An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early-Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide

NCT02400476

Informed Consent Form – Amendment 7.1

15-Aug-2019

MASTER INFORMED CONSENT TO PARTICIPATE IN RESEARCH

ONLY FOR PATIENTS ENROLLED UNDER AMENDMENT 7.1
(North America & Asia Pacific)

Information to Consider Before Taking Part in This Research Study

Puma-NER-6201: An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide

Investigator Name: [*name of principal investigator*]

You are being asked to take part in a research study. Research studies include only people who choose to take part. This document is called an informed consent form. Please read this information carefully and take your time making your decision. Ask the study doctor or study staff to discuss this consent form with you. Please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The kind of study, risks, inconveniences, discomforts, potential benefits, and other important information about the study will be reviewed with you. If you understand the study and you agree to participate, the study staff will ask you to sign this form. Additionally, the study staff will provide you with a copy of this signed form.

Please tell the study doctor or study staff if you are taking part in another research study.

We are asking you to take part in a research study called:

An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients with Early Stage HER2+ Breast Cancer Treated with Neratinib and Loperamide

The person who is in charge of this research study is [*Insert PI name*]**.** This person is called the Principal Investigator. However, other qualified study staff may be involved and can act on behalf of the Principal Investigator.

This research study will be conducted at [*List the site(s) where the participant will be expected to take part in the research*].

This research study is being sponsored by Puma Biotechnology, Inc.

PURPOSE OF THE STUDY

Neratinib is a drug being studied as a potential new treatment for patients with breast cancer that show an increased amount of a gene or protein called HER2 or otherwise known as HER2+. A previous study showed that one year of neratinib decreased the rate of breast cancer returning in patients with early stage HER2+ breast cancer who had undergone prior therapy with chemotherapy and trastuzumab (Herceptin®). Neratinib (Nerlynx®) is a FDA (Food and Drug Administration) approved drug in the United States of America.

The purpose of this study is to evaluate the occurrence and severity of diarrhea in patients being treated with neratinib for early stage HER2+ breast cancer and who take loperamide when needed to help prevent or decrease diarrhea. These patients would have received prior chemotherapy and trastuzumab (Herceptin®) treatment before joining the study.

SHOULD YOU TAKE PART IN THIS STUDY?

- This informed consent form explains this research study. After reading through this form and having the study explained to you by someone conducting this research, you can decide if you want to take part. You do not have to take part in this study to receive medical care.
- You may have questions this form does not answer. If you do have questions, feel free to ask the study doctor or the person explaining the study, at any time.
- Take your time to think about the information that is being provided to you.
- Feel Free to talk it over with your regular doctor if you wish.

This form explains:

- Why this study is being done.
- What will happen during this study and what you will need to do.
- Whether there is any chance of benefit from being in this study.
- The risks involved in this study.
- How the information collected about you during this study will be used and with whom it may be shared.

Providing informed consent to participate in this research study is up to you. If you choose to be in the study, please sign this form. If you do not want to take part in this study, you should not sign this form.

WHY ARE YOU BEING ASKED TO TAKE PART?

We are asking you to take part in this research study because you have received prior chemotherapy and trastuzumab (Herceptin®) treatment for early stage HER2+ breast cancer.

WHAT WILL HAPPEN DURING THIS STUDY?

Prior to participating in this study you will be given the opportunity to read this consent form and have all your questions answered. If you agree to participate you will be asked to sign this document and a copy will be provided to you for your files. You will participate in a screening period to determine if you are eligible to participate in the study.

A procedure to collect your blood for research will be performed at Screening, Cycle 7 Day 1, Cycle 13 Day 28 and/or at time of treatment discontinuation, or disease recurrence.

- The cell-free DNA (cfDNA) that is collected will undergo testing to identify whether there is breast cancer genetic material that may be a marker for breast cancer recurrence.
- This cfDNA testing will be done during and/or after you have participated in this study. In order to do this, genetic material from your blood will be tested. The information resulting from the analysis will be used anonymously meaning that your identity will not be revealed. You will not receive the results of this testing. Your sample will be used only for research and will not be sold. The research done with your sample may help to develop new breast cancer treatments in the future.

You will complete questionnaires called the EuroQol 5D-5L (EQ-5D-5L), Functional Assessment of Cancer Therapy Breast (FACT-B), and the Rotterdam Symptom Checklist (RSCL) at Day 1 of Cycles 1, 2, 4, 7, 10 and at Day 28 of

Cycle 13 (End of Treatment). These questionnaires will evaluate your own understanding about your symptoms and health-related quality of life. You will need to complete these questionnaires yourself (i.e. a caregiver or study personnel should not complete the questionnaires for you) and before any other study procedures are given at your study visit.

