SUMMARY OF CHANGES – Consent Form

NCI Protocol #: 10216
Local Protocol #: OSU 19016
Protocol Version Date: 09/17/2024

Protocol Title: A Phase Ib Study of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in Patients with EGFR Mutant Non-Small Cell Lung Cancer

Informed Consent Version Date: TBD

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comment
1.	Header	Updated header version date to match the updated protocol version.
2.	What exams, tests, and procedures are involved in this study?	Please delete the following language from the Informed Consent: 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.

#	Section	Comment
		It is more likely, however, that you will not be contacted by us about a medically important finding. Even if we do not contact you, it does not mean that your genes do not contain changes that are important to your health. Researchers are always learning about new and medically important changes in genes and some information may be learned in the future. Researchers will only decide to contact you about genetic test results at the time your DNA is initially sequenced. You will not be contacted or consented for any research done using your samples in the future, and you will not receive any reports or information about any medically important findings learned in the future. Also, sometimes the meaning of genetic test results can be uncertain, and we may not know for sure what the results mean for your future health. Sharing an uncertain genetic test result with you could offer little benefit, no benefit at all, or could even be harmful. Results from genetic testing will not be a part of your medical records, unless the results are confirmed by additional testing that you agreed to. See "Who will see my medical information?" for laws and risks in protecting your genetic information. **PI Response:** ***This has been deleted.***
3.	What is the purpose of this study?	Please add – "Due to issues with supply of Telaglenastat (CB-839), all protocol therapy with Telaglenastat (CB-839) will end on February 28, 2025. After that date, patients may remain on Osimertinib single agent at the investigator discretion until meeting other off-therapy criteria." The supply of Telaglenastat (CB-839) is an issue again. **PI Response*: This has been updated***

II. CIRB Requested Edits:

#	Section	Comment
	Page 2 Risks	"Risks", last paragraph, revise to state, "There may be some risks that the study …"
	Page 4 What is the purpose of this study?	Removed - "Due to issues with supply of CB-839, all protocol therapy with CB-839 will end on October 31, 2024. After that date, patients may remain on osimertinib single agent at the investigator discretion until meeting other off-therapy criteria."
	Page 4-5 What are the study groups?	a. 1st paragraph: • Insert 4th sentence to state, "The study doctor will watch each group carefully as they increase the dose.". • 6th sentence, revise to state, "Once this dose is found, the study is stopped." b. 3rd paragraph, delete. c. 5th paragraph, move to after the 2nd paragraph and revise as follows: • 1st sentence, revise to state, "You also will keep a drug diary. • 2nd sentence, revise to state, 'Each time you visit the clinic, you must bring the drug diary, any remaining pills, and the pill bottle." • Insert 2nd sentence that states, "This helps you keep track of when you take your pills." Insert 3rd sentence that states, "The study doctor will show you how to use this diary." If applicable.
	Page 7 General Risks	"General Risks", delete the 4th – 8th paragraphs.
	Page 8 Side Effects	Under "Side Effects", delete 4th bullet
	Page 8-9 Side Effects	a. Move "(Table Version Date: July 21, 2019)" under "Possible Side Effects of Telaglenastat (CB-839) HCI". Move "(CAEPR Version 2.9, February 9, 2023)" under "Possible Side Effects of Osimertinib (AZD9291)".

#	Section	Comment
	Page 11-12 What are the costs of taking part in this study?	Under "What are the costs …?": a. 2nd set of bullets • 1st bullet, delete 2nd sentence. • 2nd bullet, delete 2nd sentence 1st paragraph after 2nd set of bullets, revise to state, "You or your insurance provider … Telaglenastat (CB-839) HCI while you take part in this study."
	Page 15 Optional studies that you can choose to take part in	Under "Optional studies…", after 3rd paragraph, delete "YES" and "NO".
	Page 15 Optional Sample Collections	Under "Optional sample collections…": a. After 2nd paragraph insert the header "Known future studies". b. 3rd paragraph: • 1st sentence, delete. • 2nd sentence, move to after the 3rd sentence. 3rd sentence, revise to state, "If you choose to take part … 1 tablespoon of blood about 24 hours after your one-month visit for research on …"
	Page 16 What are the risks in this optional sample collection?	Under "What are the risks …?", 2nd bullet, add a bullet before the 2nd paragraph.
	Page 16 How will information about me be kept private?	Under "How will information about me …?": a. 1st paragraph, 1st sentence, revise to state, "Your privacy is very important to the study researchers and biobank." b. #2, delete 3rd sentence
	Page 17 What if I change my mind about this	Under "What if I change my mind …?", 2nd sentence, revise to state, "Then, any sample that remains in the biobank will be destroyed or …"

