SUMMARY OF CHANGES

NCI Protocol #: 10296
Local Protocol #: 2020-0260
Protocol Version Date: February 21, 2022

Protocol Title: Phase Ib/II trial of copanlisib in combination with trastuzumab and pertuzumab after induction treatment of HER2 positive (HER2+) metastatic breast cancer (MBC) with PIK3CA mutation or PTEN mutation

Informed Consent Version Date: February 21, 2022

page#	Section	Comments
5	What exams, tests, and procedures are involved in this study?	Added this test to align with protocol test • On day 8 of every cycle, blood about 1 tablespoon will be collected to check your blood sugar levels before you receive study drug.
6	What exams, tests, and procedures are involved in this study?	Added this test to align with protocol test • You will have medical imaging scans to check the status of disease at pre study and every 12 weeks after the start of Cycle 1 Day 1.
6	What exams, tests, and procedures are involved in this study?	Added biosimilar language • Please note: If you take part in this study, you may be given trastuzumab (or an identical drug called a bio-similar, such as trastuzumab-qyyp or trastuzumab-anns) and trastuzumab/pertuzumab or an biosimilar (e.g. phesgo [pertuzumab, trastuzumab, and hyaluronidase- zzxf]). Everything stated in this document about Trastuzumab and pertuzumab also applies to its bio-similar, including information about FDA approval status, side effects, and cost.

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of an anti-cancer drug, copanlisib, to the usual combination treatment (trastuzumab and pertuzumab) in HER2 positive (HER2+) metastatic (cancer that has spread) breast cancer (MBC) patients.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10296, **"**Phase Ib/II trial of copanlisib in combination with trastuzumab and pertuzumab after induction treatment of HER2 positive (HER2+) metastatic breast cancer (MBC) with PIK3CA mutation or PTEN mutation." (NCT # 04108858)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have advanced breast cancer that has spread outside your breast after prior treatment, and your cancer has high levels of a protein called HER2 (human epidermal growth factor receptor 2).

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

How safe and tolerable is the study drug, Copanlisib, when given in Combination with Trastuzumab and Pertuzumab in patients with HER2 positive metastatic breast cancer?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your breast cancer. The usual approach is defined as care most people

get for metastatic breast cancer that has spread to other parts of the body. This combination of drugs is not approved by the Food and Drug Administration (FDA) for the treatment of HER2 positive metastatic breast cancer. This is the first time these drugs will be tested together in humans.

What is the usual approach to my metastatic breast cancer?

The usual approach for patients who are not in a study is treatment with already FDA-approved drugs such as trastuzumab and pertuzumab, trastuzumab plus chemotherapy, T-DM1 or ado-trastuzumab emtansine as standard of care therapy.or other targeted therapies. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will get copanlisib, trastuzumab, and pertuzumab until your cancer starts to grow or the side effects become bothersome, or you desire to discontinue the study. After the last dose of study drugs, your doctor will continue to follow your condition for 3 months and watch you for side effects. You will be seen in clinic within 1 month of the last dose of the drug, and follow up visits via telephone.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the “What risks can I expect from taking part in this study?” section.

If you choose to take part in this study, there is a risk that the triplet combination of copanlisib, trastuzumab, and pertuzumab may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer and preventing it from growing.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer, or may be greater than the side effectsyou would experience with each of the study drugs individually.

Some of the most common side effects that the study doctors know about are:

- The study drug copanlisib can increase your blood pressure. If this happens, your doctor may advise you to begin taking or increase the dose of your blood pressure medication.
- While receiving the study drug copanlisib, your blood sugar can increase temporarily, requiring insulin or other medication to bring it under control.
- Your blood counts can decrease, increasing your risk of infections, bleeding and anemia.
- You may experience nausea, diarrhea, and fatigue

There may be some risks that the study doctors do not yet know about.

Benefits

There is some evidence in animals and living human cells that adding copanlisib to another usual approach may stabilize cancer. However, we do not know if this will happen in people. It is not known whether adding copanlisib will help you live any longer than the usual approach alone. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

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

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.

- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (National Cancer Institute [NCI]). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to test the safety and tolerability (side effects) of a drug called copanlisib when combined with the usual drugs for your type of breast cancer (trastuzumab and pertuzumab). Copanlisib has already been approved by the FDA to treat another cancer called lymphoma. Copanlisib has also been tested in breast cancer patients in combination with one of the usual drugs, trastuzumab. This study tests different doses of the drug copanlisib to see which dose is safer and more tolerable for people when combined with both trastuzumab and pertuzumab. There will be about 12 people taking part in this study.

Another purpose of the study is to see if there are any changes in your tumor or blood characteristics (e.g. genes, molecules, etc.).

What are the study groups?

There are two parts in this study, a safety lead-in part and a dose expansion part. Your study doctor is asking you to join this safety run-in part of the study.

In the safety lead-in part of this study, different people taking part in this study will get different doses of the study drug copanlisib.

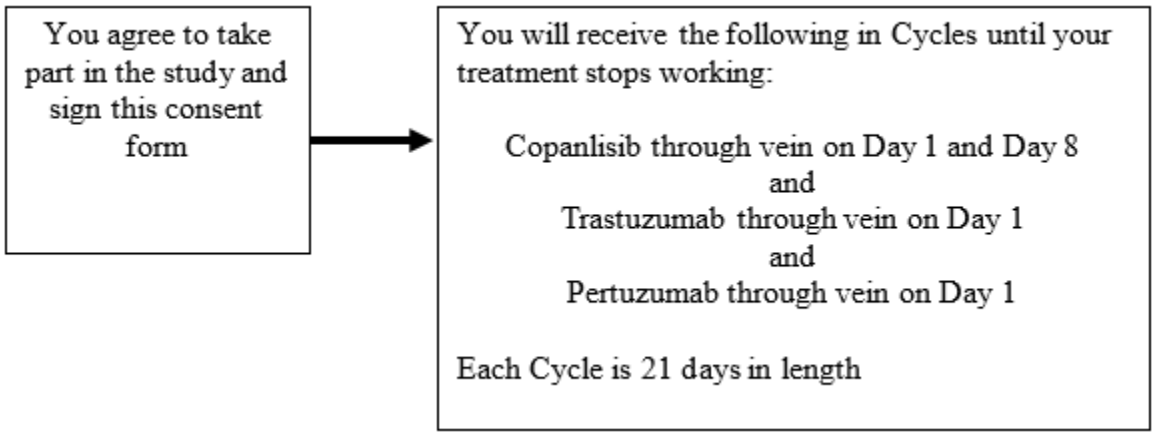
The first 3 people taking part in this study will get the highest dose that has shown to be safe in people when given alone. If the drug does not cause serious side effects, the next group of people in the study will get the same dose. The study doctor will watch each group carefully for side effects. If serious side effects develop, the dose of copanlisib will be lowered. Once this dose of copanlisib is found that is safe for combining with the usual drugs (trastuzumab and pertuzumab), the safety lead-in is stopped.

Treatment schedule: You will get copanlisib through a vein in your arm or through a port on the first and eighth day of each cycle. You will get the usual drugs (trastuzumab and pertuzumab) through a vein in your arm on the first day of each cycle. Each cycle lasts 21 days. See the study calendar for more information.

This drug combination is not approved by the FDA for treatment of your disease.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right following the lines and arrows.

Study Schema for safety lead-in part



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Physical exams done weekly for the first two weeks on the study, and then on the first day of each cycle.
- About 2 tablespoons of blood will be collected before you begin the study and then on Days 1 and 8 for the first two weeks on the study, and then on the first day of each cycle, and when you come off from the study.
- On day 8 of every cycle, blood about 1 tablespoon will be collected to check your blood sugar levels before you receive study drug.
- You will have an EKG and ECHO/MUGA to check your heart function at baseline and then ECHO/MUGA will be performed every 12-16 weeks as per treating physician discretion. After baseline, EKG will be performed if clinically indicated.
- A pregnancy test will be performed at baseline, if you can become pregnant

- About 1 tablespoon of blood will be drawn to check your blood sugar levels at pre study and thereafter every 12 weeks from cycle 4 and onwards. In addition, prior to dose of copanlisib infusion on cycle 1 day 1 and onwards, your blood sugar level will be checked.
- You will have medical imaging scans to check the status of disease at pre study and every 12 weeks after the start of Cycle 1 Day 1.

