SUMMARY OF CHANGES – Consent

NCI Protocol #: 10287
Local Protocol #: 201911082
Protocol Version Date: June 13, 2024

Protocol Title: A randomized Phase I/II trial of fulvestrant and abemaciclib in combination with copanlisib (FAC) versus fulvestrant and abemaciclib alone (FA) for endocrine-resistant, hormone receptor positive, HER2 negative metastatic breast cancer (FAC vs FA)

Informed Consent Version Date: June 13, 2024

I. Summary of Changes with Protocol Version June 13, 2024

	Section	Comments
1.	Global	Protocol version updated.

II. CIRB Letter, 11/21/2023, CIRB Approval Pending Modification of Amendment Review

#	Section	Comments
1.	Footer	Updated version date. Due to study closure, this phase II consent will no longer be used.

III. Disapproval Letter, 09/27/2023, Review of Amendment #11 of Protocol #10287*

*Of note, protocol version dated 09/07/2023 was titled Amendment 8a.

#	Section	Comments
2.	Genetic Testing Risks	*Genetic Testing Risks* *The genetic tests used in this study will test your tumor and normal tissue for genetic changes. Changes found in your normal tissue 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 test results may mean for you and your family. He or she may also suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for visits to a genetic counselor* There are NO integral genomic studies in this protocol, therefore no genomic results can be returned to patients or their doctors. This section must be removed. **PI Response: This has been updated as requested.**

IV. Disapproval Letter, 08/02/2023, Review of Amendment #10 of Protocol #10287*

*Of note, protocol version reviewed was Amendment #8 dated July 10, 2023

	Section	Comments
1.	Global	Protocol version updated.
2.	Samples for known future studies	Results will not be returned as stated under "Optional studies you can chose to take part in" Please delete the following language under "Samples for known future studies" 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 this study. YES NO **PI Response: This has been updated as requested.**
3.	Study Calendar Pg 19	Study Calendar – remove the X for copanlisib on Day 8 as Day 8 and day 22 are removed from cycles 2 and beyond. **PI Response: This has been updated as requested.**
4.	ICD Pg 19, 20 0f 19	Please correct page numbers **PI Response: This has been updated as requested.**

V. Summary of Changes in Amendment #8 of Protocol #10287, dated July 10, 2023

#	Section	Comments
1.	Global	Protocol version date updated. Minor typographical and formatting issues fixed throughout. Any references to Abemaciclib Days 1-28 day dosing removed due to RP2D dosing regimen of 5 days on, 2 days off.
2.	What are the study groups?	Clarified that the RP2D dosing regimen chosen was abemaciclib on a 5 days on, 2 days off schedule, and that for the first 4 patients randomized to FAC, the C1D1 dose is skipped due to PKs.
3.	Study Calendar	Day 8 and Day 22 removed in cycles 2 and beyond. Abemaciclib dosing updated to be regimen of 5 days on, 2 days off. Removed erroneous mention of PKs in screening. Clarified that scans will be performed every 3 cycles, not every 12 weeks.

Research Study Informed Consent Document – Phase 2

Study Title for Study Participants: A Phase 2 Study Testing the addition of copanlisib to usual treatment (fulvestrant and abemaciclib) in metastatic breast cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: 10287 A randomized phase I/II trial of fulvestrant and abemaciclib in combination with copanlisib (FAC) versus fulvestrant and abemaciclib alone (FA) for endocrine resistant, hormone receptor positive, HER2 negative metastatic breast cancer (FAC vs FA)

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 Nationsl 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 study because you have metastatic breast cancer that is hormone receptor (HR) positive and HER2 negative.

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 of more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question: what are the effects (good and bad) of adding a specific drug, copanlisib, to the usual therapy of fulvestrant and abemaciclib? We are doing this study because we want to find out if adding copanlisib is better or worse than the usual approach for your metastatic breast cancer that is HER2 negative. The usual approach is defined as care most people get for metastatic breast cancer that is HR positive and HER2 negative.

What is the usual approach to my metastatic breast cancer?

People who are not in a study are usually treated with the combination of fulvestrant, which breaks down the estrogen receptor of the cancer cells, and a drug like abemaciclib, which interferes with cell growth. This combination has received Food and Drug Administration

(FDA) approval. Fulvestrant and abemaciclib are FDA approved because patients taking this combination have no cancer growth for longer duration than patients taking fulvestrant alone.

