this exam, you will lie down on a narrow bed which will then be placed in a tunnel that is 6 feet long by 2 feet wide and open at each end. You will need to lie there quietly for about one hour, during which time there will be a loud banging noise. You may feel warm during this procedure. If necessary, gadolinium (contrast material) will first be injected into a vein. The gadolinium makes tissue and organs more visible in the MRI.

The following procedures will be done for research purposes:

- Review medications and side effects
- Evaluation of ability to carry out your daily activities
- **Electrocardiogram (ECG):** This will record the electrical activity of your heart.
 - ECG records the electrical activity of your heart. Wires or “leads” will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical „record” of your heart activity. This takes about 15-30 minutes.
- **Optional Tumor tissue sample:** If you had surgery or a biopsy when you were diagnosed with cancer, samples of your tumor (tumor tissue) may have been sent to a hospital’s pathology department that specializes in looking at tumor tissue samples. If any tumor tissue is still available, samples will be requested for possible biomarker use in the future. This is discussed further at the end of this consent form.

During the main part of the study...

You will visit the study site on Day 1, 8, 15, and 22 of each 4-week (28-day) treatment cycle (\pm 48 hours) during study treatment. You will receive nab-paclitaxel and gemcitabine on Day 1, 8, and 15 of each cycle. Nab-paclitaxel and gemcitabine will be given in the vein by IV infusion. Your infusions will take about 4-6 hours every clinic visit. On Day 1 of each cycle, you will receive enough ibrutinib to take at home for the full 28 day treatment cycle. From Day 1 through Day 28 of each cycle, you will be taking ibrutinib each day with water by mouth.

Any radiology tests (scans) and blood tests that were done at the pre-treatment visit will only be repeated if your doctor feels it is necessary. The following procedures will take place during your visits:

- Physical exam and vital signs.

- Blood samples for routine laboratory tests (2-3 tablespoons).
- You will receive your study drug infusion

The following procedures will be done for research purposes:

- Review medications and side effects
- Evaluation of ability to carry out your daily activities

PARTICIPANTS IN Part 2 of the study ONLY

You will undergo an EUS-guided biopsy before you will start taking ibrutinib by itself for one week, then stop for 5-7 days before undergoing a second biopsy. 2-3 days after the second biopsy, you will begin treatment with nab-paclitaxel and gemcitabine in the 28-day cycles as described above, with infusions on Day 1, 7, and 15 of each 28 day cycle. 5 – 7 days after the second biopsy, you will also start taking ibrutinib daily through each cycle of therapy with nab-paclitaxel and gemcitabine.

The following procedures will be done for research purposes:

- **EUS-guided Biopsy.** Biopsy of the tumor will be done with a special endoscopy which uses ultrasound to find your tumor. You will receive a medication that will sedate you prior to procedure for your comfort. A gastroenterology expert will use an instrument called an endoscope which is a thin, flexible tube with a tiny video camera and light on the end that offers a clear, detailed view of your digestive tract. Ultrasound is an imaging technique that uses sound waves to produce pictures. In an endoscopic ultrasound, a special endoscope is used that has an ultrasound processor on its tip. These instruments allow examination of both the lining of your digestive tract with the endoscope, but also of the wall of the tract and its surrounding structures such as the pancreas. Through the ultrasound the gastroenterology expert will be able to see vital organs, the pancreatic tumor, lymph nodes and blood vessels. Then the expert will place a needle into the tumor and will remove small pieces of the tumor so that we can confirm if you have pancreatic cancer. A piece of this psy will also be used to analyze your pancreatic cancer. You will have this procedure before you start treatment. If you are randomized in the second part of the study to Part 2, you will undergo this procedure again after you complete 7 days treatment with ibrutinib only. This will allow us to see how the treatment with ibrutinib only affected your pancreatic cancer tumor.

ALL PATIENTS

- If you feel light-headed, out of breath, or feel your heart palpitations, you will have an ECG to determine if you are experiencing an irregular heartbeat.

Day 1 of every Cycle:

- A physical exam and vital signs.
- Blood samples for routine laboratory tests (2-3 tablespoons).
- You will receive your study drug infusion.

The following procedures will be done for research purposes:

- Review medications and side effects
- Evaluation of ability to carry out your daily activities
- You will receive one cycle's worth of ibrutinib to take each day with water by mouth at home.
- Blood sample for immune response markers (about 5 tablespoons)

Day 8 of every Cycle:

- Your vital signs will be taken.
- You will receive your study drug infusion.
- Blood samples for routine laboratory tests (2-3 tablespoons).