This study will use genetic tests that may identify changes in the genes in your DNA. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. If the changes in your genes were inherited, the changes could also affect the health of your family members.

As part of this study, we are also studying if the combination of copanlisib with usual drugs (trastuzumab and pertuzumab) works better on tumors with abnormalities in *PTEN* or *PIK3CA* genes. Your tumor will be tested for genetic changes in *PTEN* gene and *PIK3CA* gene before you are allowed to take part in this study. However, these genetic changes will not determine whether you are eligible for the study or the type of treatment you receive.

Please note: If you take part in this study, you may be given trastuzumab (or an identical drug called a bio-similar, such as trastuzumab-qyyp or trastuzumab-anns) and trastuzumab/pertuzumab or an biosimilar (e.g. phesgo [pertuzumab, trastuzumab, and hyaluronidase- zzxf]). Everything stated in this document about Trastuzumab and pertuzumab also applies to its bio-similar, including information about FDA approval status, side effects, and cost.

You and your family may want to know about any genetic test findings that may be important to your health. You may use this form to grant us permission in advance to give this information to your doctor. If a genetic test result about you seems to be medically important and you have granted us permission to contact you, the following steps will occur:

1. Researchers will study the result further to decide if it may be medically important to you or your relatives.
2. The research laboratory that performed the genetic test will contact your doctor about the finding. The research laboratory, which will not have any identifying information about you, will provide your doctor with a code number assigned to your genetic test sample.
3. Your doctor will use the code number to identify you, and will then contact you about the medically important finding. Your doctor may try to contact you several times.
4. You will require another genetic test to confirm the results. This test must be paid for at your own expense.
5. If it is confirmed that there are changes found that could cause health problems, then your doctor will discuss your options with you. We strongly suggest that you also

talk to a genetic counselor. Genetic counseling services must be paid for at your own expense.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

Your study doctor, will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer or had surgery to remove your tumor. This sample is a required part of study. One research tumor sample (archived or biopsy) will be collected within 2 weeks before you start the study drug(s). If there is not enough tissue left over from your biopsy, your study doctor will need to do another biopsy before you begin the study drug to get this tissue. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer.

A mandatory baseline research blood samples will be collected.

Researchers will obtain genetic material (DNA and RNA) from your tumor tissue and blood samples. Your DNA and RNA will be sequenced to evaluate changes in your DNA and RNA that may occur during treatment. Levels of different proteins will be measured in your tumor. This information will be important to understand why the treatment you received worked or did not work to stop the growth of your cancer. Researchers hope to find potential "biomarkers" (changes present in tumor tissue or blood that predict if current or future treatments would stop your type of cancer from growing). You and your study doctor will not get any results of this testing.

A patient study calendar is attached at the end of this document. It shows how often these exams and tests will be done.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drug may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

Spend more time in the hospital or doctor's office.
Be asked sensitive or private questions about things you normally do not discuss.
May not be able to take part in future studies.

The study drug used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study, and for 1 month after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Genetic Testing Risks

The genetic test used in this study will test all the genes in your tumor for genetic changes / abnormalities. This is called whole exome sequencing. Some of these changes may be found in your normal tissue, and may be passed down in families. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your doctor will talk with you about what the tests results may mean for you and your family. He or she also may suggest you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for visits to a genetic counselor.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Also include whether or not the results will be available to the study participant or study doctor. Neither you nor your health care plan/insurance carrier will be billed for the collection of the research tumor biopsies or research blood tests.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur.

