Official Title	AN OPEN-LABEL, PHASE 2 BASKET STUDY OF NERATINIB IN PATIENTS WITH SOLID TUMORS WITH SOMATIC ACTIVATING *HER* MUTATIONS
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SAMPLE INFORMED CONSENT TO PARTICIPATE IN RESEARCH

Information to Consider Before Taking Part in This Research Study

Protocol Title & Number: PUMA-NER-5201, An Open-Label, Phase 2 Basket Study of Neratinib in Patients With Solid Tumors With Somatic Activating HER Mutations

Consent for ERBB2 mutated HR positive and HR negative Breast Cancer Patients

Investigator Name:

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 [Ex-US only: and includes an information sheet and a consent form]. Please read this information carefully and take your time making your decision. Ask the person in charge of this research study 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, 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.

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

An Open-Label, Phase 2 Basket Study of Neratinib in Patients With Solid Tumors With Somatic Activating HER Mutations

The person who is in charge of this research study is [*Insert PI name*]**.** 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 [*List the site(s) where the participant will be expected to take part in the research*].

This research is being sponsored by Puma Biotechnology, Inc. which means that Puma Biotechnology, Inc. is paying to conduct the study and may be referred to as the Sponsor in this consent.

PURPOSE OF THE STUDY

The purpose of this study is to find out what effects; good and/or bad, neratinib, either by itself (monotherapy) or in combination with other drugs has in solid tumors harboring somatic mutations in the ERBB gene family (EGFR, ERBB2). A mutation is an alteration of the genetic material and, in case of cancer, it is believed it contributes to the growth of tumor, replication and/or resistance to therapy. Neratinib may decrease the effects of the mutations in the growth of the tumor which harbor the mentioned mutations.

Neratinib is an experimental drug in this study and is being studied as monotherapy or in combination with other drugs. An experimental or investigational drug means it has not been approved by the national health authorities in your country for these indications.

This study enrolls patients who have any solid tumors harboring somatic EGFR or ERBB2 mutations including but not limited to breast cancer, cervical cancer, EGFR Exon 18 lung cancer, and salivary cancer. The combination of a mutation with a tumor type constitutes a cohort and it is independent of the other cohorts. The inclusion/exclusion criteria may differ, one cohort can stop, and the others will continue, based on response and tolerability.

All patients in the breast cohort will harbor an ERBB2 mutation and some are HR positive (also expressing on their surface the estrogen and/or progesterone receptors also called hormone positive). Neratinib has been already tested as monotherapy in the course of this study. Now the study wants to find out the good and bad effects of

neratinib given in combination with fulvestrant, a medicine commonly used in persons with recurrent hormone receptor positive breast cancer and the addition of trastuzumab for patients who have not been previously treated with CDK4/6 inhibitors (CDK4/6i). CDK4/6i are a class of drugs that target enzymes called CDK4 and CDK6. These enzymes are important in cell division. CDK4/6i are designed to interrupt the growth of cancer cells.

Patients with hormone receptor positive breast cancer who have been previously treated with CDK4/6i will be randomized (like the toss of a coin) to one of three treatment groups as follows: 1) fulvestrant alone; 2) fulvestrant in combination with trastuzumab; or 3) neratinib in combination with trastuzumab and fulvestrant. Patients randomized to receive fulvestrant alone or fulvestrant plus trastuzumab will be able to receive triple combination therapy (neratinib, fulvestrant, trastuzumab) upon disease progression.

In patients with breast cancers that are hormone receptor negative, neratinib has been already tested as monotherapy in the course of this study. Now the study wants to find out the good and bad effects of neratinib given in combination with trastuzumab.

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. 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
- What risks are 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 either a hormone receptor positive or hormone receptor negative breast cancer carrying an ERBB2 mutation.

For patients with HR positive breast cancer: Fulvestrant is a commercial drug in the United States, but not in several other countries. Trastuzumab is approved in the USA for metastatic breast cancer, gastric and gastroesophageal tumors which overexpressed the HER2 mutation. The combination of neratinib, fulvestrant and trastuzumab is an experimental drug combination which is studied as a potential new treatment for patients with hormone positive cancers that have a mutation in ERBB2. An experimental or investigational drug means it has not been approved by the national health authorities in your country for a particular indication.

For patients with triple negative breast cancer (TNBC) (HR negative): The combination of neratinib and trastuzumab is an experimental drug combination which is studied as a potential new treatment for patients with hormone negative breast cancer that has a mutation in ERBB2. An experimental or investigational drug means it has not been approved by the national health authorities in your country for a particular indication.