#	Section	Comment
	optional sample collection?	
	Page 17 What if I have questions about this optional sample collection?	Under "What if I have questions …?", revise to state, "If you have questions about … study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*)."
	Page 17 Samples for known future studies	Optional Studies: Please delete the language below under **Samples for known future studies** in the Optional Studies section of the Informed Consent as results will not be added to the patient medical records nor provided to the patient or the study doctor. **Remove:** "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 **PI Response: *Removed as requested.***

III. Recommendations:

#	Section	Comment
	Page 6-7 What exams, tests, and procedures are involved in this study?	Remove the following text: This study will use genetic tests that may identify changes in the genes in your tumor DNA that can be detected from the tumor sample or in the blood. 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 there are changes found that could cause health problems,

#	Section	Comment
		then your study doctor will discuss your options with you. If warranted, genetic counseling may be recommended. **PI Response**: ***Removed as recommended.***

IV. Changes in Response to RRA dated 8/20/24:

#	Section	Comment

	Page 8
	Possible Side Effects of Osimertinib (AZD9291)
		Updated Risk Profile for Osimertinib (AZD9291) (CAEPR Version 2.9, May 23, 2024)
		
		• Added New Risk:
		  • Rare: Skin changes
		
		• Decrease in Risk Attribution:
		  • Changed to Occasional from Common: Infection, especially when white blood cell count is low
		  • Changed to Also Reported on osimertinib Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): Hair loss
		
		PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to osimertinib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of a new anti-cancer drug, Telaglenastat (CB-839) HCl, to Osimertinib (AZD9291) for EGFR-mutated non-small cell lung cancers resistant to front line therapy.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10216, A Phase Ib Study of Osimertinib (AZD9291) and Telaglenastat (CB-839) HCl in Patients with EGFR Mutant Non-Small Cell Lung Cancer (NCT # 03831932)

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 Insitutes 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 non-small cell lung cancer (NSCLC) that has spread outside your lungs, and your cancer has a change in the epidermal growth factor receptor (EGFR) gene, and your cancer has not responded to one of several first line standard treatment options.

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:

Is the combination of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) safe in patients with non-small cell lung cancer?

Osimertinib (AZD9291) induces responses in NSCLC patients that have relapsed and/or are refractory to initial tyrosine-kinase inhibitor therapies and have a specific mutation in the EFGR

gene. However, absence of the mutation has been associated with resistance to Osimertinib (AZD9291). Osimertinib (AZD9291) is being combined with Telaglenastat (CB-839) HCl to determine if this combination is able to overcome the resistance in tumors that do not have the EGFR mutation.

We are doing this phase 1b study to determine the safety of this approach.

What is the usual approach to my non-small cell lung cancer?

The usual approach for patients who are not in a study is treatment with a Food and Drug Administration (FDA) approved chemotherapy.

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 Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) until your disease gets worse or the side effects become too severe.

After you finish Telaglenastat (CB-839) HCl and Osimertinib (AZD9291), your doctor will continue to follow your condition for at least 30 days and watch you for side effects. You will have at least one clinic visit with your medical team around 30 days after the last dose of your study 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 Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) may not be as good as chemotherapy at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). These side effects may be worse and may be different than you would get with the usual approach for your NSCLC.

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

- Fatigue
- Nausea and/or vomiting
- Changes in your liver function
- Changes in the number of platelets in your blood (platelets help form clots and prevent bleeding)
- Changes in the amount of white blood cells in your blood (white blood cells are infection fighting cells)
- Becoming more sensitive to light
- Decreased appetite
- Diarrhea
- Rash

Because this is a new combination, there may be some risks that the study doctors do not yet know about.

Benefits

There is some evidence in animals and in living human cells that adding Telaglenastat (CB-839) HCl to Osimertinib (AZD9291) can shrink or stabilize cancer for longer than the usual approach alone. However, we do not know if this will happen in people. It is unlikely that this study treatment will help you live 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?

This study uses a combination of drugs Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). Osimertinib (AZD9291) has already been approved by the FDA to be given by mouth to patients with advanced NSCLC with an EGFR mutation. Telaglenastat (CB-839) HCl has been studied in phase 1 and 2 trials but is not FDA-approved for any indication. Telaglenastat (CB-839) HCl has been studied in combination with other cancer drugs, but not with Osimertinib (AZD9291). The purpose of this study is to test if giving these drugs together are safe. There will be about 18 people taking part in this study.

This is a phase 1b study. The purpose of the study is to test if giving these drugs together is safe. There will be about nine to eighteen people taking part in this phase 1 study. Once the safe dose for the combination of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) has been determined, an additional cohort of 10 patients will be enrolled to gain additional information on safety and tolerability.

Due to issues with supply of Telaglenastat (CB-839), all protocol therapy with Telaglenastat (CB-839) will end on February 28, 2025. After that date, patients may remain on Osimertinib single agent at the investigator discretion until meeting other off-therapy criteria.

What are the study groups?

All patients in the study will receive the study drug Osimertinib (AZD9291) at the same dose. Different doses of the study drug Telaglenastat (CB-839) HCl will be given to several study participants. The first several study participants will receive the lowest dose. The study doctor will watch each group carefully as they increase the dose. If the drug does not cause serious side effects, it will be given to other study participants at a higher dose. The doses will continue to increase for every group of study participants until side effects occur that require the dose to be lowered. Once this dose is found, the study is stopped. You will be able to receive additional doses of the drug.

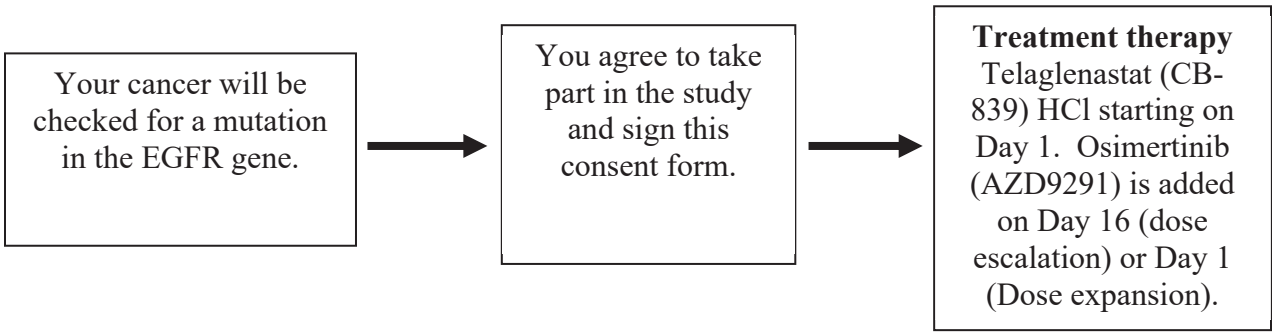
Treatment schedule: You will get Telaglenastat (CB-839) HCl as a pill you take by mouth twice a day with food. Each dose is to be taken 12 hours apart with the first dose taken immediately

after breakfast and the second dose taken approximately 12 hours later. From Day 16, you will begin taking Osimertinib (AZD9291) as a pill you take by mouth once daily as well. Each cycle lasts 28 days. There is no duration of treatment that is set. You will continue to receive treatment as long as you are tolerating it and your cancer does not grow. See the study calendar for more information.

You will not be able to get additional doses of the Telaglenastat (CB-839) HCl drug after the study ends. This drug is not approved by the FDA for treatment of your disease. Although Osimertinib (AZD9291) is FDA-approved, this does not guarantee you will be able to receive Osimertinib (AZD9291) after this study ends.