Blood Draw Risks

Some of the risks from drawing blood from your arm may include pain, bruising, light-headedness, and rarely, infection. For most people, needle punctures to get blood samples do not cause any serious harm. Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drug.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of Copanlisib (Table Version Date:June 18, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving copanlisib dihydrochloride (BAY 80-6946 dihydrochloride), more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Infection, especially when white blood cell count is low • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving copanlisib dihydrochloride (BAY 80-6946 dihydrochloride), from 4 to 20 may have:
• Anemia which may require blood transfusion • Sores in the mouth which may cause difficulty swallowing

- Vomiting
- Bruising, bleeding
- Loss of appetite
- Pain
- Damage to the lungs which may cause shortness of breath
- Rash

RARE, AND SERIOUS
In 100 people receiving copanlisib dihydrochloride (BAY 80-6946 dihydrochloride), 3 or fewer may have:

- Swelling and redness of the skin
- Itching

Risk Profile for Trastuzumab (Herceptin) and Herceptin Hylecta ™ (Table Version Date: December 14, 2021)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving trastuzumab (herceptin) and Herceptin Hylecta™ (SQ trastuzumab), more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving trastuzumab (herceptin) and Herceptin Hylecta™ (SQ trastuzumab), from 4 to 20 may have:

- Anemia which may require blood transfusion
- Infection, especially when white blood cell count is low
- Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness
- Fluid in the body
- Abnormal heartbeat
- Watering eyes
- Pain
- Diarrhea, nausea, vomiting
- Sores in the mouth which may cause difficulty swallowing
- Chills, fever
- Swelling of the body
- Flu-like symptoms including body aches
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Swelling and redness at the site of the medication injection
- Dizziness, headache
- Change in or loss of some or all of the finger or toenailsWeight loss, loss of appetite
- Changes in taste
- Numbness, tingling or pain of the arms and legs

- Depression
- Difficulty sleeping
- Stuffy nose
- Cough, shortness of breath
- Hair loss, acne, rash, hives
- Hot flashes
- High blood pressure which may cause headaches, dizziness, blurred vision
- Low blood pressure which may cause feeling faint

RARE, AND SERIOUS
In 100 people receiving trastuzumab (herceptin) and Herceptin Hylecta™ (SQ trastuzumab), 3 or fewer may have:

- Damage to organs (lungs, others) which may cause shortness of breath
- Scarring of the lungs
- Change in heart function

Possible Side Effects of Pertuzumab (Table Version Date: July 6, 2019)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving pertuzumab, more than 20 and up to 100 may have:

- Diarrhea, nausea, vomiting
- Tiredness
- Infection, especially when white blood cell count is low
- Hair loss

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving pertuzumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Watering eyes
- Pain
- Constipation, heartburn
- Sores in the mouth which may cause difficulty swallowing
- Swelling of the body
- Fever
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Swelling and redness of the area of radiation
- Loss of appetite
- Dizziness, headache
- Changes in taste
- Feeling of "pins and needles" in arms and legs
- Muscle weakness
- Numbness, tingling or pain of the arms and legs
- Difficulty sleeping

- Cough, shortness of breath
- Nose bleed
- Dry skin
- Change in or loss of some or all of the finger or toenails
- Redness, pain or peeling of palms and soles
- Itching, rash
- Hot flashes

RARE, AND SERIOUS In 100 people receiving pertuzumab, 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Change in heart function

Additional Drug Risks

The study drug could interact with other drugs such as antibiotics, herbal medication and anti-seizure medication. Your study doctor will give you a wallet card that lists your study medications. Share this information with your family members, caregivers, other health care providers, and pharmacists.

High blood pressure is frequently observed within the first 3 hours after start of infusion and hyperglycemia (increased blood sugar) is frequently observed persisting for approximately 1-3 days after the study drug has been given.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

(1) Keep your study appointments.
(2) Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study, or within a 7 month period after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer treatment. This includes:

- the costs of blood tests, exams, procedures, scans, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the FDA approved standard of care drugs (trastuzumab and pertuzumab) ready and giving it to you.
- your insurance co-pays and deductibles.
- your Transthoracic Echo (TTE) assessments and EKG.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include:

- The biopsy for testing abnormalities in genes (*PTEN* and *PIK3CA*) at the beginning of the study.
- Research biopsies and blood tests for testing protein levels and DNA/ RNA changes at baseline.

You or your insurance provider will not have to pay for the study drug (copanlisib) while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

1. You will not be asked if you agree to take part in the specific future research studies using your health information.

