THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Informed Consent

INFORMED CONSENT FORM/AUTHORIZATION FOR PARTICIPATION IN RESEARCH

Neratinib and Capmatinib combination (phase Ib/II) in metastatic breast cancer and inflammatory breast cancer patients with abnormal HER-family and c-Met pathway activity as measured by the CELsignia Signaling Analysis Test
2020-0198

Subtitle: Main Consent

Study Chair: Rachel Layman

_____ _____
Participant's Name Medical Record Number

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

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

STUDY SUMMARY

There are 2 parts to this study: Part 1b (dose escalation) and Part 2 (dose expansion).

The goal of Part 1b in this clinical research study is to find the highest tolerable dose of 2 study drugs, capmatinib and neratinib, that can safely be given to patients with breast cancer that is metastatic (has spread) or locally advanced. For patients with estrogen receptor positive breast cancer, the study will also find the highest tolerable dose of the 2 study drugs, capmatinib and neratinib in combination with a type of standard of care endocrine therapy medication known as an aromatase inhibitor.

The goal of Part 2 of this study is to learn if the dose of capmatinib and neratinib found in Part 1b can help to control the disease.

This is an investigational study. Neratinib is FDA approved and commercially available for the treatment of HER2-positive breast cancer. Capmatinib is FDA approved and commercially available for the treatment of metastatic lung cancer but is not approved to treat breast cancer. Aromatase inhibitors are FDA approved and commercially available for the treatment of estrogen receptor positive breast cancer. This drug combination is considered investigational and is currently being used for research purposes only.

The study doctor can explain how the study drugs are designed to work.

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

Your participation is completely voluntary. Before choosing to take part in this study, you should discuss with the study team any concerns you may have, including side effects, potential expenses, and time commitment. If you take part in this study, you may experience side effects, some of which may be severe or fatal. You may choose not to take part in this study because of hospitalization, a prolonged stay out of town, and/or because there are other standard options available. By participating in this study, you may be declining treatments that have been shown to improve survival. You should ask the study staff member obtaining your informed consent to describe any such treatments to you before you sign this consent form.

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

You may receive the study drugs for up to 3 years, as long as the study doctor thinks you are benefitting from the therapy. You will no longer be able to take the study drugs if the disease gets worse, if intolerable side effects occur, or if you are unable to follow study directions.

PUMA Biotechnology, Novartis and Celcuity are study supporters. Neratinib (PUMA Biotechnology) and capmatinib (Novartis) will be provided at no cost to you while you are on study. The cost of endocrine therapy agents will be the responsibility of you and/or your insurance provider. The CELsignia test for patients in Part 2 of this study will be performed and the cost covered by Celcuity.

You may choose not to take part in this study. Instead of taking part in this study, you may choose to receive standard of care therapy including chemotherapy, hormonal therapy, targeted therapy, or combination of these drugs, if appropriate. The study doctor will discuss with you which treatment options may be available outside of this study, including the possible risks and benefits of these treatments. You may choose to receive other investigational therapy, if available. You may choose not to have treatment for cancer at all. In all cases, you will receive appropriate medical care, including treatment for pain and other symptoms of cancer.

1. STUDY DETAILS

Screening Tests

Signing this consent form does not mean that you will be able to take part in this study. The following screening tests will help the doctor decide if you are eligible:

- You will have a physical exam.
- You will have an EKG and either a MUGA scan or echocardiogram (ECHO) to check your heart function.
- Blood (about 3 tablespoons) will be drawn for routine and research testing, which may include genetic testing. Blood for research testing in this study will be stored in a research bank at MD Anderson for use in future research related to breast cancer and how characteristics of the tumor (such as certain genetic features or proteins) may affect your reaction to the study drug.
- Urine sample will be obtained for routine tests.
- You will have imaging scans (such as a chest x-ray, bone scan, ultrasound, PET/CT scans or chest, pelvis, and abdominal CT scans, and/or MRIs) to check the status of the disease. The study doctor will tell you which scans you will have.
- If you are being screened for Part 2 of the study, you will have a core tumor biopsy for biomarker testing. Biomarkers are found in the blood/tissue and may be related to your reaction to the study drug. A biopsy may be taken of the tumor in the breast and/or metastatic sites (parts of the body other than the breast where the disease has spread). To perform a core biopsy, a sample of tissue is removed using a hollow core needle that has a cutting edge. A numbing drug will be given through a needle under the skin before the core biopsy.
- If you can become pregnant, urine or part of the above blood sample will be collected for a pregnancy test. To take part in this study, you must not be pregnant.

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

Study Groups

If you are found to be eligible to take part in this study, you will be assigned to a study group based on when you join this study. Up to 56 participants total (up to 27 in Part 1b and up to 29 in Part 2) will be enrolled in this study. All will take part at MD Anderson.

If you are enrolled in Part 1b, the dose of capmatinib and neratinib you receive will depend on when you join this study. Up to 4 dose levels of the study drugs will be tested. The first group of participants will receive the starting dose of capmatinib and neratinib. Each new group will receive a different dose level (which may be higher or lower) of capmatinib and neratinib from the group before it, depending on the side effects seen in previous groups. This will continue until the highest tolerable dose of capmatinib and neratinib is found.

If you are enrolled in Part 2, you will receive capmatinib and neratinib at the recommended dose that was found in Part 1b.

In both Part 1b and Part 2, if you have estrogen receptor positive breast cancer, you will also take or continue to take an aromatase inhibitor (a type of endocrine therapy drug). The study doctor will choose the aromatase inhibitor that you will receive. The study doctor will give you instructions for taking the aromatase inhibitor. In addition, if you currently have menstrual cycles, a medication to suppress the hormones produced by your ovaries will be administered to you.

The study doctor will tell you which part of the study you are in and which dose of study drugs you are receiving.

Study Drug Administration
You will receive the study drugs in 28-day cycles.

You will take neratinib tablets by mouth 1 time in the morning with food at about the same time.

You will take capmatinib tablets by mouth 2 times every day, with or without food, at the same time each day. Each dose should be taken about 12 hours apart (1 dose in the morning, 1 dose in the evening). You may take your morning dose of capmatinib at the same time as your dose of neratinib.

The study doctor will tell you how many tablets you need to take every day. Tablets should be swallowed whole; do not crush, chew, or break the tablets.

You be given a medication diary to write down when you take capmatinib and neratinib and if you miss any doses. If you miss or vomit a dose, do not take a “make up” dose or double dose; wait and take your next dose as scheduled.

Bring this diary and the medication bottles with the leftover drug (if any) to the clinic at the beginning of each cycle.

Study Visits

You will come to the clinic on **Day 1 of each cycle for up to 3 years.** At each visit:

- You will have a physical exam.
- Blood (about 1-3 tablespoons) will be drawn for routine tests.
- Urine sample will be obtained for routine tests.
- Every 2 cycles (Cycles 1, 3, 5, and so on), an additional blood sample (about 2-4 tablespoons) will be drawn for research testing, which may include genetic testing. This research blood sample will be stored in a lab at MD Anderson for use in future research and may help doctors understand your response to the study drugs.
- Every 2 cycles, you will have imaging scans as part of your standard care to check the status of the disease.

- Every 3 cycles, if the doctor thinks it is needed as part of your standard care, you will have an EKG and either an ECHO or MUGA scan to check your heart function.
- If you can become pregnant, urine or part of the above blood sample will be used for a pregnancy test.

End-of-Dosing Visit

As soon as possible after your last dose of study drugs:

- You will have a physical exam.
- Blood (about 1-2 tablespoons) will be drawn for routine tests.
- Depending on when your last scans were done, you may have imaging scans to check the status of the disease as part of your routine care.
- If you can become pregnant, urine or part of the above blood sample will be used for a pregnancy test.

Follow-Up

About 1 month after your last dose of study drugs and then every 6 months after that for up to 2 years, the study team will call you and ask how you are doing and if you have started any new anti-cancer medications. This may also be asked during a routine clinic visit, if you are planning to come to the clinic. If you are called, each call should last about 2-5 minutes.

Your participation in this study will be over after 2 years of follow-up.

2. POSSIBLE RISKS

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

Side effects will vary from person to person, and some may occur after you have stopped receiving treatment. Tell the study staff about any side effects you may have, even if you do not think they are related to the study drugs/procedures.

Capmatinib Side Effects

Common (occurring in more than 20% of patients)

• swelling (arm/leg) • fatigue	• abnormal salts, minerals, and/or acids in the blood (possible weakness, swelling, fatigue, low blood	• loss of appetite • nausea/vomiting • low red blood cell count

• abnormal blood test (possible pancreas damage) • difficulty breathing	pressure, organ failure, heart problems, changes in mental status, and/or seizure)	• abnormal liver test (possible liver damage) • abnormal kidney test (possible kidney damage)

Capmatinib may cause low blood cell counts (red blood cells). A low red blood cell count (anemia) may cause difficulty breathing and/or fatigue. You may need a blood transfusion.

Occasional (occurring in 3-20% of patients)

• skin rash • dry skin • fever • itching • constipation • diarrhea • abnormal protein in the blood	• inflammation of the pancreas (possible abdominal pain) • chest/back pain • kidney failure • weight loss	• build-up of fluid around the lungs • lung inflammation (possible difficulty breathing) • cough

The drug may cause an increased risk of infection, such as a skin infection (cellulitis). An infection may occur anywhere. It may become life-threatening. Symptoms of infection may include fever, pain, redness, and difficulty breathing.

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

• hives • severe skin rash	• inflammation of the pancreas (possible abdominal pain)

Capmatinib may cause birth defects.

Capmatinib may cross the blood-brain barrier, but it is not known what side effects this may cause. It is important that you tell your doctor if you have a headache, are dizzy, have balance problems, tremors, difficulties when you speak, mental confusion, and/or changes in your personality or vision (like blurred vision, double vision, or blind spots).

Capmatinib may cause you to get sunburned more easily. You should wear sunscreen, sun-protective clothing, a large rim hat, and sunglasses that protect you from the sun. You should also avoid direct sunlight, sunlamps, and tanning beds as much as possible.

One case of worsened cough and notable shortness of breath leading to death has been reported in one patient with lung cancer, possibly related to capmatinib.

Neratinib Side Effects

Common (occurring in more than 20% of patients)

• fatigue	• diarrhea • vomiting	• nausea • abdominal pain

Occasional (occurring in 3-20% of patients)

• skin rash • dry skin • nail changes • mouth blisters/sores (possible difficulty swallowing)	• loss of appetite • dry mouth • dehydration • upset stomach • indigestion • weight loss	• abdominal swelling • urinary tract infection • abnormal liver tests (possible liver damage) • muscle spasms • nosebleed

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

• liver damage	• kidney failure abnormal kidney test (possible kidney damage)	• lung inflammation (possible difficulty breathing)

If you have severe diarrhea, abdominal pain, nausea, fatigue, and/or vomiting, even for a short period of time, it is important that you tell the study doctor right away.

In this study, abnormal protein in the blood was reported as a serious event in 1 patient and reported by the investigator as unexpected and possibly related to Neratinib. Abnormal protein in blood has not been identified as a risk of Neratinib in other studies to date.

<u>Endocrine Therapy Side Effects</u>

Common side effects of aromatase inhibitors (such as anastrozole, letrozole, and exemestane) include:

• fatigue • weakness	• hot flashes • flushing	• digestive issues • joint pain

Common side effects of ovarian suppressors (such as goserelin and leuprolide) include:

• swelling (arm/leg) • headache • depression • mood swings	• sweating • hot flashes • flushing • acne-like rash • oily skin	• decreased sex drive • sexual disorder • decrease in size of the breast • vaginal inflammation

Potential side effects will vary depending on which drug you receive. The study doctor can tell you more about specific information.

Using the study drugs together and in combination with endocrine therapy agent(s) may cause side effects that are not seen when each is given alone and may also increase the frequency and/or severity of the side effects listed above.

Other Risks

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

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

Diagnostic procedures, such as **EKGs, bones scans, X-rays, and CT, PET/CT, and MRI scans**, are part of your standard of care. You may discuss the risks of these scans with the study staff/study doctor if you have questions about them.

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

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

Taking part in this study can result in risks to an unborn or breastfeeding baby, so you should not become pregnant, breastfeed a baby, or father a child while on this study.

If you can become pregnant or father a child and you are sexually active, you must use birth control during the study and for at least 7 days after your last dose of study drugs. Acceptable forms of birth control include:

- Hormonal birth control methods (shots/injections, implants, or patches)
- Intrauterine device (IUD) or intrauterine system (IUS)
- Use of two (2) barrier methods (each partner must use 1 method) plus spermicide. Barrier methods include condoms, diaphragm, cervical cap, or sponge.