What are my other 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 either get copanlisib along with abemaciclib and fulvestrant or you will get abemaciclib and fulvestrant alone, until your disease gets worse or the side effects become too severe.

After you finish your treatment, your doctor and study team will watch you for side effects. They will also check on you for every 3 months for 5 years after treatment.

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 study approach may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

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. Some side effects may be mild. Other side effects may be serious and even result in death.

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

- Nausea
- fatigue
- elevated blood sugar.

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

Benefits

It is however, not known if the study drugs will extend your life compared to the usual approach. This study will help the study doctors learn things that will help 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
- You become pregnant while on the study
- The study is stopped by the Institutional Review Board (IRB), or 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 good and bad effects of adding a specific drug, copanlisib, to the usual therapy of fulvestrant and abemaciclib. The addition of copanlisib to fulvestrant and abemaciclib could shrink your cancer and prevent tumor growth based on studies done in the laboratory but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the addition of copanlisib should increase the amount of time before a person's disease progresses by six months or more compared to the usual approach. This drug, copanlisib, stops a protein called phosphoinositide 3-kinase (PI3K) that is often changed (or mutated) in cancer cells and causes resistance to treatment. It is already FDA-approved for use in follicular lymphoma but is not FDA-approved for the treatment of breast cancer. There will be about 194 people taking part in this study 24 people in the first part of the study and about 170 people in the second part of the study.

What are the study groups?

The first part of the study determined the best dose of copanlisib that would be used in the second part. This consent form covers the second part of the study.

During the second part of this study, now that the appropriate doses of copanlisib and abemaciclib have been determined, participants will be assigned to one of two study groups.

Group 1 will receive the usual treatment for this type of cancer (abemaciclib and fulvestrant) along with the study drug, copanlisib. Group 2 will receive the usual treatment for this type of cancer on its own.

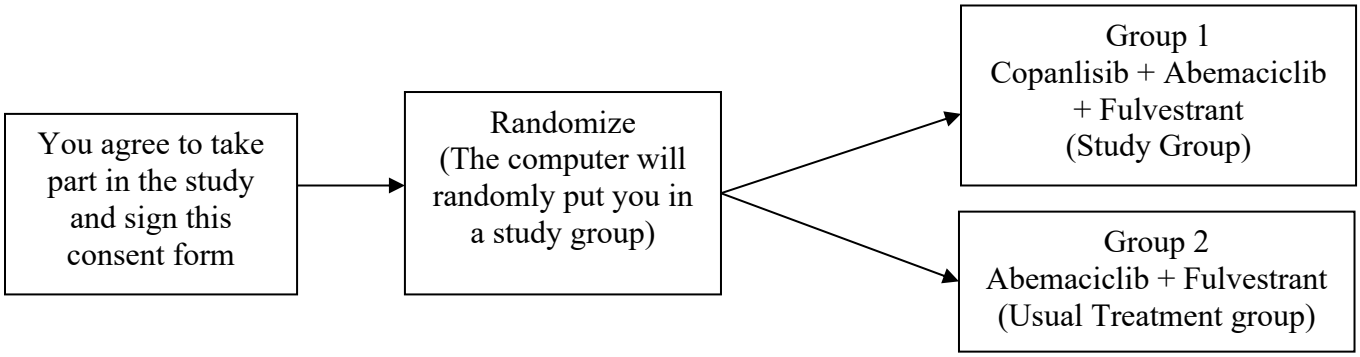
Copanlisib and fulvestrant will be administered in the clinic. Copanlisib is given as an intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle in patients assigned to Group 1. Fulvestrant is given as intramuscular injections on Days 1 and 15 of the first cycle and on Day 1 of every cycle after that. Abemaciclib is an oral drug which you will take at home twice a day for 5 days followed by a two day rest period each week.

For the first 4 patients in Group 1, in Cycle 1 only, the schedule for fulvestrant and abemaciclib is altered by one to test the study treatment assignment interactions in your blood. In these patients, fulvestrant is given Days 2 and 16 of the first cycle and on Day 1 of every cycle after that. The first 2 doses of abemaciclib on Day 1 will be skipped and dosing will start on Day 2 and continue through Day 5, and then Days 8-12, 15-19, and 22-26.

We recommend that, on the days when copanlisib is admistered (if receiving fulvestrant, abemaciclib and copanlisib), you bring your abemaciclib with you and not to take the morning dose of abemaciclib until 1 hour after completing the infusion of copanlisib. Do not eat within 4 hours of each copanlisib dose. You made need to discuss with your dietician if you need to change your normal diet to avoid foods that raise your blood sugar. Take the evening dose of abemaciclib approximately 12 hours from the morning dose.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you if you enroll during the second part of 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.



You will be expected to complete a medication diary when you take abemaciclib at home.

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.

- Blood tests to see how your blood is clotting before you begin the study
- Blood test to check your average blood sugar over the last few months before you begin the study
- Blood tests to see whether you have hepatitis before you begin the study
- Echocardiogram or multigated acquisition (MUGA) scan to check how your heart is functioning before you begin the study
- Electrocardiogram to check how your heart is functioning before you begin the study
- Blood tests to monitor blood sugar for all patients receiving copanlisib before administration of copanlisib, 60 minutes after the start of the copanlisib infusion, 1 hour after the end of the infusion (Day 1 only), and 2 hours after the end of the infusion (Day 1 only)
- Monitoring of blood pressure for all patients receiving copanlisib on each dosing day

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.

Tumor biopsy for research: Small pieces of cancer tissue removed by surgery (biopsies) will be taken for the study before you begin treatment. This sample is required if there are cancer sites that can be biopsied safely, in order for you to take part in this study because the research on the sample is an important part of the study. There is also an optional research biopsy on Cycle 1 Day 15 and again if your disease progresses. The research biopsy is done in a similar way to biopsies done for diagnosis. The tissue collected will be used for research to look for some specific genetic mutations or markers in the cancer cell that might predict response to treatment. If you agree, any specimen leftover will be stored for biobanking. This will be discussed in the section on optional studies. In addition, pieces of cancer tissue removed from your previous biopsies or surgeries for the breast cancer will be tested for mutations or markers that may predict response to therapy.

Blood collection for research: A blood sample will be taken for the study before you begin treatment and at the following time points:

- Cycle 1 Day 8 (a cycle is 28 days of treatment)
- Cycle 1 Day 15
- Cycle 2 Day 1
- Cycle 4 Day 1
- Every 3 cycles

- Before you begin your next treatment after you come off study treatment

In addition, research blood draws to look at how your body processes copanlisib and abemaciclib will be done for the first 4 patients in Group 1; these blood draws will take place at 6 different time points on Cycle 1 Day 1, one time point on Cycle 1 Day 2, and again at 6 different time points on Cycle 1 Day 15, and one time point on Cycle 1 Day 16; then again at 4 different time point on Cycle 1 Day 22 and one time point on Cycle 1 Day 23.

The samples described above are required in order for you to take part in this study because the research on the sample is an important part of the study. The blood will be collected at the same time as routine blood draws when possible to minimize the number of extra needlesticks you have. The blood collected will be used for research to study whether specific markers in the blood may be associated with treatment response. If you agree, any specimen leftover will be stored for biobanking. This will be discussed in the section on optional studies.

A study calendar that shows how often these tests and procedures will be done is attached to the end of this consent form.

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

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer. The schedule of taking abemaciclib for 5 days and then having a 2-day rest period is a change from the standard daily dosing schedule; this may result in your disease not responding as well to treatment, even when copanlisib is added.

You may also have the following discomforts:

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

The treatment 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 3 months after you have completed the study if you have child bearing potential.

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 can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

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. The frequent research blood draws to look at how your body processes copanlisib and abemaciclib can cause some discomfort and maybe inconvenient to your schedule

Risk of Radiation Exposure from MUGA

To determine whether you are eligible to participate in the study, a MUGA scan may be used to check your heart function (if this is the test your physician prefers over an echocardiogram). MUGA scan involves exposure to radiation. The risk of this procedure is small and is similar to that received from clinical x-ray and nuclear medicine studies. The amount of radiation exposure that you will receive from this procedure is equivalent to a uniform whole body exposure of 700 millirem. This is equal to 2.33 times the amount of natural background radiation that the average person in the United States receives each year (300 millirem**).**

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 be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs. Some side effects may be mild. Other side effects may be serious and even result in death.