2. You and your study doctor will not be told when or what type of research will be done.
3. You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor, (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).
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For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with your cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies and storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

If you choose to take part in this optional study, researchers will collect tumor tissue through biopsy before you begin treatment even if enough tumor tissue is present from your earlier biopsy. Fresh tumor tissue will be used for research on abnormalities in RNA and levels of different proteins that are present in the tumor before beginning treatment. It is also optional to have tumor biopsies on the 15th day of the first cycle, and when the cancer starts to grow despite treatment with the study drugs. The tumor tissue from these biopsies will be used for research on changes in proteins during and after treatment in order to find out why the treatment works better for some people than others.

You may also choose to allow researchers to collect blood samples to study changes in cancer genes at different timepoints on treatment. If you choose to take part in this study, the first blood sample will be collected before you begin the study drug. Additional blood samples will be taken on Day 1 of Cycles 2 and 3, and then every 9 weeks (when you undergo testing to find out the amount or spread of cancer in the body). You may also choose to allow researchers to take blood for research when the cancer starts to grow despite study drugs. Research on abnormalities in genes of cancer cells that are present in the blood will help to develop better treatments for the future.

Researchers will obtain genetic material (DNA and RNA) from both your tumor cells and your blood. Your DNA and RNA will be used for genomic sequencing, which is sequencing of all or part of your DNA. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems. The genomic sequencing will be done by an NCI-supported laboratory in Frederick, Maryland, known as the Molecular Characterization (MoCha) Laboratory at the Frederick National Laboratory for Cancer Research. The laboratory will compare the genomic sequences from your tumor and

blood cells to identify how they differ. The differences between genomic sequences of your tumor and blood cells may be important to understand why the treatment you received worked or did not work. Researchers hope to find potential "biomarkers" (changes present in tumor tissue that predict how if current or future treatments would stop the growth of your type of cancer). This optional study may improve the ability to select future treatments or treatment combinations for others in the future. This optional study will not affect the cancer treatment or approach that you receive.

Neither you nor your study doctor will be informed when the genetic sequencing research will be done. You and your study doctor will not receive reports of these studies, as they are intended for research purposes only and cannot be used to plan treatment.

Unknown future studies

If you choose to take part in this optional study, any tumor tissue and blood samples left over from planned research studies (sequencing of tumor for abnormalities in DNA and RNA, protein levels), will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Nationwide Children's Hospital in Columbus, Ohio, and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use. Your genomic sequence will also be stored in a secure NIH database for future use. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood and/or tissue samples. This means that:

You will not be asked if you agree to take part in the future research studies.

You and your study doctor will not be told when or what type of research will be done.

You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down

through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

Samples of tissue will be collected from optional extra biopsies. An optional biopsy procedure will be performed before beginning the study to collect fresh tumor tissue even if tumor tissue is available from your earlier biopsies/ surgery. Optional tumor biopsies will also be performed on the 15th day of the first cycle, and if the cancer starts to grow despite treatment with the study drugs. For the biopsy procedure, the study doctor will use a needle to take pieces of your tumor. This process may be repeated several times in the same appointment in order to get enough tissue. Blood will also be collected from a vein in your arm. Up to 2 teaspoons of blood each will be collected at the end of the study / when cancer starts to grow despite study drugs.
Your samples (tumor tissue and blood) will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.

Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

The most common risks related to a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur. The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.

Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.

Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is

very small. However, the risk may increase in the future as people find new ways of tracing information.

In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information. Only your study doctor and a few study researchers will have access to the master list linking the code numbers to names. The biobank and the genomic sequencing laboratory will receive your samples with the following information only: your sample code number; your age, race/ethnicity, and gender; your type of cancer; any previous treatments you received for your cancer; and the treatment you will receive for this current study.
Researchers who study your samples and information will not know who you are. They also must agree that they will not try to find out who you are. The researchers must be trained in the handling of private information. Any researcher who wants to study your stored samples and genetic information must apply and be approved to do so.

Your personal information will not be given to anyone unless it is required by law.
If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance for exams, tests, and procedures done for research purposes only; these include the biopsy, blood draw, DNA/RNA sequencing, protein levels in tumor tissue, and biobanking of your specimen(s). You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I need my tissue or blood samples to be returned?