1. The EQ-5D-5L is a questionnaire that measures your health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety. General health is also measured by a vertical visual analog scale.
2. The FACT-B is a questionnaire assessing physical, social, emotional, and functional well-being and additional concerns that are more specific to women with breast cancer.
3. The RSCL is a self-report measure to assess the quality of life of cancer patients.

At some sites, a stool sample will be collected during the study to look at the effect that the study drug may have on the gut bacteria.

Before You Begin the Study (Screening Period)

A schedule of procedures is provided in the table below (Study Calendar). In addition to the procedures listed below, unscheduled clinic visits and additional procedures may be performed. An unscheduled visit and/or additional procedures may be required if your study doctor believes it is necessary to assess symptoms and concerns that you may have reported; to confirm or rule out potential return of your cancer, and/or for your safety.

You will need to have the following exams, tests or procedures to find out if you can participate in the study. These exams, tests or procedures are part of your regular cancer care and may be done even if you do not take part the study. If you have had any of them completed recently, they may not need to be repeated, depending on when you last completed the tests. Your study doctor will decide what exams, tests and/or procedures may need to be done.

- Research blood sample for cfDNA testing (about 4 teaspoons)
- Medical history - a discussion of your past and present health issues, including a discussion of your cancer, treatments and past cancer related surgeries
- Demographics – date of birth, sex and race
- Medication history – a review of all other medications you have taken in the last 30 days
- Vital signs (blood pressure, breathing rate, heart rate and temperature)
- Height and weight
- Performance status - an evaluation of how well you perform normal daily activities
- Physical exam
- Routine blood tests (about 4 teaspoons)
    - Measure your blood counts (make sure you are not anemic)
    - See how well your liver, kidneys and other organs are working
- Electrocardiogram (ECG) will be obtained to make sure your heart is functioning normally
- Echocardiogram (an ultrasound of the heart) or MUGA (a special x-ray) to make sure your heart is pumping normally
- Pregnancy test- If you are a woman who can have children
    - This can be done with a blood draw or using a urine sample
- Stool sample- at select study centers
- Possibly a bone scan or positron emission tomography (PET) scan (imaging test to rule out the spread of cancer to bone) if you have a specific abnormal laboratory test before starting the study that shows possible indicated bone involvement, called alkaline phosphatase

- Possibly a computed tomography (CT) scan, magnetic resonance imaging (MRI) or ultrasound of the abdomen and chest (special imaging tests) if the liver blood tests before starting the study shows possible liver involvement
- Other imaging may be performed if your physician thinks it necessary

The Cycle 1 Day 1 physical examination and routine blood tests may be omitted if the screening values and a physical examination were obtained within 72 hours prior to initiation of treatment.

During the Active Treatment Stage

This is an open-label study which means that you and your study doctor will know exactly what treatment you will receive. You will take neratinib by mouth with the following schedule:

- Week 1- Week 2 (C1D1-C1D14): 160 mg (four 40mg tablets)
- Week 3- Week 4 (C1D15-C1D28): 200 mg (five 40mg tablets)
- Week 5 through the End of Treatment (C2D1-EOT): 240 mg (six 40mg tablets)

This 28-day period of time is called a cycle (C). Missed dose(s) of neratinib (i.e., any dose that is not administered per your doctor's instructions) will not be made up. Please take neratinib with food, preferably in the morning; however, neratinib may be taken in the evening. It is important that you take neratinib at the same time every day. Neratinib must be stored at room temperature and out of direct sunlight.

For female patients of child-bearing potential, for months that you do not have a scheduled visit (Cycles 5, 6, 8, 9, 11, 12, 13 and/or the Safety follow-up): You will be asked to take a monthly urine pregnancy test at home. The Investigator or research staff will contact you during each cycle to confirm that you have performed the pregnancy test and to collect the results of the pregnancy test.

Your study doctor will assign you to the group listed below for the first 28 days (Cycle 1). This group will enroll approximately 100 patients.

Group: Neratinib dose escalation (Amendment 7): neratinib + loperamide (as needed)

- Along with neratinib 160 mg (four 40mg tablets) for week 1 through the end of week 2, 200 mg (five 40mg tablets) for week 3 through the end of week 4, and then 240 mg (six 40mg tablets) for week 5 through the end of treatment date. You can take loperamide on an as needed basis.

If you experience loose stools after you take your first dose of neratinib, please note the following loperamide dosing instructions:

- The first dose of loperamide 4mg (2 tablets/capsules) right after the first loose stool
- Then take 2 mg (1 tablet/capsule) every 4 hours or after every loose stool until you have not had any loose stools for at least 12 hours
- You are allowed to up dose to keep your loose stools controlled (1-2 a day)
- The maximum dose of loperamide is 8 tablets (16 mg) in any 24-hour period

If your diarrhea continues after taking 8 tablets (16 mg loperamide) in one day, or if you are constipated, call your doctor or nurse immediately. Do not stop taking loperamide or your study medications unless instructed by your doctor.