The following procedures will be done for research purposes:

- Review of any side-effects

Day 15 of every Cycle:

- A physical exam and vital signs.
- Blood samples for routine laboratory tests (2-3 tablespoons).
- You will receive your study drug infusion.

The following procedures will be done for research purposes:

- Review medications and side effects
- Evaluation of ability to carry out your daily activities **(Cycle 1 and 2 only)**

Day 22 of Every Cycle:

- You will receive your study drug infusion.

The following procedures will be done for research purposes:

- Review of any side-effects

Every 8 Weeks while on study treatment (starting cycle 2 day 22):

- You will have a CT scan of the chest. You may also have a CT or MRI scan of the abdomen and pelvis if the study doctor feels it is necessary. If it is discovered from these scans that your cancer has become worse, you will be discontinued from the study.

End of Treatment Visit

If your cancer gets worse, within 30 days after you stop taking the study drug, you will come to the clinic to make sure that you are not having any health problems or pain. If you had to stop

participating in the study because you had severe side effects, you may also have scans, such as CT scans, done at this visit.

- A physical exam and vital signs.
- Blood samples for routine laboratory tests (2-3 tablespoons).
- Scans to see how your disease has responded to the treatment. You will have a CT scan of the chest, a CT or MRI scan of the abdomen and pelvis if your physician feels it is necessary.

The following procedures will be done for research purposes:

- Review medications and side effects
- Evaluation of ability to carry out your daily activities

Every 8 Weeks After Treatment Ends:

If you stop participating in the study for any reason other than because your cancer becomes worse, you will go to the study center every 8 weeks after your treatment ends. You will have scans, such as CT scans done at this visit. This visit will be to check whether your cancer is becoming worse.

The information that will be collected and the tests that will be done at this visit are:

- A physical exam and vital signs.
- Scans to see how your disease has responded to the treatment. You will have a CT scan of the chest, a CT scan of the abdomen and pelvis if your physician feels it is necessary. These tests produce a picture of your body using a small amount of radiation.

The following procedures will be done for research purposes:

- Review of any side effects
- Evaluation of ability to carry out your daily activities

How long will I be in the study?

Your treatment in this study will continue until you decide to no longer take part in it, or if your cancer gets worse, you have severe side effects, the study ends, or if you have finished study treatment.

Once you have stopped study treatment, you will have your regular routine care visits or will be contacted on the telephone by someone from the study staff every 2 months for up to 2 years. At these times, you will answer questions about any medical or surgical procedures for your cancer you might have had. If you are asked to go to the study center for any of these visits, you may have scans done to check the status of your cancer.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. Your study doctor will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

Are there any other medications I can or cannot take while I am participating in the study?

You will not be allowed to receive any other treatment for your cancer while you are in this study. You may be able to have other treatments for your cancer after your study treatment ends.

You should tell your doctor at each visit about any over-the-counter and prescribed medications that you take. This way, your doctor will be able to make sure that you are not taking something that shouldn't be taken with the study drugs. If you require any of these medications and a replacement cannot be found, you will not be able to take part in this study.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects you experience while taking part in the study.

Drug Combination Risk: The side effects of the combination of gemcitabine, nab-paclitaxel, and ibrutinib are not yet known. It is possible that this combination of drugs will cause new or more serious side effects than taking these drugs separately. You will be monitored closely for side effects and your doctor may change your medications if it appears that this combination is causing serious side effects. You should tell your doctor about any side effects you experience while on this study. When additional information about side effects is known, you will be notified of any further study drug related effects. To date there are no known risks associated with gemcitabine combined with nab-paclitaxel.

Risks of ibrutinib

The risks/side effects that have been observed with the use of IBRUTINIB are listed below:

Likely: *(these effects occur in 20% or more of subjects taking IBRUTINIB)*

- Occurrence or increase in frequency of loose or watery stools (Diarrhea)
- Low white blood cell count (cells that help fight infection) (Neutropenia)
- Nausea
- Muscle and joint pain (Musculoskeletal pain)
- Bruising (Contusions)
-

Less Likely *(these effects occur in at least 10% of subjects taking IBRUTINIB)*

- Sores in the mouth (Stomatitis)
- Sinus infection (Sinusitis)
- Fever (Pyrexia)
- Low platelet count [cells that help blood to clot] (Thrombocytopenia)
- Constipation
- Swelling of the hands or feet (Peripheral edema)
- Joint aches (Arthralgia)
- Common cold (Upper respiratory tract infection)
- Vomiting
- Skin infection
- Pneumonia
- Headache
- Muscle spasms
- High blood pressure (Hypertension)