WHAT WILL HAPPEN DURING THIS STUDY?

Prior to participating in this study you must 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 copy will be provided to you for your files. You will participate in a screen period to determine your eligibility.

Before You Begin the Study (Screening Period)

A schedule of procedure is provided in the table below (Study Calendar). In addition to the procedures listed below, unscheduled clinic visits and procedures may be performed should your study doctor feel that it is necessary to assess symptoms and concerns that you may have reported and to confirm or rule out potential recurrence, and or for your safety.

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are generally part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- 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 4-5 teaspoons)
    - Measure your blood counts
    - See how well your liver, kidneys and other organs are working
- Whole blood sample for germline DNA research
- Research blood sample for exploratory biomarker testing. “Biomarkers” are laboratory tests related to your disease. Four test tubes of blood (about 8-10 teaspoons) will be drawn
    - It is expected that these banked plasma specimens will subsequently be used for cell -free DNA (cfDNA) mutational analysis to investigate mechanisms of primary and/or acquired resistance to neratinib therapy
- Urine tests will be taken to make sure your kidneys are functioning normally
- Electrocardiogram (ECG) will be obtained to make sure you heart is functioning normally
- Echocardiogram (an ultrasound of the heart) or MUGA (a special x-ray) to make sure your heart is pumping normally
- Radiographic tumor assessment to measure your tumor using CT or MRI and PET/CT (required) and tumor marker (blood) analysis to see how your tumor responds to treatment. The tumor markers will be collected as part of your standard of care.
- Pregnancy test (blood or urine) – if you are a woman who can have children
- A pretreatment fresh tissue biopsy within 28 days before starting treatment
- Patient-reported health outcomes questionnaire (FACT-G)

The Day 1 physical examination, ECOG performance status assessment, urine and blood sample may be omitted if the screening values were obtained within 72 hours prior to initiation of treatment.

If your genetic mutation was confirmed by a liquid biopsy, a fresh tumor biopsy will be required if the leftover tissue sample cannot be provided.

During the Active Treatment Stage (Cycle 1 Day 1 & greater)

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.

The following tests and procedures will be performed at each cycle (every 4 weeks for patients receiving fulvestrant alone and every 3 weeks for patients receiving the combination treatment of fulvestrant and trastuzumab or neratinib, fulvestrant and trastuzumab). In addition to the procedures listed below, unscheduled clinic visits and procedures may be performed should your study doctor feels that it is necessary to assess symptoms and concerns that you may have reported and to confirm or rule out potential recurrence, and or for your safety:

- Vital signs, weight, physician exam
- Routine blood tests (about 4-5 teaspoons)

- Performance status - an evaluation of how well you perform normal daily activities
- Phone call on Cycle 1, days 2, 3, and 4 after starting neratinib to see how you are feeling
- Review of symptoms and side effects
- Medication review – a review of all medications you are currently taking, including the study medication
- Patient-reported health outcome questionnaire (FACT-G). You will be required to complete the questionnaire at cycle 1 day 1 and monthly (per study visit and prior to drug administration) for up to 6 months or at the end of treatment, whichever comes first.
- Dispense and collect study medication at the beginning and end of each cycle visit.
- You will be given a diary to track the study medication (neratinib and loperamide pills) you take each day. You will also record the number of stools per day and the dose of loperamide taken each day for the first two cycle of therapy only. You will be required to record all doses of neratinib for the entire duration of the study.

<u>For patients receiving fulvestrant treatment (4-week cycles):</u>

The following test will be performed at cycle 3 (beginning of week 9), every 2 cycles and end of treatment:

- Research blood sample (about 8-10 teaspoons) for biomarker testing

The following procedure will be performed at cycle 3 (beginning of week 9) day 1 and then every 2 cycles for 1 year. After one year (13 cycles) on therapy, scans may move to every 3 months. After two years (26 cycles) on therapy, scans may move to every 4 months thereafter:

- Radiographic tumor assessment to measure your tumor using CT or MRI and PET/CT and tumor marker (blood) analysis to see how your tumor responds to treatment. The tumor markers will be collected as part of your standard of care.

If during treatment your disease progresses, you will be eligible to have neratinib and trastuzumab added to your treatment regimen and will then follow the procedures outlined below.

<u>For patients receiving fulvestrant and trastuzumab or combination treatment with neratinib (3-week cycles):</u>

The following test will be performed at cycle 4 (beginning of week 10), every 3 cycles and at the end of treatment:

- Research blood sample (about 8-10 teaspoons) for biomarker testing

The following procedure will be performed at cycle 4 (beginning of week 10), every 3 cycles for 1 year. After one year (13 cycles) on therapy, scans may move to every 4 cycles. After two years (26 cycles) on therapy, scans may move to every 5 cycles:

- Radiographic tumor assessment to measure your tumor using CT or MRI and PET/CT and tumor marker (blood) analysis to see how your tumor responds to treatment. The tumor markers will be collected as part of your standard of care.

The following procedure will be performed before starting treatment at cycle 5 (beginning of week 13), every 4 cycles (12 weeks) and then at the end of treatment:

- Echocardiogram (an ultrasound of the heart) or MUGA (a special x-ray) to make sure your heart is pumping normally

<u>For all treatment groups:</u>

The following procedure will be performed and collected for research purposes during screening or within the first cycle of treatment:

- Most recent metastatic tumor tissue: a sample of your tumor tissue from a surgery or biopsy you have had in the past (if it is available) will be requested as part of this study during screening or within the first cycle of neratinib

The following procedure will be performed at the time of disease progression and/or end of treatment:

- An optional fresh tumor tissue biopsy: Your study doctor may perform an optional fresh core tumor tissue biopsy if possible, at the time of disease progression and/or end of treatment

The following test and procedures will be performed for research purposes and will be collected only once (preferably during screening or within the first cycle):

- Blood sample for DNA testing (1 test tube of blood, about 2 teaspoons).
    - The purpose of this addition research is to:
        - Re-test your tumor to make sure it has an ERBB2 mutation
        - Look at genetic reasons why neratinib may or may not work in your tumor
    - This DNA testing will be done during or after you have participated in this study. In order to do this, genetic material from your tumor and 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 products in the future
    - The U.S. and individual states 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 your 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.

This testing will be done 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.

This study will be open label which means that you and your study doctor will know exactly the treatment you will receive.

Randomized Cohort Treatment Arms:

Tumor Group	Randomized Treatment
Breast HR Positive **(with prior CDK4/6i)**	• Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter **Or** • Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks If you are assigned to the fulvestrant or fulvestrant and trastuzumab arm, you will be eligible to have neratinib or neratinib and trastuzumab added to your treatment regimen upon disease progression and will be assigned the treatment below. **Or** • Neratinib: 240 mg daily • Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks

Non-randomized Treatment Groups:

Tumor Group	Assigned Treatment
Breast HR Positive **(CDK4/6i naive)**	• Neratinib: 240 mg daily • Fulvestrant: 500 mg on Study Day 1, 15, and 29; once every 28 days thereafter • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks
Breast	• Neratinib: 240 mg daily • Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks

Tumor Group	Assigned Treatment
TNBC (HR Negative)	

All treatment groups:

The cycle will be repeated until your study doctor tells you to stop. Each cycle is numbered in order. You will take the study medications as long as you are not having serious side effects, your cancer is not getting worse or you withdraw consent. If your doctor believes that fulvestrant and/or trastuzumab is causing adverse effects but you may benefit by continuing neratinib alone, you may do so with sponsor approval. If your cancer is getting worse, but in the opinion of the study doctor you may benefit from continuing study treatment you may continue protocol therapy if approved by the sponsor.

In addition to taking neratinib, you need to take loperamide (Imodium™), for the first two cycles 56 days for 4 week cycles and 42 days for 3 week cycles to prevent or lessen diarrhea caused by neratinib. You will take 2 tablets (4mg) of loperamide by mouth three times a day for the first 14 days, with the first dose (2 tablets) taken at the same time with the first treatment of neratinib. After two weeks on study, you will take 2 tablets (4mg) of loperamide by mouth two times a day until the end of cycle 2. Thereafter, loperamide will be administered as needed throughout neratinib treatment. Your doctor or nurse will contact you each of the first three days after you start taking neratinib to ask how much diarrhea you have and make any treatment adjustments. If diarrhea continues despite taking loperamide, call your doctor or nurse. If you are constipated, call your study doctor but do not discontinue Loperamide unless specifically instructed by your doctor.

NOTE: Your study doctor will provide you with a separate instruction sheet which will review how to manage diarrhea.

You will be given a patient calendar (diary) to complete through the study. You will use this to record the time and number of neratinib and loperamide pills you take each day. Additionally, your study doctor will instruct you to record the number of stools per day and the dose of loperamide taken each day for the first two cycle of therapy. You will be required to record all doses of neratinib for the entire duration of the study.

You will need to bring the calendar to the doctor's office before each cycle. You must also bring any unused study medications and pill bottles (even if empty) to the doctor's office before each cycle.

When I am finished taking study drug (End of Treatment Visit)

You will need the following tests and procedures within 28 days (+14 days) after stopping treatment. They are part of regular cancer care. These tests or procedures are detailed below:

- Vital signs, weight, physician exam
- Medication review – a review of all medications you are currently taking, including the study medication
- Review of symptoms and side effects
- Routine blood tests (about 4-5 teaspoons)
- Electrocardiogram (ECG) will be obtained to make sure you heart is functioning normally
- Echocardiogram (an ultrasound of the heart) or MUGA (a special x-ray) to make sure your heart is pumping normally
- Radiographic tumor assessment: to measure your tumor using CT or MRI and PET/CT (required), if you are stopping neratinib for any reason other than your tumor growing, you did not have another radiologic assessment in the prior 4 weeks and we need to see if your tumor responded or continued to respond to the therapy
- Research blood sample (about 8-10 teaspoons) for biomarker testing
- Patient-reported health outcomes questionnaire (FACT-G)
- Collect study medication
- Optional tumor biopsy
- Collect medication diary

Long-term Follow-up

After you stop taking the study medication(s) the following test and procedures will be performed:

- Your study doctor will continue to monitor you for any symptoms or side effects until the 28th day after taking the last dose of study medication(s).
- If you stopped taking the study medication(s) for any reason other than your tumor growing, a radiographic tumor assessment will be collected every 2 cycles if you are on the Fulvestrant alone arm or every 3 cycles if you are on combination therapy with fulvestrant and trastuzumab or

neratinib, fulvestrant and trastuzumab (±7 days) until your tumor grows. You will be contacted via phone call, office visit or email every 12 weeks (±14 days) to discuss your overall health status until you start a new anti-cancer therapy.

- After your last dose of trastuzumab, cardiac safety assessments (echocardiogram or MUGA) will be performed every 6 months up to 24 months.

Study Calendar for patients on fulvestrant treatment: This study calendar is a summary of the events that will occur at each scheduled visit. It is not intended to capture duplicate information from the list above.

Event	**Before Treatment**		**Treatment – 4 Week Cycles**			**After Treatment**
Visit	**Within 28 days of Cycle 1 Day 1**	**Within 14 days of Cycle 1 Day 1**	**Cycle 1, Day 1**	**Each Additional Cycle Day 1**	**End of Treatment**	**Long Term Follow-up**
Informed consent	X					
Demographics		X				
Medical, cancer, and medication history		X				
Physical examination		X	X (only if not done 72 hours before starting Cycle 1)	X	X	
Vital signs		X	X	X	X	
Electrocardiogram		X			X	
Echocardiogram or MUGA	X				X	
Urine Test		X				
Pregnancy test (if you are capable of getting pregnant)		X	X (only if not done 72 hours before starting Cycle 1)			
Routine Blood Test		X	X (only if not done 72 hours before starting Cycle 1)	X	X	
Performance Status		X	X (only if not done 72 hours before starting Cycle 1)	X		
MD/RN Phone Call			X (only Cycle 1, day 2, 3, & 4)			X (every 12 Weeks)

Event	**Before Treatment**		**Treatment – 4 Week Cycles**			**After Treatment**
Visit	**Within 28 days of Cycle 1 Day 1**	**Within 14 days of Cycle 1 Day 1**	**Cycle 1, Day 1**	**Each Additional Cycle Day 1**	**End of Treatment**	**Long Term Follow-up**
Radiographic tumor assessment (CT or MRI and PET/CT (required)) and tumor marker assessments	X			X (done every 2 cycles starting from the first dose of IP)	X (if you stop neratinib before your tumor grows)	X (every 8 weeks, if you stop neratinib before your tumor grows)
Blood Sample for cfDNA Biomarker Research		X		X (done every 2 cycles)	X	
Most recent metastatic tumor tissue sample for research	X					
Required fresh pretreatment tumor biopsy	X					
Optional fresh core tumor tissue biopsy for research					X (and/or at time of progression)	
Patient-reported health outcomes questionnaire (FACT-G)	X		X (cycle 1)	X (monthly for up to 6 months)	X	
Blood Sample for DNA Testing		X	X (if not obtained during screening)			
Fulvestrant			X (given on cycle 1, days 1 and 15, and 29 and then day 1 of every cycle)			
Loperamide			X (mandatory for C1-C2)			
Patient Diary			X			
Collect/Review of Medications	X					
Collect/Review of Side Effects	X					

Study Calendar for patients receiving fulvestrant and trastuzumab or combination treatment with neratinib:
This study calendar is a summary of the events that will occur at each scheduled visit. It is not intended to capture duplicate information from the list above.

Event	Before Treatment		Treatment – 3 Week Cycles			After Treatment
Visit	**Within 28 days of Cycle 1 Day 1**	**Within 14 days of Cycle 1 Day 1**	**Cycle 1, Day 1**	**Each Additional Cycle Day 1**	**End of Treatment**	**Long Term Follow-up**
Informed consent	X					
Demographics		X				
Medical, cancer, and medication history		X				
Physical examination		X	X (only if not done 72 hours before starting Cycle 1)	X	X	
Vital signs		X	X	X	X	
Electrocardiogram		X			X	
Echocardiogram or MUGA	X			X (every 12 weeks)	X	
Urine Test		X	X (only if not done 72 hours before starting Cycle 1)			
Pregnancy test (if you are capable of getting pregnant)		X	X (only if not done 72 hours before starting Cycle 1)			
Routine Blood Test		X	X (only if not done 72 hours before starting Cycle 1)	X	X	
Performance Status		X	X (only if not done 72 hours before starting Cycle 1)	X		
MD/RN Phone Call			X (only Cycle 1, day 2, 3, & 4)			X (every 12 Weeks)
Radiographic tumor assessment (CT or MRI and	X			X (done every 3 cycles starting	X	X (every 9 weeks, if you stop neratinib

Event	Before Treatment		Treatment – 3 Week Cycles			After Treatment
Visit	**Within 28 days of Cycle 1 Day 1**	**Within 14 days of Cycle 1 Day 1**	**Cycle 1, Day 1**	**Each Additional Cycle Day 1**	**End of Treatment**	**Long Term Follow-up**
PET/CT (required)) and tumor marker assessments				from the first dose of IP)		before your tumor grows)
Blood Sample for cfDNA Biomarker Research		X		X (done every 3 cycles)	X	
Most recent metastatic tumor tissue sample for research	X					
Required fresh pretreatment tumor biopsy	X					
Optional fresh core tumor tissue biopsy for research					X (and/or at time of progression)	
Patient-reported health outcomes questionnaire (FACT-G)	X		X (cycle 1)	X (monthly for up to 6 months)	X	
Blood Sample for DNA Testing		X	X (if not obtained during screening)			
Neratinib, Fulvestrant and Trastuzumab			X (neratinib taken every day, trastuzumab administered at the beginning of each cycle and fulvestrant given on cycle 1, days 1, 15 and 29 and then once every 4 weeks)			
Loperamide			X (mandatory for C1-C2)			
Patient Diary			X			
Collect/Review of Medications	X					
Collect/Review of Side Effects	X					

TOTAL NUMBER OF PARTICIPANTS AND STUDY DURATION

- About 650 individuals will take part in this study. The study will be conducted at several centers and in multiple countries.
- A total of [number of participants] individuals will participate in the study at this site.
- It is anticipated that you will be on study for approximately 18 months. The exact length of time will depend on how you are doing. If you agree, you can remain in the study as long as you are not having uncontrollable side effects and your cancer is not progressing. If your cancer appears to worsen but, in the opinion of the study doctor, you may benefit from continuing study treatment you may continue protocol therapy if approved by the Sponsor.
- Overall study duration is approximately 102 months.

ALTERNATIVES

You do not have to participate in this research study. Your other choices may include:

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

Talk to your doctor about your choices before you decide if you will take part in this study.

FALSE POSITIVE RISK

Risk of Incorrect Laboratory Diagnosis:

There is a low risk that your tumor may have been incorrectly diagnosed as having a specific gene mutation and that you may therefore be mistakenly selected for participating into this study. If you are misdiagnosed as having the correct gene mutation for this study, you may be exposed unnecessarily to neratinib treatment. As with all patients participating in this research study, it is unclear if you will receive any benefits. You will be exposed to same safety risks as any other appropriately identified patient receiving neratinib as described in the risk section below.

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. This information may help future cancer patients.

RISKS OR DISCOMFORT

Risks of Neratinib

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] ≥10%*

- Diarrhea
- Nausea
- Abdominal pain
- Vomiting
- 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 enzyme that measures the function of the liver)
- Increased blood levels of aspartate aminotransferase (an enzyme that measures the function of the liver)
- Increased blood levels of creatinine (an increase in a byproduct of proteins that measures the function of the kidney)
- Dyspepsia (indigestion)
- Abdominal distension
- Urinary tract infection
- Weight loss

- Dehydration
- Nosebleed
- 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 a byproduct of your red blood cells that measures the function of the liver)
- Renal failure (damage to the kidney which decreases 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 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 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 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 liver function tests.

- Interstitial lung disease:
  One patient with non-small cell lung cancer who was treated with neratinib experienced interstitial lung disease (an inflammation 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.

Risks of Fulvestrant

When taking fulvestrant alone or in combination you may experience some or none of the side effects associated to the treatment with either drug alone. Additional unknown side effects may occur. You will be monitored closely for

all side effects including any that are unexpected. Make sure to let your study doctor know if you develop any side effects while taking the drug(s). If symptoms develop, your study doctor will start appropriate treatment to prevent or treat these side effects.

Very common side effects

- Nausea
- Increased liver enzymes which could indicate liver damage
- Weakness
- Injection site reactions excluding injection site bleeding, injection site hematoma (blood pooling under the skin at the site of injection
- Hot flashes
- Allergic reactions (including chills, rashes, hives, itching, redness, swelling, low blood pressure, cough and shortness of breath)
- Rash
- Joint and muscle pain

Common side effects

- Decreased number of blood platelet cells (which can increase the risk of bleeding)
- Vaginal bleeding
- Urinary tract infections
- Loss of appetite
- Headache
- Blood clots
- Vomiting
- Diarrhea
- Back pain
- Nerve pain radiating from the back down the leg
- Prickling of tingling in the hands or feet
- Increased blood levels of bilirubin (an increase in a byproduct of your red blood cells that measures the function of the liver)

Uncommon side effects

- Liver failure
- Hepatitis
- Increased gamma-GT (an increase in an enzyme that measures the function of the liver)
- Vaginal yeast infection
- Whitish or yellowish vaginal discharge
- Injection site bleeding, hematoma (blood pooling under the skin at the site of injection)
- Nerve pain

Risks of Trastuzumab

When taking trastuzumab in combination with either fulvestrant or neratinib, you may experience some or none of the side effects associated to the treatment with either drug alone. Additional unknown side effects may occur. You will be monitored closely for all side effects including any that are unexpected. Make sure to let your study doctor know if you develop any side effects while taking the drug(s). If symptoms develop, your study doctor will start appropriate treatment to prevent or treat these side effects.

Very common side effects of trastuzumab: which may affect more than 1 in 10 subjects (≥ 10%)

- infections
- diarrhea
- constipation
- heartburn
- weakness
- skin rashes
- chest pain
- abdominal pain
- joint pain
- low counts of red blood cells and white blood cells (which help fight infection) sometimes with fever
- muscle pain
- conjunctivitis
- watery eyes
- nose bleeds
- runny nose
- hair loss
- tremor
- hot flush
- dizziness
- nail disorders
- weight loss

- loss of appetite
- inability to sleep (insomnia)
- altered taste
- low platelet count
- numbness or tingling of the fingers and toes
- redness, swelling or sores in your mouth and/or throat
- pain, swelling, redness or tingling of hands and/or feet
- breathlessness
- headache
- cough
- vomiting
- nausea

Common side effects of trastuzumab: which may affect up to 1 in 10 subjects (≥ 1%)

- allergic reactions
- throat infection
- bladder and skin infections
- shingles
- inflammation of the breast
- inflammation of the pancreas or liver
- kidney disorders
- increased muscle tone or tension (hypertonia)
- pain in the arms and/or legs
- itchy rash
- sleepiness (somnolence)
- bruising
- hemorrhoids
- itchiness
- dry mouth and skin
- dry eyes
- sweating
- feeling weak and unwell
- anxiety
- depression
- abnormal thinking
- asthma
- infection of lungs
- lung disorders
- back pain
- neck pain
- bone pain
- acne
- leg cramps

Uncommon side effects of trastuzumab: which may affect up to 1 in 100 subjects (≥ 0.1%)

- deafness
- bumpy rash
- blood infection

Rare side effects of trastuzumab: which may affect up to 1 in 1,000 people (≥ 0.01%)

- weakness
- yellow discoloration of the skin and white of the eyes which may indicate liver damage (jaundice)
- inflammation or scarring of the lungs

Uncommon but Serious side effects of trastuzumab: which may affect up to 1 in 100 subjects (≥ 0.1%)

- Severe infusion reactions including symptoms such as:
    - difficulty breathing
    - low blood pressure or high blood pressure
    - wheezing
    - spasm or tightening of the breathing airway (bronchospasm)
    - rapid and irregular heart beats
    - reduced level of oxygen in the blood
    - severe allergic reaction which develops rapidly and may cause death. Symptoms include an itchy rash, throat swelling, and low blood pressure (anaphylaxis)
    - hives
    - swelling of the lips, throat, eyes and face (angioedema)
- Severe lung problems including:
    - severe lung infection
    - shortness of breath
    - lungs filling with fluid
    - low levels of oxygen in the blood
    - permanent injury
- Heart problems including weakening of the heart muscle possibly leading to heart failure, inflammation (swollen, red, hot and painful) of the lining around the heart and heart rhythm disturbances. This can lead to symptoms such as:
    - breathlessness (including breathlessness at night)
    - cough
    - swelling in the legs or arms (fluid retention)
    - heart fluttering or irregular heartbeat (palpitations)

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
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.

Risk of other cancer treatment
If you have disease progression your physician may decide to add a treatment to neratinib therapy. It may include the following drug fulvestrant. Please review the package insert of the selected product with your doctor before starting the particular medication as to understand the risks and discomforts associated with the product.

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 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 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 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, 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. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. The CT scan gives your body the equivalent of about 3 extra years' worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests.

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 the PET-CT
Positron emission tomography (PET) scan is a test that uses radioactive glucose (sugar) that is injected into a vein. In rare instances, this might cause a major allergic reaction. You'll need to wait 30 to 60 minutes for the sugar to be absorbed by your body. Sugar is absorbed mainly by organs and tissues that use the most energy. Because cancer cells tend to use more energy than healthy cells, they absorb more of the radioactive sugar. It only stays in your body for a short time and the risk of negative effects from it is low. When you are ready, you'll lie on a narrow, padded table that slides into the tunnel shaped scanner. If you're afraid of enclosed spaces, you may feel nervous while in the scanner. During the scan you'll need to lie very still so that the images aren't blurred. It takes about 30 minutes to complete the test. The machine makes buzzing and clicking sounds. In some cases you may have a CT and PET scan in the same machine during the same appointment. The CT scan will be done first and take about 10 minutes. You'll need to drink plenty of fluids to help flush the materials from your body. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. The PET scan gives your body the equivalent of about 6 extra years' worth of this natural radiation.

Risks of Tumor Biopsy
It is possible that you could have pain during the procedure. Bruising, bleeding, tissue discoloration, infection, swelling, or scarring can occur where the biopsy sample is taken is possible.

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 receiving any study medication. 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 while enrolled in the study. Your doctor can discuss effective birth control methods with you. In addition, you must continue to use medically effective birth control for the following time periods based upon the investigation medication(s) you are taking:

For neratinib only, birth control must be used for 28 days after the last dose of neratinib.

Treatments containing trastuzumab, birth control must be used for 7 months after the last dose of trastuzumab.

Treatments containing fulvestrant, birth control must be used for 1 year after the last dose of fulvestrant.

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 neratinib, your study doctor will ask to follow the outcome of your pregnancy and the condition of your newborn.

The effects of neratinib on an unborn child (embryo or fetus) fathered by a man taking neratinib are unknown. Men with partners of childbearing potential must use a medically effective method of birth control throughout the study and for 3 months after the last dose of neratinib.

Unknown Risks

Neratinib, fulvestrant, trastuzumab and study procedures 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. Your participation in this study may contribute to the development of commercial products from which the Sponsor company (Puma Biotechnology, Inc.) or others may derive economic benefit. You will have no rights to any products, patents or discoveries arising from this research, and you will receive no economic benefit.

The study center will be paid to conduct this research 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. You may be reimbursed for reasonable accommodations and travel expenses. Please contact the study coordinator for more information and to see if you qualify.

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.*]

[US ONLY]

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 an assigned 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 organization 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 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 a central laboratory and the samples will be tested. In order to do this, genetic material 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 15 years after the end of the study. They will be used only for research and will not be sold. The research performed with your samples may help to develop new products in the future.

The U.S. and induvial states 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.

[EU ONLY]

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, health information, and data that is obtained from any biological sample taken from you such as your blood, tissue or saliva. This information is referred to as "Personal Data".

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 patient identification number or code. The study doctor will keep the list that matches the patient identification numbers to patient 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 to the code 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 a longer time period required under local law.

The following parties may access your medical records at the study center to ensure the study is being performed properly: 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). These parties may be able to identify you.

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 health information, 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 that you specifically consent to the collection, use and sharing of your sensitive Personal Data as described in this Patient Information Sheet. If you do not consent to the collection, use and sharing of your sensitive Personal Data as described in this Personal Information Sheet, 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 above your signature, you may withdraw that consent at any time. If you 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 to the collection, use and sharing of your sensitive Personal Data, please contact your study doctor.

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 your 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 [COUNTRY] 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 are kept by the study center and the Sponsor including the rights to access your study data and the right to correct incomplete or inaccurate study data. If you wish to exercise any of your rights, you should contact the study doctor who can explain to you what these rights are. You also have a right to bring a complaint to the regulatory authority responsible for the protection of Personal Data in your country.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by United States Law. This website will not include information that can directly or indirectly identify you. At most, the website will include a summary of the results. You can search this website 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. If you do not agree to have biological samples collected from you as described in this Patient Information Sheet, you cannot participate in the study.

Some biological samples collected during the study may be tested immediately at a central laboratory. The remainder of the samples will be sent to the biorepository determined by the Sponsor and kept for future testing. The samples will be identified only by a code and not by your name, national identity number, address, telephone number, or by any other direct personal identifier. Only the study doctor [and the study staff] will have access to the list that matches names to the codes, and that list will not be provided to the Sponsor. Some samples will be saved for future scientific research by the Sponsor and parties working with the Sponsor on future scientific research. Only the Sponsor, parties working with the Sponsor, and representatives of the regulatory authorities will have access to your coded samples.

If you change your mind about taking part in the study, no further samples will be collected from you. However, the Sponsor may retain and use both any study data derived from the samples already taken from you and any samples that have already been collected and sent to the Sponsor by the study center in order to maintain the quality of the study and for future scientific research.

THE SPONSOR AND SOME RECIPIENTS OF YOUR BIOLOGICAL SAMPLES 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 [COUNTRY] OR IN THE EUROPEAN UNION. HOWEVER, THE SPONSOR AND ITS AUTHORIZED REPRESENTATIVES WILL TAKE REASONABLE MEASURES TO KEEP YOUR SAMPLES CONFIDENTIAL UNDER APPLICABLE LAWS. BY PARTICIPATING IN THIS STUDY AND SIGNING THE ATTACHED CONSENT FORM, YOU CONSENT TO TRANSFERRING YOUR BIOLOGICAL SAMPLES TO THESE COUNTRIES.

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 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 The Sponsor is 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 and information about your health which may be referred to as vital statistics by checking publicly available sources.

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 and vital statistics 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 finder 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 or determine your vital statistics. 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 clarify 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 as soon as possible if such information becomes available.

[US ONLY]

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 911 [*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. [I*nsert 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 you be compensated for research related injuries?

If you feel that you have been injured as a result of taking the study drug 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 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 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.

[EU ONLY]

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:

[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 [country]. The insurance policy has been taken out with [Insurance name & address], under Policy Number [insert number]. 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.

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 consent form 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.

- Your study doctor will tell you how to stop safely and 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.

- If you decided to stop, you will be asked to return all study drug and related study material (e.g., patient diary, etc.)

Even if you want to stay in the study, there may be reasons the study doctor will need to withdraw you from the study. You may be taken out of this study if it is no longer safe for you to stay in the study or if you are not coming for the study visits when scheduled. You will be told 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 [insert (###) ##-####].

SAMPLE INFORMED CONSENT TO PARTICIPATE IN RESEARCH

[US ONLY]

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 (dd/mmm/yyyy)

_____

Printed Name of Person Taking Part in Study

[EU ONLY]

CONSENT FORM

STUDY TITLE: [insert]

PROTOCOL NUMBER: [insert]

EUDRACT NUMBER: [insert]

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 and use of my 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 TO AND AUTHORIZE THE TRANSFER OF MY STUDY DATA AND BIOLOGICAL SAMPLES WITHIN AND OUTSIDE THE EUROPEAN UNION, TO COUNTRIES, INCLUDING THE UNITED STATES, WHICH MAY NOT HAVE THE SAME LEVEL OF DATA PROTECTION AS IN [COUNTRY] OR IN THE EUROPEAN UNION. I AGREE THAT MY STUDY DATA SND BIOLOGICAL SAMPLES 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.

SAMPLE INFORMED CONSENT TO PARTICIPATE IN RESEARCH

I CONSENT TO AND AUTHORIZE THE USE OF MY STUDY DATA AND BIOLOGICAL SAMPLES FOR THE PURPOSE OF ANY FUTURE SCIENTIFIC RESEARCH THAT IS CONDUCTED IN ACCORDANCE WITH RECOGNIZED ETHICAL STANDARDS EVEN THOUGH THE NATURE OF THAT FUTURE SCIENTIFIC RESEARCH MAY NOT BE KNOWN TODAY.

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

_____ _____

Signature of Person Taking Part in Study Date (dd/mmm/yyyy)

_____

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 patient speaks the language that was used to explain this research and is receiving an informed consent form in the appropriate language. Additionally, this patient 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 patient 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 patient 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 (dd/mmm/yyyy)

_____

Printed Name of Person Obtaining Informed Consent / Research Authorization