Your doctor or nurse will contact you by phone each of the first three days after you start taking neratinib to ask how much diarrhea you have and make any treatment adjustments. In addition, your doctor or nurse will also contact you by phone the end of the second and fourth weeks of treatment to make sure you have taken your neratinib correctly. ***NOTE: Your study doctor will provide you with a separate instruction sheet which will provide direction on how to manage your diarrhea.***

You are required to use a patient electronic diary (eDiary) or access an eDiary web link to record the number of neratinib and loperamide tablets (if taken) each day for the first two cycles of the study. After the first two cycles, the eDiary web link or use of a patient electronic diary (eDiary) will continue to be available or you may switch to a paper diary to be completed on a daily basis throughout the remainder of the study. Additionally, your study doctor will instruct you to record the number of stools you have each day. You will be required to record all doses of neratinib in the eDiary for only the first two cycles of the study.

If you are given an eDiary device, you will need to bring your eDiary to your doctor's office before each cycle visit. You should also bring any unused study medications and pill bottles (even if empty) to your doctor's office at every visit.

The cycle (28 days) will be repeated for 13 cycles. Each cycle is numbered in order. You will receive treatment unless your disease worsens or you have a side effect from neratinib that requires you to stop treatment.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. Most are part of regular cancer care. In addition to the procedures listed below, unscheduled clinic visits and procedures may be performed if your study doctor believes that it is medically necessary to assess symptoms and concerns that you may have reported and to confirm or rule out potential return of your cancer or for your safety. If recommended by your study doctor, patients that experience significant diarrhea can choose to have an optional colonoscopy with biopsy completed. The sponsor will pay for the costs of the colonoscopy and the biopsy.

<u>The following tests and procedures will be performed at **Day 1 of Cycles 1, 2, 3, and 4** (every 4 weeks):</u>

- Patient-reported health outcomes questionnaires (EQ-5D-5L, FACT-B, and RSCL)
    - Collected on Day 1 of Cycles 1, 2, and 4
- Vital signs, weight, and targeted physical exam
- Routine blood tests (about 4 teaspoons)
- Phone calls on day 1, day 2, and day 3 after starting neratinib to see how you are feeling
- Phone calls at the on the following days during cycle 1:
    - Day 14 or Day 15 to remind you to increase your dose from 160mg to 200 mg
    - Cycle 1 Day 28 or Cycle 2 Day 1 to remind you to increase your dose from 200mg to 240 mg
- Review of symptoms and side effects
- Medication review – a review of all medications you are currently taking
- Pregnancy test – If you are a woman who can have children
    - This can be done with a blood draw or using a urine sample
    - Collected within 72hrs of the first dose of Cycle 1, and on Day 1 of Cycles 2-4

- Stool kit will be provided to collect a small amount of stool - at select study centers
    - Collected on Day 1 of Cycles 2 and 4
- Electrocardiogram (ECG)
    - Collected on Day 1 of Cycles 2 and 4

The following tests and procedures will be performed at **Day 1 of Cycles 7 and 10** (every 12 weeks):

- Patient-reported health outcomes questionnaires (EQ-5D-5L, FACT-B, and RSCL)
- Research blood sample for cfDNA testing (about 4 teaspoons)
    - Collected on Day 1 of Cycle 7
- Vital signs, weight, and targeted physical exam
- Routine blood tests (about 4 teaspoons)
- Review of symptoms and side effects
- Medication review – a review of all medications you are currently taking
- Pregnancy test – If you are a woman who can have children
    - This can be done with a blood draw or using a urine sample
- Electrocardiogram (ECG)

When you finish taking Neratinib (Cycle 13, Day 28 / End of Treatment Visit)

You will need the following tests and procedures within 5 days after stopping treatment. They are part of your regular cancer care. These tests and procedures are detailed below:

- Patient-reported health outcomes questionnaires (EQ-5D-5L, FACT-B, and RSCL)
- Research blood sample for cfDNA testing (about 4 teaspoons)
- Vital signs, weight, and physical exam

  Medication review – a review of all medications you are currently taking
- Pregnancy test – If you are a woman who can have children
    - This can be done with a blood draw or using a urine sample
- Review of symptoms and side effects
- Routine blood tests (about 4 teaspoons)
- Electrocardiogram (ECG) will be obtained to make sure your heart is functioning normally
- Echocardiogram (an ultrasound of the heart) or MUGA (a special x-ray) to make sure your heart is pumping normally
- Stool kit will be provided to collect a small amount of stool – at select study centers, will be collected if your End of Treatment is earlier than Cycle 4.