Here are important points 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, or some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may mild. Other side effects may be serious and even result in death.

You can ask your study doctor questions about side effects at any time:

- 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 the 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.

Study Group 1 and Group 2 – Possible side effects of abemaciclib + fulvestrant

Possible Side Effects of Abemaciclib

COMMON, SOME MAY BE SERIOUS In 100 people receiving abemaciclib (LY2835219), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Tiredness • Bruising, bleeding • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving abemaciclib (LY2835219), from 4 to 20 may have:
• Belly pain • Dry mouth • Sores in the mouth which may cause difficulty swallowing • Infection, especially when white blood cell count is low • Changes in taste • Headache • Hair loss

RARE, AND SERIOUS In 100 people receiving abemaciclib (LY2835219), 3 or fewer may have:
• Damage to the lungs which may cause shortness of breath • Blood clot which may cause swelling, pain, shortness of breath

Possible Side Effects of Fulvestrant

COMMON, SOME MAY BE SERIOUS In 100 people receiving fulvestrant, more than 20 and up to 100 may have:
• Pain • Tiredness • Increased sweating • Hot flashes, flushing • Swelling and redness at the site of the medication injection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving fulvestrant, from 4 to 20 may have:
• Constipation, diarrhea, nausea, vomiting, loss of appetite, heartburn • Swelling of the body • Loss of bone tissue, broken bone, or decreased height • Dizziness, headache

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving fulvestrant, from 4 to 20 may have:
• Difficulty sleeping • Fluid around lungs • Swelling of the liver which may cause belly pain • Worry, depression, mood swings • Hair thinning • Cough

RARE, AND SERIOUS In 100 people receiving fulvestrant, 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Liver damage which may cause yellow eyes and skin • Vaginal bleeding • Blood clot which may cause swelling, pain, shortness of breath • Heart attack or heart failure which may result in chest pain, shortness of breath, swelling of ankles, and tiredness • Stroke which may cause weakness, paralysis

Study Group 1 – in addition to side effects outlined above, people who are in the first part of the study or in Group 1 of the second part of the study may also experience the possible side effects of copanlisib listed below.

Possible Side Effects of Copanlisib dihydrochloride
(Table Version Date: April 2, 2023)

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 • 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 • Nausea, 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:
• Change in the heart rhythm • Swelling and redness of the skin • Itching

Patients with diabetes may need to increase or change their diabetic medications to better control their diabetes.

Additional Drug Risks

Abemaciclib has been known to cause inflammation of the lungs. Copanlisib in combination with the other two drugs (FA) could cause an exacerbation of any side effect currently known to be caused by the other drug, or the combination of drugs and may result in side effects never previously associated with either of the three drugs.

What are my responsibilities in this study?

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

- Keep your study appointments.
- 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.
- Write down in your medication diary when you take the abemaciclib at home.

Ways to keep from getting pregnant:

Do not get pregnant or breastfeed while taking part in this study. Tell your study doctor right away if you think that you have become pregnant during the study or within 3 months after your last dose of study drug. Use barrier method (condoms, diaphragms, or cervical caps) of birth

control or abstinence for the duration of your study participation and for 6 months after your last day of study treatment.

For men: Do not father a baby while taking part in this study, or donate sperm for three (3) months following the last dose of your study drugs.

Acceptable Birth Control Methods:

- Condoms **with spermicide** AND one of the following:
  - Oral contraceptive or hormonal therapy (*e.g.*, hormone implants, skin patches, intravaginal device, hormone shots).
  - Placement of an intra-uterine device (IUD; *e.g.*, Mirena®).
  - Vasectomy, with participant assurance that the vasectomy was successful.
  - Tubal occlusion (*i.e.*, getting your tubes tied).
- Total sexual abstinence, when this is in line with your usual and/or preferred lifestyle. **Periodic abstinence** (*e.g.*, calendar, ovulation), the rhythm method, **and withdrawal are not acceptable methods of contraception**.