Rare *(these effects occur in at least 1% of subjects taking IBRUTINIB)*

- Blurry vision
- Abnormal heart rhythm (Atrial fibrillation)
- Increase in white blood cell counts (Leukocytosis)
- Severe infection throughout the body (Sepsis)
- Low white blood cell counts with fever (Febrile neutropenia)
- Increased level of uric acid in the blood (Hyperuricemia)
- Dizziness
- Urinary tract infection
- Nosebleeds (Epistaxis)
- Small red or purple spots caused by bleeding under the skin (Petechiae)
- Non-melanoma skin cancer:
 - Type of non-melanoma skin cancer (Basal cell carcinoma)
 - Type of non-melanoma skin cancer (Squamous cell carcinoma)
- Redness of the skin (Erythema)
- Breaking of the nails (Onychoclasia)

- Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease)
- Increase in lymphocyte count (Lymphocytosis)

Very Rare (*these effects occur in less than 1% of subjects taking IBRUTINIB*)

- Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures. (Tumor lysis syndrome)
- Itchy rash (Urticaria)
- Bleeding around the brain (Subdural hematoma)
- Inflammation of the fatty tissue underneath the skin (Panniculitis)
- Swollen face, lip, mouth, tongue or throat (Angioedema)
- High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome)
- Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome)
- Liver failure (Hepatic failure)
- Abnormal rapid and/or irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (Ventricular tachyarrhythmia).

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.

You should tell your study doctor or medical team about any side effects you are having. Your study doctor may be able to give you medications to help treat the side effects and prevent them from becoming worse. 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.

Bleeding effects

You may experience bruising or bleeding during treatment with ibrutinib. Rarely, serious internal bleeding may occur, such as bleeding in your stomach, in your intestine, or in or around your brain may occur, 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. Call your study doctor immediately 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. Also, call your study doctor if you have signs or symptoms of serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.

Effects on the heart

Abnormal rapid and/or irregular heart rhythm (atrial fibrillation, atrial flutter, and/or ventricular tachyarrhythmia) have been reported in patients treated with ibrutinib, especially when they also have heart conditions, increased blood pressure, infections, or had abnormal heartbeat in the past. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart, dizziness, weakness, feeling light-headed, shortness of breath, chest discomfort or fainting. If you develop any of these symptoms while on the study drug, you should tell your study doctor immediately.

Infections

You may experience viral, bacterial, or fungal infections. Some of these infections have been associated with hospitalization and death. Contact your study doctor if you have fever, chills,

weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath—these could be signs of a serious 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 tell your study doctor immediately.

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.

Allergic reactions

Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction to ibrutinib, 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 sweating.

Before starting the study drug, you must tell your study doctor about any drug allergies. You should tell the study doctor right away 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 2-3 weeks or longer after starting ibrutinib. There have been rare reports of severe rash (involving more than 50 % of the body) or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas (Stevens-Johnson Syndrome). This 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.

Non-melanoma Skin Cancer and Other Cancers

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) 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. The causal relationship with ibrutinib is unknown. You should tell your study doctor if you develop a new cancer while in the study.

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 stools, confusion, nausea, loss of appetite, and 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.

Interstitial lung disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Randomized, controlled Phase 3 studies did not show an increased incidence rate of ILD in subjects treated with ibrutinib as compared to subjects treated with active control. Subjects should be monitored and evaluated for symptoms (e.g., dyspnea, cough or pyrexia) and treated symptomatically, including interruption of the suspected agent as appropriate.

Interference with other drugs

Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body processes ibrutinib. This interference could cause the amount of ibrutinib in your body to be higher or lower than expected. It is also possible that taking the study drug with your regular medications or supplements, 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.

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. Please contact your study doctor if you have any planned surgical procedures. 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 as soon as possible and your study doctor will tell you when to stop ibrutinib and when to restart it following a surgical procedure.

Gemcitabine

The risks/side effects that have been observed with the use of gemcitabine are listed below:

Likely

- Low white blood cell count with increased risk of infection
- Low platelet count with increased risk of bleeding
- Low red blood cell count (anemia) with symptoms like tiredness, weakness, or shortness of breath
- Nausea
- Vomiting
- Loss of appetite
- Tiredness (fatigue)
- Fever
- Swelling of the arms and legs or other parts of the body
- Abnormal blood tests, which suggest that the drug is affecting the liver or kidneys. Your doctor will discuss the importance of this finding with you.