Safety Follow-up

Twenty Eight days after you stop taking neratinib the following tests and procedures will be performed:

- Medication review – a review of all medications you are currently taking
- Pregnancy test- If you are a woman who can have children
    - This can be done with a blood draw or using a urine sample
- Review of symptoms and side effects

Study Calendar: *This study calendar is a summary of the events that will occur at each scheduled visit.*

Event	Before Treatment	During Treatment			After Treatment
Visit	**Within 28 days of Cycle 1, Day 1**	**Cycles 1-4 (Every 4 weeks)**	**Cycles 7 & 10 (Every 12 weeks)**	**End of Treatment/ Cycle13, Day28**	**Safety Follow-up**
Informed consent	X				
Demographics	X				
Medical, cancer, and medication history	X				
Physical examination	X			X	
Targeted Physical exam		X	X		
Vital signs	X	X	X	X	
Health outcomes questionnaires		Cycle 1, 2 & 4	X	X	
Blood sample for cfDNA testing	X		Only Cycle 7	X	
Electrocardiogram	X	Cycle 2 & 4	X	X	
Echocardiogram or MUGA	X			X	
Pregnancy test (if required) via blood or urine (for months that you do not have a scheduled visit, you will take a monthly urine pregnancy test at home.).	X	X (within 72 hours of the first dose)	X	X	X
MD/RN Phone Call (Note: the Investigator or research staff will contact you during each cycle to confirm that you have performed the pregnancy test and to collect the results of the pregnancy test).		Cycle 1, after day 1, 2, & 3 AND At the end of the first two weeks (day 14 or 15) and end of Cycle 1 (C1D28 or C2D1)			
Routine Blood Test	X	X	X	X	
Stool Swab Sample (at select study centers)	X	(Only Cycle 2 & 4)		Collected if your End of Treatment is earlier than Cycle 4	
Performance Status	X				
Neratinib for Group Neratinib dose escalation		Week 1-Week 2: 160mg; Week 3-Week 4: 200mg; Week 5 through the End of Treatment: 240mg			

Event	Before Treatment	During Treatment			After Treatment
Visit	Within 28 days of Cycle 1, Day 1	Cycles 1-4 (Every 4 weeks)	Cycles 7 & 10 (Every 12 weeks)	End of Treatment/ Cycle13, Day28	Safety Follow-up
Loperamide for Group Neratinib dose escalation		As needed			
Patient Diary		Required Web/handheld Cycle 1 & 2	Web/ handheld or paper diary	Web/ handheld or paper diary	
Collect/Review of Medications	Throughout Study Period				
Collect/Review of Side Effects		Throughout Study Period			

NERATINIB AND LOPERAMIDE SUGGESTED DOSING TIMES:

Group Neratinib dose escalation - Neratinib Suggested Dosing Times					
	7a.m.	9a.m	2p.m.	5p.m.	9p.m.
WEEK 1 – WEEK 2 (C1D1-C1D14)	Neratinib 160mg (four 40mg tablets) with food				
WEEK 3- WEEK 4 (C1D15-C1D28)	Neratinib 200 mg (five 40mg tablets) with food				
Week 5 - End of Treatment (C2D1-EOT)	Neratinib 240 mg (six 40mg tablets) with food				

Loperamide 2 tablets (4mg) will be self-administered orally by patients on an as needed basis only, from the start of neratinib dosing (not exceeding 8 tablets/16 mg per day).
Please take neratinib with food, preferably in the morning. It is important that you take neratinib at the same time every day.

TOTAL NUMBER OF PARTICIPANTS AND STUDY DURATION

- About 750 individuals will take part in this study. The study will be conducted at approximately 74 centers. Amendments will continue to enroll without interruption, in sequence. Thus enrollment may exceed initial projections
- It is anticipated that you will participate in the study for approximately 14 months. The exact length of time will depend on how you are doing.
- Overall study duration is approximately 7 years.

ALTERNATIVES

You do not have to participate in this research study.

Talk to your study doctor about your choices before you decide if you will take part in this study. Alternatives to participating in the study include:

- Receiving treatment or care for your cancer without being in a study
- Taking part in another study
- Receiving no treatment
- Receiving comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by your 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.

BENEFITS

We are unsure if you will receive any benefits by taking part in this research study, however, the information gained from this study will help study doctors learn more about neratinib as a treatment for cancer. This information may help future cancer patients.

RISKS OR DISCOMFORT

The following risks may occur:

Based on safety information from previous subjects treated with neratinib, the following side effects have been observed:

Very common (≥ 1/10) [*may occur in 10 or more subjects in 100]*

- Diarrhea
- Nausea
- Vomiting
- Abdominal pain
- Pain, redness, swelling or sores in the mouth, and/or throat
- Fatigue
- Decreased appetite
- Muscle spasms
- Rash (includes red, flat, patchy rash or raised small bumps which may cause itchiness and may occur in more than one area of the body, and/or may contain fluid or pus)

Common (≥1/100 and <1/10) [*may occur between 1 and 9 subjects in 100*]

- Increased blood levels of alanine aminotransferase (an increase in an enzyme that measures the function of the liver, also known as ALT)
- Increased blood levels of aspartate aminotransferase (an increase in an enzyme that measures the function of the liver, also known as AST)
- Increased blood levels of creatinine (abnormally high level of creatinine in the bloodstream which may indicate kidney disease)
- Dyspepsia (indigestion)
- Abdominal distension
- Urinary tract infection
- Weight loss
- Dehydration

- Nose bleed
- Nail disorder (inflammation/infection, breaking or discoloration)
- Dry skin
- Deep skin cracking
- Dry mouth

Uncommon (≥1/1000 and <1/100) [may occur in less than 1 subject in 100]

- Increased blood levels of bilirubin (an increase in an enzyme that measures the function of the liver)
- Renal failure (damage to the kidney which may decrease its functioning)

Diarrhea and vomiting can quickly lead to a loss of too much water from your body (dehydration). If you get very dehydrated, this could make your blood pressure low and could make it hard for your kidneys to clean your blood. If your dehydration is not treated, this could lead to a subtype of kidney failure called pre-renal failure. This type of kidney failure gets better when fluids are given. Patients who suffered from pre-renal failure in neratinib trials have all fully recovered their renal function.

Symptoms of mild dehydration include thirst, decreased urine volume, abnormally dark urine, unexplained tiredness or fatigue, irritability and negative mood, headache, dry mouth and dry skin, dizziness when standing, and in some cases can cause insomnia. Other possible symptoms include cloudy urine, and burning sensation during urination.

Make sure you drink enough liquids each day (8 to 10 large glasses or cups). If you have severe diarrhea and/or vomiting, even for a short period of time, call your study doctor immediately to prevent the signs of dehydration described above.

Other Potential Side Effect of Neratinib

The side effects listed below have been reported with neratinib however, the relationship of these events to treatment with neratinib is unknown at this time. They occurred uncommonly (≥0.1% - <1%) between 1 and 9 subjects in 1000, but can be ultimately life-threatening if not treated rapidly. Call your study doctor immediately if you experience any of the symptoms described in the section below.

- Severe liver damage:
  There have been reports of patients taking neratinib, who have had severe changes in liver function tests, which may indicate important liver damage. Based on the reports observed so far, these changes appear to be reversible when neratinib is stopped. If you experience multiple loose bowel movements in a day or any worsening of fatigue, nausea, vomiting, abdominal pain or tenderness, fever or rash, notify your doctor immediately as these may be associated with changes in your liver function.

- Interstitial lung disease:
  One patient with non-small cell lung cancer who was treated with neratinib experienced interstitial lung disease (inflammation and scarring of the lungs that is similar to pneumonia). This lung problem could have been caused by neratinib. The patient's health improved when she stopped taking neratinib and began to take steroids and anti-infection medication to treat this side effect. If you feel shortness of breath along with fever or cough, please let your study doctor know immediately.

You may experience some, all, or none of these side effects. However, life-threatening and even fatal side effects could occur. You will be monitored closely for all side effects including any that are unexpected. If symptoms

develop, your study physician will start appropriate treatment. You must tell the study doctor about any new health problems that develop while you are participating in this study.

Information on other risks:

Risks of Taking Neratinib with Acid-Reducing Medication
The absorption of neratinib in the stomach is dependent on stomach acidity. Medications that reduce the secretion of acid in the stomach such as antacids, proton pump inhibitors (such as Lansoprazole), and H2-receptor antagonists (such as ranitidine) may affect how neratinib dissolves in the stomach. It has been observed that a single 240-mg dose of neratinib combined with a proton pump inhibitor lowered the absorption of neratinib up to seven-fold. It is not known whether separating the time of taking a proton pump inhibitor and neratinib reduces the interaction. If you are required to take a H2-receptor antagonist (such as ranitidine) to reduce stomach acid, take neratinib 10 hours after taking the medication and at least 2 hours before the next dose of that medication. If antacids are necessary, the antacid dose and the neratinib dose should be separated by 2 to 4 hours. If you have any questions, you should consult with your doctor about what type of acid-reducing medication you are taking.

Risk of Loperamide
Loperamide may be taken to treat diarrhea during the course of the study. Taking loperamide might be associated with, but is not limited to the following symptoms: constipation (decreased or absence of bowel movements), dry mouth, abdominal pain or discomfort, nausea and vomiting. Drowsiness, dizziness and fatigue may occur with loperamide as well. Difficulty or inability to completely void the bladder (difficulty to urinate) has been reported less often. Allergic reactions such as skin rash and itching including severe forms have also been reported; however, other medications may have caused or contributed to some of these cases. Please refer to the loperamide package insert for additional information.

Risks of the Blood Collection
You may have pain, swelling, or bruising around the vein where your blood is collected. You may feel dizzy or you may faint. An infection may develop on your body where your blood is collected.

Risks of the ECG (EKG)
During an electrocardiogram, leads (wires) connected to small metal disks will be attached to certain points on your body to measure the electrical activity of your heart. Placement of the leads may cause skin irritation, redness, or burning of the skin at the site where the leads are attached.

Risks of an ECHO
An echocardiogram is a type of ultrasound test that uses sound waves to create pictures of the heart. The technician will put gel on your chest to help the sound waves pass through your chest. A probe is passed over your chest which picks up echoes of sound waves as they bounce off different parts of the heart. There are no known risks associated with this test.

Risks of the MUGA Scan
A MUGA scan measures how well your heart pumps blood. During a MUGA scan, a radioactive dye is injected into a vein, and special equipment is used to measure the pumping capacity of your heart. You will be exposed to radiation from the injection given for the MUGA scan. The needle puncture into the vein for the MUGA scan may cause bruising, inflammation, or infection at the site of the puncture.

Risks of the Bone Scan
A bone scan is done to detect or rule out malignant bone lesions. It is not necessary to fast before the bone scan, but it is best to avoid eating a meal or drinking large amounts of fluids before the test. A tourniquet will be applied to your arm, and a radioactive dye will then be injected into a vein. You may have pain when the needle is inserted into your arm. You will have to wait 2-3 hours after the injection before the scan can be performed. You will lie on

your back on a table within the scanner, and you must be as still as possible during the test. You may be asked to assume various positions on the table in order for all of the necessary images to be taken. The scanner will move back and forth slowly, recording images for about 1 hour. After the test, you should drink plenty of fluids. You will be exposed to a small amount of radiation from the injection given for the bone scan.

Risks of the Chest X-Ray

A chest x-ray is done to detect and rule out lesions in the lung. During the test, you may be asked to stand and hold your breath as they take an image of your chest. It is very important during a chest x-ray to not move in order to produce a clear picture of your lungs. The procedure will only take a few minutes, and the time you will be asked to hold your breath is a matter of a few seconds. You will be exposed to a small amount of radiation during this test.

Risks of the CT scan

A CT scan takes about 30 to 60 minutes. If a contrast dye is to be used for the scan, you must not drink or eat anything for 4 hours before the test. You will be asked to remove all jewelry. A tourniquet will be applied to your arm, and a dye will be injected. You may have pain when the needle is inserted into your arm. When the contrast medium is injected during the CT scan, you may experience nausea, flushing, warmth and/or a salty taste. You might be allergic to the contrast medium. During the test, you will lie on your back on an x-ray table. A strap will be placed across the body part to be scanned; this is done to prevent movement so that the x-ray picture will be clear. The table will then slide into a large, tunnel-shaped machine. You might be uncomfortable while you are in the tunnel-shaped machine. Some patients have felt claustrophobic during this test. When the CT scan is finished, you may immediately resume your usual activities and diet. You will be exposed to radiation during this test.

Risks of the MRI

An **MRI** scan is performed like a CT scan. It is in a large, tunnel-shaped machine but it does not use x-rays. The MRI uses radio frequency waves, like those in an AM/FM radio, and has a powerful magnet. You must not have any metal objects on or in your body, for example, brain aneurysm clips or a pacemaker, and remove all jewelry to be able to have a MRI scan. Similar to CT scans, IV contrast dye may be used for MRI scans. Rarely, patients can have allergic reactions to MRI contrast agents.

Risks of Colonoscopy

A colonoscopy poses few risks however in rare instance, complications of this procedure may include:

- Adverse reaction to the sedative used during the examination
- Bleeding from the site where a tissue sample (biopsy) was taken or a polyp or other abnormal tissue was removed from site
- A tear in the colon or rectum wall (perforation)

Risks to Unborn Children

It is not known whether neratinib may cause side effects to pregnant women, to an unborn child (an embryo or a fetus), or to children of nursing women. In a study with pregnant animals, administration of neratinib caused harm, including birth defects and death to the fetuses. Because of these unknown risks, if you are pregnant or trying to become pregnant you cannot enter the study. If you are nursing a child, you may not be entered in the study.

If you are a female who is able to have children, you must have a negative pregnancy test before receiving investigational drug . You are considered able to have children if you have not completed menopause or are not surgically sterile.

If you are not surgically sterile or postmenopausal, or are a male patient, you must agree and commit to the use of a highly effective non-hormonal method of birth control while enrolled in the study. Your doctor can discuss highly effective non-hormonal birth control methods with you. After your last dose of the investigational drug you must continue to use medically highly effective non-hormonal birth control for 28 days.

If you miss a period or think you might be pregnant during the study, you must tell your study doctor immediately. If you become pregnant during the study or within 28 days after your last dose of investigational drug, your study doctor will ask to follow the outcome of your pregnancy and the condition of your newborn.