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 this study, just as you would if you were getting the usual care for your cancer. This includes:

- the cost of tests, exams, procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects
- the costs of getting the copanlisib, abemaciclib, and fulvestrant ready and giving it to you
- ECG
- Echo/MUGA
- your insurance co-pays and deductibles

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 research biopsies and research blood draws

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

Neither you nor your health care plan/insurance carrier will be billed for the collection of the tissue and blood that will be used for 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 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, medicines you took, and the results of any tumor and blood genetic testing will be kept by the study sponsor in a central research 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 may also 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:

- Bayer Pharmaceuticals (makers of copanlisib) or any drug 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 records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- 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 information.
- Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and re-identified data could potentially be used to discriminate against or stigmatize participants, their families, or groups. In addition, there may be unknown risks.

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).*

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 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 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 the 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/or 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, leftover tissue and blood from other research collections will be collected. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by Nationwide Children's Hospital in Columbus, Ohio, and is supported by the NCI..

Unknown Future Studies

If you choose to take part in this optional study, leftover tissue and blood will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by Nationwide Children's Hospital in Columbus, Ohio, and is supported by the NCI. 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 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.

What is involved in this optional sample collection?

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

1) A sample from the tissue that was collected at the time of your research biopsies and blood that was collected at the time of your research blood draws will be sent to the Biobank, as well as the additional biopsies that will be performed on Cycle 1 Day 15 and at the time of disease progression.
2) Your sample and some related health information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the risks in this optional sample collection?

- 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.
- 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. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

- 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 that 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 or 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 researchers and the biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. 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.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the possible 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. 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 for main trial*), at (*insert telephone number of study doctor for main trial*), 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 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 for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

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

Additional (2nd) Tumor Biopsy

Please circle your answer: I choose to permit an additional tumor biopsy on Cycle 1 Day 15

YES NO

Additional (3rd) Tumor Biopsy

Please circle your answer: I choose to permit an additional tumor biopsy if the study treatment appears to help me, but my cancer later starts to grow.

YES NO

Samples for known future studies

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

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

This is the end of the section about optional studies.

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

STUDY CALENDAR

	Screening	Pre-treatment	Cycle 1*							Cycles after Cycle 1*		End of Treatment[C*]
			Day 1	Day 2	Day 8	Day 15	Day 16	Day 22	Day 23	Day 1	Day 15	
Physical exam	X		X		X[B]	X[B]				X		
Disease Assessment Imaging[†]	X											X
Blood for safety labs	X		X		X[B]	X		X		X	X	
Echo/MUGA	X											
ECG	X	As clinically indicated thereafter										
Pregnancy test	X[D]											
Hepatitis panel	X											
Urinalysis	X											
Blood pressure (group 1)			X		X[B]	X				X	X	
Randomization		X										
Fulvestrant			X[A]			X[A]				X		
Abemaciclib			5 days with 2 days rest each week [A]									
Copanlisib (if applicable)			X			X				X	X	
Archival tumor tissue	X											
Fresh tumor biopsy	X					X**						X**
Blood for research	X		X	X	X	X [A]	X			X[E]		X

A. Note that in patients who participate in the copanlisib PK studies (the first 4 patients randomized to FAC in this Phase II portion), the first two doses of abemaciclib on C1D1 are skipped and fulvestrant is delayed to C1D2 following the 24 h blood draw for copanlisib PK. Abemciclib is therefore administered on C1D2-5 (4 days) the first week due to the 5 days on and 2 days off schedule each week. C1D15 fulvestrant dose is delayed to C1D16 following the 24 h blood draw for copanlisib PK.

B. Only if receiving copanlisib.

C. Follow up for survival status occurs every 3 months (+/- 7 days) for 5 years after removal from the study or until death, whichever occurs first. In addition, patients removed from study due to unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

D. Pregnancy test is only applicable for patients with pregnancy potential. Pregnancy tests will be performed at screening and every 3 cycles on study.

E. On Day 1 of Cycles 2 and 4 and then every 3 cycles after that.

** Optional

*Visits can occur in ± 2 day window to allow for holidays, inclement weather, *etc*

[†] Disease Assessment Imaging will be performed at screening, at the end of Cycle 3 (+/- 7 days), then every 3 cycles (+/- 7 days).