Less likely

- Diarrhea
- Sores in mouth or on lips
- Flu-like symptoms (headache, muscle aches, fever)
- Trouble breathing or shortness of breath
- Skin rash
- Infection
- Swelling of hands, ankles, or face
- Hair loss or thinning, which may include face and body hair

- Itching

Rare

- Sleepiness or drowsiness (sedation)
- Numbness or tingling
- Bleeding
- Allergic reaction
- Death due to kidney failure, liver failure, lung damage, infection, or other causes

Nab-Paclitaxel

The risks/side effects that have been observed with the use of nab-paclitaxel are listed below:

Likely

- Low white blood cell count with increased risk of serious infection
- Numbness, tingling, or pain in the hands, feet, or elsewhere
- Nausea/vomiting
- Diarrhea
- Hair loss
- Feeling weak
- Feeling tired
- Muscle or joint pain

Less likely

- Sores in the mouth or on the lips
- Retaining fluid (may include swelling in hands or feet)
- Shortness of breath
- Low red blood cell count (anemia)
- Abnormal blood tests which suggest that the drug is affecting the liver (Your doctor will discuss the importance of this finding, if any).

Rare

- Lowered blood platelet count with increased risk of bleeding
- Changes in heart rhythm
- Low blood pressure
- Allergic reaction (fever, flushing, itching, rapid heart rate), which can sometimes worsen into trouble breathing, swelling throat or mouth, and dizziness
- Pain, redness or swelling at the infusion site
- Nails changing color or becoming brittle
- Cough
- Excess tears from the eyes
- Abnormal blood tests which suggest that the drug is affecting the kidneys (Your doctor will discuss the importance of this finding, if any)
- Loss of vision due to swelling inside the eyeball (cystoid macular edema)
- Lung inflammation (interstitial pneumonitis), which can make it hard to breathe
- Deaths due to liver damage, infection, allergic reaction, lung inflammation, or other causes

Other risks related to this study include:

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.

Biopsies obtained at the time of endoscopy: The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure can be unsuccessful and require a repeat biopsy to get enough tissue. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

Electrocardiogram (EKG/ECG) risks: The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own. Please let your doctor know if you are aware of any allergies.

No radiation risk beyond routine clinical care: This study involves radiation exposure as part of routine clinical care. You will not receive additional radiation as a result of participating in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

Computerized Tomography (CT) scan risks: CT scans involve the risks of radiation (see above). In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

Magnetic Resonance Imaging (MRI) scan risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event

from happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

Drug Interaction Risks: You must also review with your study doctor all of your medications (including supplements and herbal or natural substances) at every visit, as well as notify your study doctor before starting any new medications, supplements, or herbal treatments while participating in the study because there is a risk of serious interaction with ibrutinib.

Dose Escalation Risks: Since patients will be assigned to different doses of study drug, some patients may receive a dose of the drug that is too small to be effective while others may receive a higher dose that may cause increased side effects. You can ask your study doctor what dose you will be given.

Safe Handling of Medications: Handling ibrutinib and having contact with any urine, feces or vomit from patients receiving ibrutinib may pose some risk to you and your caregivers. To avoid exposure to ibrutinib and any associated risks, you and your family members/caregivers will be educated by a member of the study team on how to safely handle, properly dispose of, and clean products that may be contaminated with ibrutinib.

Infusion: As with most intravenous products, you may experience pain, irritation, swelling or bruising, or a slight chance of infection at the site where the intravenous catheter (small tube) is inserted into your vein. These side effects may also be observed at the site where blood is drawn for laboratory tests.

Intravenous line: The temporary placement of an intravenous line may cause discomfort when inserting the needle, as well as bruising; bleeding; and rarely, infection.

Hepatitis Testing: Being tested for Hepatitis may cause anxiety regardless of the test results. Receiving positive results may make you very upset. If your test is negative, there is still the possibility that you could be infected with the Hepatitis virus and test positive at some time in the future. There is always the possibility that the test results could be wrong.

Hepatitis B and C Reporting: California regulations require laboratories to report new cases of Hepatitis B and C infection to the county public health department. The reports include the patient's name, social security number, and other identifying information. Information about these new infections is used to track the disease statewide and nationwide. Other than this required reporting, your results will be treated confidentially by the study staff. Personal identifying information will not be reported to other departments or agencies.

Reproductive Risks: You should not become pregnant while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important to understand that you need to use birth control while on this study and for 1 month (women) or 3 months (men) after you stop taking study treatment, to prevent pregnancy in either you or your partner. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

If you agree to take part in this study, there may or may not be direct benefits to you. The study treatment may lessen symptoms from your disease, shrink your tumor, and/or may lengthen your survival; however, no guarantees can be made. Information from this study may help other cancer patients in the future.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your study doctor about your choices before deciding if you will take part in this

study.

Will my medical information be kept private?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The University of California
- Oregon Health and Science University (OHSU) and affiliated sites
- Pharmacyclics, LLC, its affiliates and its collaborators (e.g. Janssen Biotech, Inc.)
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

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.

What are the costs of taking part in this study?

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for taking part in studies. Check with your study team to find out what will be billed to insurance and what will be covered by the study. Taking part in this study may or may not cost you or your insurance company more than the cost of getting routine cancer care.

Pharmacyclics, LLC, will provide ibrutinib free of charge to study participants. Procedures done for the purposes of research (noted as research purposes), such as biopsies and blood collection for immune response markers, will be covered by the study. Other procedures considered routine care and will be paid for by you or your insurance. Gemcitabine and Nab-Paclitaxel will be paid for by you and/or your health plan/insurance company.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Will I be paid for taking part in this study?

You will not receive payment of any kind for being in the study.

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

It is important that you tell your study doctor(s), Margaret Tempero, M.D, and Andrew Ko, M.D., if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call [REDACTED]

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor(s) Margaret Tempero, MD and Andrew Ko, M.D. [REDACTED].

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the Office of the Committee on Human Research at 415-476-1814.

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Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say "no" to taking part in any of these additional studies.

About Using Tissue samples for Research

We would like to store the remaining tissue sample from your previous biopsies for future research. If you had surgery or a biopsy when you were diagnosed with cancer, samples of your tumor (tumor tissue) may have been sent to a hospital's pathology department that specializes in looking at tumor tissue samples. If any tumor tissue is still available, the researchers would like to use your tumor tissue for possible biomarker use in the future.

Reports about research done with your tissue sample will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us store and use your tissue for future research is optional and is up to you. No matter what you decide to do, it will not affect your care.

The samples may be stored indefinitely or until there is no more of your tumor tissue sample left. You have a say in how your leftover stored samples are used in future research. You can still take part in the treatment part of this study even if you do not allow future research on your tumor tissue samples. Your tissue will be used only for research and will not be sold. The research done with your tissue may lead to the development of new products in the future. You will not receive any money that may result from any such commercial tests or treatments.

Pharmacyclics, LLC, its affiliates, and its collaborators (Janssen Biotech, Inc.) may study your data and tissue, blood, or other specimens collected from you. Your tissue, blood or other specimens 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. You will not be compensated for any patents or discoveries that may result from your participation in this research. Your signature on this form indicates that you understand and accept this.

The tumor samples will be labeled with a study identifier and subject code that is unique to you and which does not allow you to be identified by personnel working at the place where your tumor tissue is stored or processed.

If you decide later that you do not want your specimens and information to be used for future research, you can notify the study doctor in writing [REDACTED]:

[REDACTED]

Benefits

There is no get any direct benefit from donating your samples for long-term storage; however this research may help patients like you in the future.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small. To further safeguard your privacy, information obtained in this part of the study will not be placed in your medical record.

Your tissue samples will be coded so that your name cannot be readily identified. Reports about research done with your tissue samples will not be put in your health/medical record and will be kept confidential to the best of our ability within state, federal and national law.

In the future, researchers studying your samples may need to know more about you, such as your medical history, and other information such as your age, gender and race. If this information is already available because of your participation in a study, it may be provided to the researcher. Personal identifiers such as your name, social security number or anything that might identify you personally will NOT be provided. If you agree to be re-contacted, you may still change your mind about providing information in the future.

You can say "yes" or "no" to each of the following options. Please mark your choice for each option.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, check whether or not you agree to donate your tumor tissue samples for future testing.

1. I allow my archived tissue sample to be banked for future biomarker research.

☐ Yes ☐ No Please initial here: _____ Date: _____

2.

I allow my samples to be stored and used for future research about other health problems (for example: causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).

☐ Yes ☐ No Please initial here: _____ Date: _____

3. I agree that someone may contact me in the future to ask me to take part in more research.

☐ Yes ☐ No Please initial here: _____ Date: _____

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Participant's Name (print)

Date

Participant's Signature for Consent

Date

Person Obtaining Consent

Date

Witness (only required if the participant is a
non-English speaker)

Date