The effects of the investigational drug on an unborn child (embryo or fetus) fathered by a man taking the test article are unknown. *Male patients with a female partner of childbearing potential must agree and commit to use condoms and in addition the female partner must agree and commit to use a highly effective method of contraception (ie, hormonal contraception associated with inhibition of ovulation) throughout the study and for 3 months after the last dose of investigational drug.*

Unknown Risks

The investigational drug and procedures in this study may have risks that are not known at this time.

You will be told in a timely manner of new information that may affect whether you will want to continue to participate in this study.

COMPENSATION

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

COST

There will be no additional costs to you as a result of being in this study. However, routine medical care for your condition (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further.

CONFLICT OF INTEREST STATEMENT

[*If the Principal Investigator, research staff, or their family members have conflicting interest associated with this research, insert Conflict of Interest information here. Explain how the conflict will be managed to ensure that the integrity of the study data. If there is no conflict or potential conflict, delete this section.*]

PRIVACY AND CONFIDENTIALITY

Your signature on this consent form gives permission for the research study staff to collect and use information that can identify you. Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified on any study form by name, social security number, address, telephone number or any other direct personal identifier. Instead, the research study doctor will use your initials and you will be assigned a patient identification number. The study doctor will keep a list that matches patient identification numbers to patient names, but the study doctor will not send that list to the study sponsor. However, the study

forms will contain other information about you, such as your age, sex and medical history. It is possible that this other information could be used to identify you even though your name does not appear.

The results of this research may be presented at scientific or medical meetings or published in scientific journals. In this case, your identity will not be made known.

Other groups may need to look at your medical records and study forms to make sure that the information is correct and to evaluate the conduct of this research study. These include the following:

- The sponsor of this study (Puma Biotechnology, Inc.) and its designees, including any contract research organizations helping the sponsor with the research study
- Collaborators and other parties working with the study sponsor
- The Institutional Review Board that approved this research study
- Regulatory agencies in the United States, such as the Food and Drug Administration, Department of Health and Human Services and the Office for Human Research Protections, as well as regulatory agencies in other countries where the sponsor seeks approval of the study drug or where the study is being conducted.

You can change your mind about being in the study at any time. If you do change your mind about taking part in the study, no further data will be collected from you. However, the sponsor needs to retain and use any study results that have already been collected in order to maintain the quality of the study.

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.

In addition to this Informed Consent Form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information." This authorization will give more details about how your information will be used for this study, and who may see and/or get copies of your information.

BIOLOGICAL SAMPLES
WHAT WILL HAPPEN TO ANY SAMPLES I GIVE?

Your biological samples (such as blood, urine, or tissue) may be collected, processed and reported as necessary for the purposes of the study. Any sample that you provide will be coded to ensure that your identity remains confidential. Your samples will be transferred to U.T. MD Anderson Cancer Center, [redacted] and the samples will be tested. In order to do this, genetic material (if applicable) from your tumor and blood will be tested.

Testing will be done during or after you have participated in this study. The information resulting from the analysis will be used anonymously, meaning that your identity will not be revealed. You will not receive the results of this testing. Your samples will be stored for up to 20 years after the end of the study. They will be used only for research and will not be sold. The research done with your samples may help to develop new products in the future.

The U.S. and some states (including New York) have laws that forbid using your genetic information as a reason to fire you or not to give you a job. Under these laws, genetic information cannot be used to deny you health insurance or to raise the cost of your current health insurance. However, we cannot fully guarantee you that no one will ever use your test results against you, and these laws do not apply to life or disability insurance, or if you are a member of the military.

VOLUNTARY PARTICIPATION / WITHDRAWAL

You should only take part in this study if you want to volunteer. You should not feel that there is any pressure to take part in the study. You are free to participate in this research or withdraw at any time. There will be no penalty or loss of benefits you are entitled to receive if you stop taking part in this study. [*If participants are employees, include as applicable: "decision to participate or not to participate will not affect your job status."*]

You will be withdrawn from the study if:

- Your disease progresses
- Your study doctor believes it is in your best interest for any reason, including the need to start another anti-cancer treatment
- You have serious side effects that would make it unsafe to continue on the study
- You do not follow the study rules
- The sponsor suspends or terminates the study or part of the study at any time for any reason

NEW INFORMATION ABOUT THE STUDY

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

WHAT IF YOU GET SICK OR HURT WHILE YOU ARE IN THE STUDY?

If you need emergency care:

- Go to your nearest hospital or emergency room right away or call [*insert country specific #, if applicable*] for help. It is important that you tell the doctors at the hospital or emergency room that you are participating in a research study. If possible, take a copy of this informed consent form with you when you go. [*Insert facility name*] does not have an emergency room or provide emergency care.
- Call the study doctors as soon as you can. They will need to know that you are hurt or ill. Call [*Name of Study Doctor at Telephone #*] or [*alternate telephone #*].

If you do NOT need emergency care:

- Go to your regular doctor. It is important that you tell your regular doctor that you are participating in a research study. If possible, take a copy of this informed consent form with you when you go.
- The [*insert facility name*] may not be able to give the kind of help you need. However, let the study doctor know of your illness either before or during your next scheduled study visit.

Will I be compensated for research related injuries?

[*This section should be modified only as required by the Clinical Study Agreement, the IRB or local laws.*]
If you feel that you have been injured as a result of taking the study drug or any of the anti-diarrhea drugs in this study, you should contact your study doctor. If the study doctor and the sponsor determine that the injury is a direct result of effects of the study drug or one of the anti-diarrhea drugs or the study procedures performed due to your participation in the study, the sponsor will reimburse you for the reasonable cost of emergency and/or acute medical care incurred by you for treatment if you do not have commercial medical insurance or to the extent that those medical expenses are not covered by your commercial medical insurance. Injury resulting from the use of the study drug, or one of the anti-diarrhea drugs or a study procedure does not include the normal progression

of your disease or any underlying pre-existing medical conditions. Other compensation (including without limitation) for such things as lost wages, disability, or discomfort due to this type of injury is not available. You understand, however, that you have not waived any of your legal rights by signing this consent form.

The study doctor will ask to follow up with you if you are injured.

WHAT HAPPENS IF YOU DECIDE NOT TO TAKE PART IN THIS STUDY?

If you decide not to take part in the study you will not be in trouble or lose any rights you normally have. You will still have the same health care benefits and get your regular treatments from your regular doctor.

You can decide after signing this informed consent document that you no longer want to take part in this study for any reason at any time. If you decide you want to stop taking part in the study, tell the study staff as soon as you can.

- We will tell you how to stop safely. We will tell you if there are any dangers if you stop suddenly.
- If you decide to stop, you can continue getting care from your regular doctor.
- [*Describe the procedures for the orderly termination of participation by the participant.*]

Even if you want you to stay in the study, there may be reasons we will need to withdraw you from the study. You may be taken out of this study if we find out it is not safe for you to stay in the study or if you are not coming for the study visits when scheduled. We will let you know the reason for withdrawing you from this study.

YOU CAN GET THE ANSWERS TO YOUR QUESTIONS, CONCERNS, OR COMPLAINTS.

If you have any questions, concerns or complaints about this study, call [*name of principal investigator*] at [*telephone #*].

If you have questions about your rights, general questions, complaints, or issues as a person taking part in this study, call the [*insert facility name*] Institutional Review Board (IRB) at (###) ##-####.

MASTER INFORMED CONSENT TO PARTICIPATE IN RESEARCH

CONSENT TO TAKE PART IN RESEARCH

It is up to you to decide whether you want to take part in this study. If you want to take part, please read the statements below and sign the form if the statements are true.

I freely give my consent to take part in this study and authorize that my health information as agreed above, be collected/disclosed in this study. I understand that by signing this form I am agreeing to take part in research. I have received a copy of this form to take with me.

_____ _____

Signature of Person Taking Part in Study Date

_____

Printed Name of Person Taking Part in Study

STATEMENT OF PERSON OBTAINING INFORMED CONSENT AND RESEARCH AUTHORIZATION

I have carefully explained to the person taking part in the study what he or she can expect from their participation. I hereby certify that when this person signs this form, to the best of my knowledge, he/ she understands:

- What the study is about;
- What procedures/interventions/investigational drugs or devices will be used;
- What the potential benefits might be; and
- What the known risks might be.

I can confirm that this research subject speaks the language that was used to explain this research and is receiving an informed consent form in the appropriate language. Additionally, this subject reads well enough to understand this document or, if not, this person is able to hear and understand when the form is read to him or her. This subject does not have a medical/psychological problem that would compromise comprehension and therefore makes it hard to understand what is being explained and can, therefore, give legally effective informed consent.
This subject is not under any type of anesthesia or analgesic that may cloud their judgment or make it hard to understand what is being explained and, therefore, can be considered competent to give informed consent.

_____ _____

Signature of Person Obtaining Informed Consent / Research Authorization Date

_____

Printed Name of Person Obtaining Informed Consent / Research Authorization

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Functional Area: Business Development
Meaning Of Signature: I am approving this document
Date/Time: 8/16/2019 10:41:52 AM

Signed By: [redacted]
Functional Area: Clinical Development
Meaning Of Signature: I have reviewed and agree with the content of this document
Date/Time: 8/16/2019 10:50:19 AM

Signed By: [redacted]
Functional Area: Executives
Meaning Of Signature: I am approving this document
Date/Time: 8/16/2019 12:58:31 PM

Signed By: [redacted]
Functional Area: Quality
Meaning Of Signature: I am approving this document
Date/Time: 8/19/2019 11:13:15 AM