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

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

Getting pregnant will result in your removal from this study.

3. COSTS AND PAYMENTS

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

Samples that are collected from you in this study may be used for the development of treatments, devices, new drugs, or patentable procedures that may result in commercial profit.

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

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

If you get sick or hurt and it is related to your participation in this study call your personal doctor right away (or in an emergency, call 911) or call the study chair Dr. Rachel Layman, at 713-745-8401. Tell your doctor or staff that you are in this study (try to give them a copy of this consent form or show them your participant card)

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson or Novartis, Puma Biotechnology, or Celcuity for this injury.

You may also contact the Chair of MD Anderson's IRB at 713-792-6477 with questions about study-related injuries.

By signing this consent form, you are not giving up any of your legal rights.

Additional Information

4. You may ask the study chair (Dr. Rachel Layman, at 713-745-8401) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792-6477 with any questions that have to do with this study or your rights as a study participant.

5. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, please inform the study chair in writing. It is recommended for your safety that you first talk to your doctor. If you withdraw from this study, you can still choose to be treated at MD Anderson. The study staff may ask if they can continue collecting the results of routine care from your medical record.

6. This study or your participation in it may be changed or stopped without your consent at any time by the study chair, Novartis, Puma Biotechnology, Celcuity, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson.

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

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

9. This study is sponsored and/or supported by: Novartis; Puma Biotechnology; Celcuity.

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

Future Research

Data

Your personal information (name, full date of birth, age, gender, biological samples, etc.), is being collected as part of this study. These data may be used by researchers at MD Anderson, and Novartis and its authorized agents, Puma Biotechnology, and Celcuity, and/or shared with other researchers and/or institutions for use in future research.

Samples

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

future research. This is a required part of this study. Samples will not be sent to Novartis or Puma (other study supporters).

Before being used or shared for future research, every effort will be made to remove your identifying information from any data and/or research samples. If all identifying information is removed, you will not be asked for additional permission before future research is performed.

In some cases, all of your identifying information may not be removed before your data or research samples are used for future research. If future research is performed at MD Anderson, the researchers must get approval from the Institutional Review Board (IRB) of MD Anderson before your data and/or research samples can be used. At that time, the IRB will decide whether or not further permission from you is required. The IRB is a committee of doctors, researchers, and community members that is responsible for protecting study participants and making sure all research is safe and ethical.

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

Genetic Research
Samples collected from you as part of this study may be used for genetic research, which may include whole genome sequencing. Whole genome sequencing is a type of testing in which researchers study your entire genetic makeup (DNA). This may help researchers learn how changes in the ordering of genes may affect a disease or response to treatment. If genetic research is done with your samples, those who have access to those samples may be able to identify you. The results of this research may also be able to be linked to you. The same level of data protection that covers your individual data does not apply to summary results (when data from the whole study is combined).

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

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

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

Conflict of Interest

Outside relationships are disclosed to and approved by the Conflict of Interest Committee, which reviews these relationships for compliance with institutional policy. This review helps the IRB to assure that financial relationships do not have an impact on the conduct of this study. The following members of the study staff have disclosed compensation from the funding source(s) of this study:

- Dr. Rachel Layman (Study Chair)
- Dr. Azadeh Nasrazadani (Co-Investigator)

Outside Care

Part of your care may be provided outside of MD Anderson by your home doctor(s).

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During the course of this study, MD Anderson will be collecting and using your PHI (name, full date of birth, age, gender, biological samples, etc.), including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:
   - Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
   - The IRB and officials of MD Anderson
   - Novartis and their authorized agents; Puma Biotechnology; and Celcuity, who are all sponsors or supporters of this study
   - Any future sponsors/supporters and/or licensee(s) of the study technology
   - Study monitors and auditors who verify the accuracy of the information
   - Individuals who put all the study information together in report form.
   - Governmental agencies in other countries where the study drug may be considered for approval.

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

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

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

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

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

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

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

CONSENT/AUTHORIZATION

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

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT

I was present during the explanation of the research to be performed under Protocol 2020-0198.

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

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

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT

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

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____	_____	_____
NAME OF TRANSLATOR	SIGNATURE OF TRANSLATOR	DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line below.)