Tumor tissue or blood samples that remain in the biobank can be returned if needed for medically necessary events or procedures to assure appropriate medical care, such as for DNA or RNA analysis. Specimens may also be returned if tissue is needed to determine eligibility for enrollment in a research protocol or clinical trial. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness.

Tumor tissue or blood samples and genetic material (DNA and RNA) that is no longer in the biobank or that has already been given to or used by researchers cannot be returned. No samples will be returned for matters related to patients needing or wanting genetic testing to determine medically important risks.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory studies described above.

YES NO

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to learn about results from these studies.

YES NO

Samples for unknown future studies:

I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

Select and sign ONE option from below:

You have my permission to release my genetic test results to **any and all** family members involved, in the event that I am unable to or have not survived to grant permission myself.

Participant's signature

Date of signature

Witness's signature

Date of signature

You have my permission to release my genetic test results or stored DNA **only** to the family members listed. Please write the name of the family member(s) in the space provided below.

Participant's signature

Date of signature

Witness's signature

You do NOT have my permission to release my genetic test results or stored DNA to any family members. I request that this information be kept private.

Participant's signature

Date of signature

Witness's signature

This is the end of the section about optional studies.

Patient Study Calendar

	Pre-Study	Baseline	Cycle 1			Cycle 2			Cycle 3			Cycle 4+			Restaging	Progression / Off Study[d]
			D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D5		
Copanlisib[a]			X	X		X	X		X	X		X	X			
Trastuzumab[b]			X			X			X			X				
Pertuzumab[c]			X			X			X			X				
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X		X|----------X													
Physical exam	X		X	X		X			X			X				X
Vital signs	X		X	X		X	X		X	X		X	X			X
Height	X															
Weight	X		X			X			X			X				X
Performance status[e]	X		X			X			X			X				X
CBC w/diff, plts	X		X			X			X			X				X
Serum chemistry[f]	X		X	X		X	X[L]		X	X[L]		X	X[L]			X
EKG[g]		X														
ECHO/MUGA[g]	X	X										X				
HbA1c[h]	X											X				X
Adverse event evaluation	X		X ----------X													
Tumor measurements	X		Tumor measurements are repeated every ~~9~~ 12 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease													
Pregnancy test[i]	X															
Archived tumor collection		X														
Tumor Biopsy (PTEN Expression)		X[j]														
Tumor Biopsy (WES)		X[j]														X[k]
Tumor Biopsy (RNA Seq)		X[j]			X[k]											X[k]
Tumor Biopsy (Ki-67 and caspase 3)		X[j]			X[k]											X[k]
Frozen tumor biopsy (RPPA assay)		X			X[k]											X[k]
Blood collection (ctDNA)		X[k]				X[k]			X[k]						X[k]	X[k]
Blood collection (WES)		X														

a: Copanlisib: Dose as assigned; Days 1 and 8 of each 21 day cycle. Copanlisib is administered after Trastuzumab and Pertuzumab.

b: Trastuzumab: Dose as assigned; Day 1 of each 21 day cycle.
c: ~~Pertuzumab~~: Dose as assigned; Day 1 of each 21 day cycle.
d: Off-study evaluation.
e: Note: Performance status evaluations are based on a 3 week cycle. At minimum, performance status should be evaluated at the beginning of every cycle.
f: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, fasting glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
g: ~~EKG and ECHO or MUGA will be performed at baseline, and then~~ ECHO/MUGA ~~will~~ to be performed at baseline and every 12-16 weeks ~~weeks~~ as per treating physician's discretion. After baseline, EKG will~~can~~ be ~~performed~~repeated if clinically indicated.

~~physician's discretion. After baseline, EKG will be performed if clinically indicated.~~
h: HbA1c will be performed at baseline, day 1 of every 3rd cycle (4, 7, 10, etc.), and at end of treatment (if last test was >4 weeks ago).
i: Pregnancy test for women of childbearing potential.
j: Fresh tumor sample can be collected in lieu of archival tissue
k: Optional tumor biopsies ~~and blood samples~~ should be strongly encouraged if clinically feasible.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature