An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib

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MASTER INFORMED CONSENT TO PARTICIPATE IN RESEARCH - PORTUGAL

Information to Consider Before Taking Part in This Research Study and Informed Consent Form

Study Title: An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients with HER2 Amplified Breast Cancer Treated with Neratinib

Protocol Number: PUMA-NER-6203

EudraCT nº: 2019-001896-35

Investigator Name: [redacted]

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 and includes an information sheet and a consent form. Please read this information carefully and take your time making your decision. Ask the researcher 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 nature of the study, risks, inconveniences, discomforts, potential benefits, and other important information about the study will be reviewed with you. Once you understand the study and you agree to participate, you will be asked by the study staff to sign this form. Additionally, the study staff will provide you with a copy of the signed form.

Please tell the study doctor or study staff if you are taking part in another research study. Before reading, please check with your private health insurance or health subsystem if they agree with your participation in this study.

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

An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients with HER2 Amplified Breast Cancer Treated with Neratinib

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

The research will be conducted at Hospital CUF Descobertas, Lisbon (Portugal).

This research study has been approved by the Ethics Committee for Clinical Research (CEIC) and the National Authority for Medicines and Health Products, I.P. (INFARMED), in accordance with the current legislation in force, namely Law No. 12/2005, of January 26th, and Decree-Law No. 131/2014, of August 29th, regulating personal genetic and health information, and Laws No. 21/2014, of April 16th, approving the law of clinical research, and No. 73/2015, of July 27th, establishing the conditions under which monitors, auditors and inspectors may access the records of clinical trials' participants. The study will also be carried out in accordance with the current revised version of the Declaration of Helsinki and Good Clinical Practice and any other legislation, where applicable.

This research is being sponsored by Puma Biotechnology, Inc.

PURPOSE OF THE STUDY

The purpose of this study is to:

- Increase our understanding of how your colon (the largest portion of the large intestine) is affected while taking the anticancer drug neratinib.

SHOULD YOU TAKE PART IN THIS STUDY?

- This form tells you about this research study. After reading through this form and having the research explained to you by someone conducting this research, you can decide if you want to take part in it. Please note that you do not have to take part in this research 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, as you go along.

- Take your time to think about the information that is being provided to you.

- Feel free to talk it over with your regular doctor.

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, then you should sign the 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 been diagnosed with HER 2+ breast cancer.

WHAT WILL HAPPEN DURING THIS STUDY?

If you have early stage breast cancer and decide to participate in this study and your doctor determines that you are eligible, you will receive the study drug, neratinib, taken by mouth, daily with food for approximately one year. You will not be required to make up missed doses of neratinib.

If you have metastatic breast cancer and decide to participate in this study and your doctor determines that you are eligible, you will receive the study drug, neratinib, taken by mouth, daily with food for a period of 28 days. After your second colonoscopy is completed (following the initial 28 day dosing period), your treatment will continue in 21 day periods called cycles. During each of these cycles of treatment, you will receive the study drug on days 1 to 21 of each cycle in combination with another anti-cancer drug called capecitabine. Capecitabine is a tablet. Your study doctor will calculate your dose based on your most recent height and weight. You will take a total daily dose of 1500 mg/m^2 (supplied as 150 mg and 500 mg tablets), <u>divided in 2 doses</u> to be taken once in the

morning and once in the evening by mouth **every day for the first 14 days** of each 21 day cycle starting at Cycle 1/Day 1. The doses may be adjusted by your study doctor depending on how you are tolerating the treatment. There will be 7 days in each cycle that you do not take capecitabine, but you should continue taking the neratinib as directed by your study doctor. Capecitabine should be taken with water within 30 minutes after a meal.

- The study drug, neratinib, is a medicine for women who have HER 2+ breast cancer. In patients with HER2+ breast cancer, neratinib works to block the growth pathways of cancer cells that have too many HER2 receptors.

- Prior to starting treatment with and following the first 28 days taking the study drug, you will undergo a colonoscopy. A colonoscopy is a procedure where a doctor will use an instrument to examine the inside of your colon. During each colonoscopy, the doctor will perform approximately 8 biopsies (collection of small pieces of tissue) at various locations in your colon. Prior to the collection of each biopsy the doctor will take a photograph of the area. In addition, a blood sample (5 ml) and a stool sample will be collected at the time of each colonoscopy for laboratory analysis of markers of inflammation. Patients participating in the study will complete a total of 2 colonoscopies about 4 weeks part. This procedure is being performed to determine how the study drug affects your colon.

- Your blood will be collected at screening and on the first day of taking the study drug just prior to dosing. Blood samples will be tested to determine the number of your red blood cells, white blood cells and parts of your blood which control bleeding. Additional tests will be made on your blood to determine the state of your liver function, kidney function and overall health. Approximately 15 ml of blood will be collected during the screening and first day of taking the study drug. Your doctor may perform additional blood tests during the study as he or she feels is necessary.

- During screening, you will receive several tests to determine how well your heart functions. The first test, called an electrocardiogram, measures the electrical activity of your heart. The second test determines how well your heart works to pump your blood. This second test may be referred to as a MUGA or ECHO test by your doctor. Your doctor may perform additional heart tests during the study as he or she feels is necessary.

- Women who are capable of having children will be required to take a pregnancy test during screening.

- Your doctor will perform a full physical examination during screening and a shorter physical exam on the first day of the first cycle of study drug. Your vital signs (heart rate, blood pressure and temperature) will be determined during these visits. These tests are used by your doctor in evaluating your overall health.

- After you are determined to be eligible for study participation, you will begin taking six (6) 40 mg tablets (240 mg) of neratinib daily.

- A common side effect of neratinib is diarrhea. In order to prevent or lessen the severity of diarrhea, you will be taking loperamide (also known as Imodium). During the first two weeks of treatment, you will take 4 mg (2 tablets) of loperamide 3 times a day. The first dose of loperamide will be taken with the first dose of neratinib. During the second half of the first 28 days of treatment, you will take 4mg (2 tablets) 2 times a day. After the first 28 days of treatment with neratinib is completed, you will take further doses of loperamide on an as needed basis. During the first 28 days of taking neratinib, you will be asked to record your daily dose of neratinib and loperamide in a diary. If you take any other medications to control diarrhea, these will also be recorded in the diary.

- For patients with early stage breast cancer, your doctor will perform a brief physical exam and collect a blood sample to measure your liver function approximately every 3 months. Five milliliters of blood will be collected at each of these study visits.

- For patients with metastatic breast cancer, your doctor will perform a brief physical exam including vital signs and collect blood samples to measure your kidney function, liver function, electrolytes, white and red blood cell counts and platelets (blood component involved in clotting) at the start of each 21 day cycle of treatment. Approximately fifteen milliliters of blood will be collected at each of these study visits. Tests to assess your heart function (electrocardiogram, ECHO or MUGA) will be performed on Day 1 of Cycle 3, Day 1 of Cycle 6 and on Day 1 of every sixth subsequent cycle of treatment.

- An end of treatment visit with your doctor will take place on Day 28 of Cycle 13 for early breast cancer patients, followed by Safety Follow-up Visit 28 days after the last dose of neratinib. For patients with metastatic breast cancer, your end of treatment visit will be conducted by your doctor on Day 21 of your last cycle of treatment. A Safety Follow-up visit will take place 28 days after your last dose of neratinib. You will be required to complete an end of study visit in the event your disease reoccurs, progresses or if you are unable to tolerate neratinib.

TOTAL NUMBER OF PARTICIPANTS AND STUDY DURATION

- About 5 individuals will take part in this study. A total of 2 to 3 individuals will participate in the study at each site in the following countries: USA and Portugal.

- The duration that each patient will participate in the study is approximately 1 year for patients with early stage breast cancer. For patients with metastatic breast cancer, treatment will continue until disease progression or until unacceptable side effects occur.

- Overall study duration of the study is approximately 1.5 years.

ALTERNATIVES

In the event that you do not want to receive the treatment proposed for this study, your doctor will inform you of the therapeutic alternatives available for the treatment of your disease. There are other alternatives in addition to the treatment strategies that will be used in this clinical trial. You will be able to discuss the advantages and inconveniences of each of these alternative treatments with your doctor. Alternatives to participating in the study include:

- Starting a different anticancer treatment and/or research study
- No additional treatment for your breast cancer at this time

BENEFITS

It cannot be guaranteed that your participation in this study will benefit you. The potential benefits of participating in this research study include:

- Decreased risk of recurrence of your breast cancer (early breast cancer patients)
- Improvement or stabilization of your metastatic breast cancer
- Examination of your colon for any instances of a finding your doctor would consider abnormal

It is also possible that you may not benefit personally from your participation in this study, but that the information obtained in the study may be useful in the treatment of other patients with the same disease in the future.

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 (an abnormally high level of creatinine in the bloodstream 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 the dehydration is not treated, this could lead to a subtype of kidney failure called pre-renal failure. This 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 stinging 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 the study doctor immediately to prevent the signs of dehydration described above.

Other Potential Side Effects 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 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 liver function tests.

- Interstitial lung disease:

  One patient with non-small cell lung cancer who was treated with neratinib experienced interstitial lung disease (which is inflammation and scarring of the lungs). 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.

Risks of Taking Capecitabine (metastatic breast cancer patients)

If you have metastatic breast cancer, you will need to take another anti-cancer drug, capecitabine, in combination with neratinib. Taking capecitabine may result in the following side effects: diarrhea, heart problems (heart attack, changes in electrical activity of your heart, problems with your heart muscle), dehydration, kidney failure, skin reactions (rash, blisters, peeling), mouth sores, changes in the sensation in your hands and feet, liver problems and decreases in the number of your white blood cells, red blood cells and platelets (a component of your blood involved in clotting). 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.

Risks of Taking Loperamide

You will need to take loperamide to treat diarrhea during the course of the study. Taking loperamide might be associated with, but not limited to, the following symptoms: constipation (decrease 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 frequently. 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 Colonoscopy

As part of this study you will have two colonoscopies about 4 weeks apart. You doctor will follow the hospital procedure for preparing for the colonoscopy. A serious but uncommon (1 in 2000 procedures) risk during colonoscopy is rupture of your bowel. You would require immediate surgery if this were to happen. Another risk of the procedure is bleeding resulting from tissue sample collection. Delayed bleeding may occur during the first week following the procedure. A repeat colonoscopy may be necessary in the event that this bleeding is not self-limiting.

Anesthesia is routinely given to patients undergoing colonoscopy. The risks involved with anesthesia include heart and lung problems such as a drop in blood pressure or a lowered concentration of oxygen in your blood. Other less common risks of anesthesia include an increased risk of blood clots, heart attack or stroke. Risks associated with anesthesia will be managed during the procedure by an anesthesiologist and the doctor performing the colonoscopy.

Medications (laxatives) given to clear your colon prior to each colonoscopy can result in dehydration. Patients must drink sufficient amounts of fluid when preparing for the procedure to prevent dehydration. Severe dehydration can result in damage to your kidneys. Symptoms of dehydration include headache, tiredness, confusion, light headedness, and decrease in the volume of urine when emptying your bladder. You should inform your doctor if you experience any of these symptoms during the day you prepare for or the day of your colonoscopy.

Risks of the Blood Collection

You may have pain, swelling, or bruising around the vein where your blood is collected. There may be risk of infection. You may feel dizzy or you may faint. You may get an infection at the place on your body from which the blood is collected.

Risks of the ECG/EKG and ECHO

Placement of the leads may cause skin irritation, redness, or burning of the skin at the site where the leads were attached.

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 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 able to have children, you must have a negative pregnancy test before participating in the study. 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, you must agree and commit to the use of a reliable method of birth control (i.e., a highly effective non-hormonal method of contraception) while enrolled in the study. For women of childbearing potential, examples of reliable methods would be intrauterine device, bilateral tubal ligation, vasectomized partner, or abstinence (only when it is the preferred lifestyle). Male patients with a female partner of childbearing potential should agree and commit to use condom, and the female partner must agree and commit to use any of the above reliable methods, or hormonal contraception associated with inhibition of ovulation, while on treatment and for 3 months after last dose of investigational products.

Your doctor can discuss acceptable birth control methods with you. After your last dose of the investigational drug you must continue to use medically acceptable 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 test article, 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. Men with partners of childbearing potential must use a medically acceptable method of birth control 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 not receive payment or other compensation for taking part in this study. You will not have to pay any expenses connected with the drugs or any examinations carried out in the course of the study. Expenses for travelling and meals that may be considered legitimate within the framework of this clinical trial will be reimbursed on presentation of confirmatory receipts. These amounts will be paid to you via the study team or the financial department of the hospital, after these receipts have been delivered and checked.

Your health information and biological samples (such as blood, urine, or tissue) collected during this study may be used for the development of new or improved drugs or other products, tests, processes, or services that could have value and be sold for profit by the sponsor or by others for the sponsor's benefit or the benefit of the study doctor or third parties. The sponsor does not intend to provide you with financial compensation or to share with you any of the profits that may be earned as a result of any research conducted by the sponsor on these samples.

Please be aware that the performance of this study entails specific research work and, therefore, both the hospital and the professionals participating in the study, including your doctor, will receive financial compensation from the sponsor.

COSTS

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

PRIVACY AND CONFIDENTIALITY

Your study doctor and the study staff will collect and use information about you for the study. This may include your identification number, location information, and health information, and data that is obtained from any biological samples taken from you such as your blood, tissue or saliva. This information is referred to as "Personal Data". Your Personal Data will be handled in accordance with the Regulation (EU) 679/2016, of 27 April 2016 (hereinafter, GDPR).

In this study, the Personal Data the study doctor and study staff will collect, use share, and transfer out of the EU as part of your coded Study Data, may include sensitive information about you such as your race, ethnic origins, genetic data and biometric data. If you want to consent to the collection, use and sharing of your sensitive Personal Data, then you should check the box next to the statement above your signature so we know you understand what your sensitive Personal Data may include, and specifically consent to the collection, use sharing, and transfer outside of the EU of that sensitive Personal Data as described in this Informed Consent Form. If you do not consent to the collection, use and sharing of your sensitive Personal Data as described in this Informed Consent Form, then you may not be in this study.

If you consent to the use and sharing of your sensitive Personal Data as part of the coded Study Data by checking the box below, you have a right to withdraw that consent at any time and for whatever reason. If you do withdraw your consent, the Sponsor may continue to use your sensitive Personal Data that has already been collected as part of the coded Study Data. If you wish to withdraw your consent as to the collection, use and sharing of your sensitive Personal Data, please contact your study doctor.

Your identity will be kept confidential as required by applicable law, but there is always a risk that some of your Personal Data may be disclosed.

You will not be identified on any study form or study document by name, national identity number, address, telephone number, or by any other direct personal identifiers. Instead, you will be identified by an assigned subject identification number (code). The study doctor will keep the list that matches the subject identification numbers to subject names. That list will not be provided to the sponsor, and only the study doctor will have access to the list. The Personal Data together with other information collected about you during the study is referred to as the "Study Data" and will be coded before it is transferred outside the study center. Study Data and the key reconnecting the Study Data to you will be kept by the study center for up to 25 years after the study is completed or for such longer time period that may be required under local law.

The sponsor, parties working with or on behalf of the sponsor, the ethics committee responsible for approving the conduct of the study, local regulatory authorities and regulatory authorities in other countries where the sponsor may seek approval for the study drug, such as the United States Federal Food and Drug Administration, may access your medical records to make sure the study has been done properly, and may be able to identify you. Your medical records will be reviewed only at the study center.

The Study Data will be used by the sponsor to carry out the study, to develop the study drug, to meet its legal obligations in connection with the conduct of the study and to make publications and presentations about the study. In addition, the sponsor and parties working with or on behalf of the sponsor may use your Study Data to perform additional unknown future research. Although the exact nature of the research that may be performed is not known at this time, such research will be in connection with patient care and public health, including the development of new drugs and treatments for diseases. The sponsor will limit and monitor access to your Study Data and put appropriate restrictions in place so that efforts are made to not identify you and to ensure that your Study Data are only used for the purposes described in this Patient Information Sheet. For certain reasons, you may have a right to oppose the use of your Study Data for additional future unknown research. If you wish to object to such use, please contact your study doctor.

If you consent to the use and sharing of your Study Data by signing the attached Consent Form, you have a right to withdraw that consent at any time and for whatever reason. If you do withdraw your consent, the sponsor may continue to use the Study Data that has already been collected. If you wish to withdraw your consent, please contact your study doctor.

THE SPONSOR AND SOME OF THE RECIPIENTS OF YOUR STUDY DATA MAY BE BASED IN COUNTRIES OUTSIDE THE EUROPEAN UNION, SUCH AS THE UNITED STATES, THAT MAY NOT HAVE THE SAME LEVEL OF DATA PROTECTION AS IN PORTUGAL OR IN THE EUROPEAN UNION. HOWEVER, THE SPONSOR AND ITS REPRESENTATIVES WILL TAKE REASONABLE MEASURES TO KEEP YOUR STUDY DATA CONFIDENTIAL IN ACCORDANCE WITH APPLICABLE LAWS. BY PARTICIPATING IN THIS STUDY, YOU CONSENT TO THE TRANSFER OF YOUR STUDY DATA TO THESE COUNTRIES.

The results of this study may be published and presented to the public, and used for educational purposes. Information that could directly or indirectly identify you (like your name) will not be used in any publication or presentation.

You have certain rights to your Study Data that is kept by the study center and the sponsor including the rights of access, rectification, restriction, and data portability. If you wish to exercise any of your rights, you should contact the study doctor. You also have a right to bring a complaint to the regulatory authority responsible for the protection of Personal Data in your country. In accordance with the applicable legislation, you are entitled to exercise the rights contained in the previous paragraph, and you can discuss them by contacting the doctor who is treating you in this study.

Should you wish to know more about how your Personal Data is protected by the study sponsor, you may contact the sponsor at info@pumabiotechnology.com.

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

BIOLOGICAL SAMPLES

WHAT WILL HAPPEN TO ANY SAMPLES I GIVE?

Biological samples will be collected from you as described in this Patient Information Sheet.

Some biological samples collected during the study may be tested immediately at the local laboratory of the site where the research is being conducted in Portugal and then destroyed in accordance the site's procedures. Some samples will be sent for testing to the University of South Alabama College of Medicine (Division of Gastroenterology), Mobile, Alabama (United States). In addition, some of the samples will be retained by the sponsor until the samples have expired and are no longer usable. These samples may be used by the sponsor and third parties working with the sponsor, in future research in connection with the development of the study drug, other drugs and diagnostics. The samples will not be marked with information that can identify you. The data derived from the use of these samples in future research will be maintained as confidential in the same way as the rest of the data obtained during this study (see section on Privacy and Confidentiality).

If you change your mind about taking part in the study, no further samples will be collected from you. However, the sponsor needs to retain and use any samples that have already been collected and sent to the sponsor in order to maintain the quality of the study.

You do not have to agree with this future use. If you decide to say no, you will be able to continue participating in the study. This decision will not affect the medical care that you are entitled to receive outside of the study.

According to the Law No. 12/2005, of January 26th, and Decree-Law No. 131/2014, of August 29th, regulating personal genetic and health information, you have the right to know, if you so choose, about the genetic data obtained from the analysis of the samples taken. If you decide to request your genetic data, talk with your study doctor about what this may mean for you and your family.

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.

You will be withdrawn from the study if:

- 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

FOLLOW UP

It is very important for the success of the study that we are able to collect information on your response to the study drug throughout the duration of the study.

If for some reason your study doctor loses contact with you (for example, there is no response after calling or mailing information to your home, after contacting the individuals that you provided as additional contact names at the start of the study or after contacting your private doctor) the study doctor will try to obtain your updated contact information by checking publicly available sources, such as information available on the computer.

If updated contact information is not available and your study doctor is unable to contact you, your personal information/personal data (name, address, telephone and date of birth) may be given to the Sponsor's representative (a patient finder company) in order to find more accurate contact information for you, through publicly available sources. The new information will be provided to your study doctor's office so they may re-establish contact with you and further assess your current health status. No personal information/personal data will be provided to the Sponsor from the patient locater service.

If your personal information/personal data is given to the Sponsor's representatives they will not share or distribute this information to any other party. They will keep this information in a protected location to help prevent unauthorized use, access, or disclosure. The information provided will be limited to information that is needed to try to re-establish contact with you. Your personal information will be kept confidential by the Sponsor's representatives until the study is completed, and then the information will be destroyed.

If you choose to no longer participate in the study and you withdrawal your consent completely, you will be asked to confirm this decision in writing.

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 through your study doctor as soon as possible if such information becomes available.

In addition, when receiving new information, your doctor may consider that it is best for you to be withdrawn from the study. Your doctor will explain the reasons and will be responsible for ensuring that your medical care continues.

WHAT IF YOU ARE INJURED WHILE YOU ARE IN THE STUDY?

You will get medical treatment if you are injured as a result of taking part in this study. If you experience any injury or side effects, you should contact your study doctor at:

<site to insert contact name and telephone number>

Your study doctor will explain the treatment options to you and tell you where you can get treatment.

The sponsor has obtained an insurance policy which covers you as a study participant in accordance with the laws of Portugal. The insurance policy has been taken out with Lloyd's Insurance Company S.A. with address at Bastion Tower, Marsveldplein 5, 1050 Brussels (Belgium), under Policy Number WIBCEQ19036. Your study doctor can provide more information about this insurance.

Other compensation (including without limitation) for such things as lost wages, disability, or discomfort due to this type of injury is not available. Please note that your participation in this study may affect the general and

specific conditions (coverage) of your insurance policies (life, health, accident, etc.). Therefore, we recommend that you contact your insurer to determine whether your participation in this study will affect your current insurance policy.

You will not lose any of your legal rights by signing the Consent Form.

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.

- The study doctor will tell you how to stop safely. The study doctor 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.
- Your doctor will perform the following procedures within 5 days of your last dose of study drug if you decide to stop participating in the study: ask if you have any new symptoms or concerns about your health, perform a physical exam and collect vital signs including your weight.

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 the study doctor finds out it is not safe for you to stay in the study or if you are not coming for the study visits when scheduled. Your study doctor 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 [redacted] at [*telephone #*].

The Comissão de Ética para a Investigação Clínica (CEIC) and the Autoridade Nacional do Medicamento e Produtos de Saúde I.P. (INFARMED) are the national regulatory authorities, which are directly involved in the process of evaluation and approval of this clinical trial. Therefore, they are equally available for any clarification, so do not hesitate to contact them.

If you have questions about your rights as a patient in a clinical trial, or questions or complaints regarding this trial, please contact the Comissão de Ética para a Investigação Clínica:

CEIC - Comissão de Ética para a Investigação Clínica
Av. do Brasil, 53 – Pavilhão 17-A
1749-004 Lisboa
Tel.:21 7985340
Fax: 21 7987209

e-mail: ceic@ceic.pt

INFORMED CONSENT FORM

STUDY TITLE:	An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib
PROTOCOL NUMBER:	PUMA-NER-6203
EUDRACT NUMBER:	2019-001896-35

I have received verbal (spoken) information on the above study and have read the attached written information. I have been given the chance to discuss the study and ask questions.

I voluntarily consent to participate in this study, including all assessments, lifestyle restrictions, contraception requirements, and taking of biological samples.

I understand that I am free to withdraw from this study at any time. I understand that if I choose to not participate or to withdraw, my current medical care will not be affected by this decision.

I understand that I will receive and may keep a copy of this signed and dated Patient Information Sheet and Consent Form.

By signing and dating this Consent Form, I have not waived any of the legal rights that I would have if I were not a participant in a medical research study.

I CONSENT AND AUTHORIZE THAT MY STUDY DATA MAY BE TRANSFERRED WITHIN AND OUTSIDE THE EUROPEAN UNION, TO COUNTRIES, INCLUDING THE UNITED STATES, WHERE DATA MAY NOT HAVE THE SAME LEVEL OF DATA PROTECTION AS IN PORTUGAL OR IN THE EUROPEAN UNION. I AGREE THAT MY STUDY DATA MAY BE MADE AVAILABLE TO THE SPONSOR AND PARTIES WORKING WITH THE SPONSOR AS WELL AS TO OTHER PARTIES/ENTITIES IDENTIFIED IN THE PATIENT INFORMATION SHEET FOR THE PURPOSES STATED IN THE PATIENT INFORMATION SHEET.

I AGREE THAT THE BIOLOGICAL SAMPLES COLLECTED FROM ME MAY BE USED AND DISCLOSED FOR THE PURPOSES STATED IN THE PATIENT INFORMATION SHEET. I ALSO AGREE THAT MY CODED BIOLOGICAL SAMPLES MAY BE TRANSFERRED OUTSIDE OF MY COUNTRY TO OTHER COUNTRIES, SUCH AS THE UNITED STATES, WHICH MAY NOT HAVE THE SAME LEVEL OF DATA PROTECTION AS IN PORTUGAL OR IN THE EUROPEAN UNION.

BY SIGNING THIS FORM I CONSENT AND AUTHORIZE THE COLLECTION, USE AND SHARINGOF MY SENSITIVE PERSONAL DATA AS PART OF THE CODED STUDY DATA WITH THE SPONSOR AND OTHER PARTIES AS DESCRIBED IN THIS INFORMED CONSENT FORM.

☐ **BY CHECKING THIS BOX I CONSENT AND AUTHORIZE THE USE OF MY BIOLOGICAL SAMPLES AS PART OF THE CODED DATA BY THE SPONSOR AND OTHER PARTIES FOR POSSIBLE FUTURE STUDIES AS DESCRIBED IN THIS INFORMED CONSENT FORM.**

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 Investigator Obtaining Informed Consent / Research Authorization Date

_____

Printed Name of Investigator Obtaining Informed Consent / Research Authorization

IMPARTIAL WITNESSES' INFORMED CONSENT FORM

STUDY TITLE:	An Open-Label Phase 2 Study to Characterize Colon Pathology in Patients With HER2 Amplified Breast Cancer Treated With Neratinib
PROTOCOL NUMBER:	PUMA-NER-6203
EUDRACT NUMBER:	2019-001896-35

I, ……., declare under my responsibility that:
(Full Witness's Name)

……..
(Full Patient's Name)

The patient has received verbal (spoken) information on the above study and has read the attached written information. The patient has been given the chance to discuss the study and ask questions.

He/she voluntarily consents to participate in this study, including all assessments, lifestyle restrictions, contraception requirements, and taking of biological samples.

He/she understands that he/she is free to withdraw from this study at any time. He/she understands that if he/she chooses to not participate or to withdraw, his/her current medical care will not be affected by this decision.

He/she understands that he/she will receive and may keep a copy of this signed and dated Patient Information Sheet and Consent Form.

By signing and dating this Consent Form, he/she has not waived any of the legal rights that he/she would have if he/she was not a participant in a medical research study.

THE PATIENT CONSENTS AND AUTHORIZES THAT HIS/HER STUDY DATA MAY BE TRANSFERRED WITHIN AND OUTSIDE THE EUROPEAN UNION, TO COUNTRIES, INCLUDING THE UNITED STATES, WHERE DATA MAY NOT HAVE THE SAME LEVEL OF DATA PROTECTION AS IN PORTUGAL OR IN THE EUROPEAN UNION. HE/SHE AGREES THAT HIS/HER STUDY DATA MAY BE MADE AVAILABLE TO THE SPONSOR AND PARTIES WORKING WITH THE SPONSOR AS WELL AS TO OTHER PARTIES/ENTITIES IDENTIFIED IN THE PATIENT INFORMATION SHEET FOR THE PURPOSES STATED IN THE PATIENT INFORMATION SHEET.

HE/SHE AGREES THAT THE BIOLOGICAL SAMPLES COLLECTED FROM HIM/HER MAY BE USED AND DISCLOSED FOR THE PURPOSES STATED IN THE PATIENT INFORMATION SHEET. HE/SHE ALSO AGREES THAT HIS/HER CODED BIOLOGICAL SAMPLES MAY BE TRANSFERRED OUTSIDE OF HIS/HER COUNTRY TO OTHER COUNTRIES, SUCH AS THE UNITED STATES, WHICH MAY NOT HAVE THE SAME LEVEL OF DATA PROTECTION AS IN PORTUGAL OR IN THE EUROPEAN UNION.

BY SIGNING THIS FORM HE/SHE CONSENTS AND AUTHORIZES THE COLLECTION, USE, PROCESSING AND SHARING OF HIS/HER SENSITIVE PERSONAL DATA AS PART OF THE CODED STUDY DATA WITH THE SPONSOR AND OTHER PARTIES AS DESCRIBED IN THIS INFORMED CONSENT FORM.

☐ BY CHECKING THIS BOX HE/SHE CONSENTS AND AUTHORIZES THE USE OF HIS/HER BIOLOGICAL SAMPLES AS PART OF THE CODED DATA BY THE SPONSOR AND OTHER PARTIES FOR POSSIBLE FUTURE STUDIES AS DESCRIBED IN THIS INFORMED CONSENT FORM.

SIGNATURE OF IMPARTIAL WITNESS	**DATE**

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.

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_____ _____

Signature of Investigator Obtaining Informed Consent / Research Authorization Date

_____

Printed Name of Investigator Obtaining Informed Consent / Research Authorization