You will also keep a drug diary. Each time you visit the clinic, you must bring the drug diary, any remaining pills, and the pill bottle. The study doctor will show you how to use this diary.

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.



All protocol therapy with CB-839 will end on 10/31/24. After that date, patients may remain on osimertinib single agent at the investigator discretion until meeting other off-therapy criteria. CB-839 will not be available after 10/31/24.

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:

- An electrocardiogram (EKG) before you begin the study, on Day 1 of Cycle 2, and at the end of study.
- An echocardiogram (MUGA) before you begin the study and at the end of study, unless you have cardiac risk factors which warrant more frequent monitoring.
- Research PET/CT imaging will be performed on patients treated at Ohio State University (in the expansion cohort only).

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.

You will need to have a blood sample taken for the study. This will be taken before you begin study drug, on Day 15 of treatment, after a month of treatment, and at the end of the trial. The study blood sample will be used to determine changes in the tumor DNA make-up that may be affected by the study treatment. You and your study doctor will not get the results of this testing.

During this study, blood tests will also be taken at multiple time points during the first month in order to learn how taking Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) may affect how the body processes each drug. These tests are called pharmacokinetics and are done in most phase 1 studies. You and your study doctor will not get the results of this testing. You will need to have blood drawn before dosing on Day 15 of treatment (for patients enrolled in dose escalation cohort) and at 2, 4, 6, and 8 hours after you take your dose of medication. These same blood tests will be repeated at the same time intervals after the first month of treatment.

Your study doctor will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is a required part of the study. This tumor specimen will be used to confirm the type of EGFR mutation found in your tumor, and also to explore additional mutations or changes that may make your tumor more or less sensitive to the study treatment. You and your study doctor will not get the results of this testing.

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. You and your study doctor will not get any results of this testing.

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 Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) may not be as good as the usual approach for your cancer 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 Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) 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 120 days (4 months) 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 your tumor for genetic changes, including EGFR mutation. Though rare, we may identify other mutations that may 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.

Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. If you want to find out if the change is in your normal tissue, then you will need to get other tests done outside of this study.

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

Side Effect Risks

The study drugs Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) 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 drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.

2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. 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.

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 Telaglenastat (CB-839) HCl
(Table Version Date: July 21, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Telaglenastat (CB-839) HCl, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Telaglenastat (CB-839) HCl, from 4 to 20 may have:
• Anemia which may require blood transfusion • Discomfort from light • Nausea, vomiting • Bruising, bleeding • Loss of appetite

Possible Side Effects of Osimertinib (AZD9291)
(CAEPR Version 2.9, May 23, 2024)

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving osimertinib (AZD9291), from 4 to 20 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, nausea, vomiting • Sores in the mouth which may cause difficulty swallowing • Tiredness • Infection, especially when white blood cell count is low • Change in the heart rhythm • Bruising, bleeding • Loss of appetite • Cough • Damage to the lungs which may cause shortness of breath • Dry skin • Change in or loss of some or all of the finger or toenails • Itching, acne, rash

RARE, AND SERIOUS In 100 people receiving osimertinib (AZD9291), 3 or fewer may have:
• Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Dry eye • Visual disturbances • Swelling and redness of the eye • Fluid around lungs • Skin changes • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

Additional Drug Risks

The study drugs could interact with other drugs. This may result in increased exposure to study drugs and therefore increase side effects, or it could result in lower levels of drug exposure and therefore decrease the chances of the drugs working to stabilize the cancer. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

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

Imaging Risks

The PET scan that you get in this study will expose you to more radiation than you get from everyday background radiation. The amount of radiation from this scan is the same as 4 years' worth of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

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 drug diary when you take the study drug at home.

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 120 days (4 months) 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. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety and prevent and treat side effects.
- 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 EKGs in this study done before you begin the study, on Day 1 of Cycle 2, and at end of treatment.
- The echocardiograms done before you begin the study and at end of treatment.
- The blood tests done for research or pharmacy studies (blood tests to determine the levels of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in your body).

You or your insurance provider will not have to pay for the Osimertinib (AZD9291) or Telaglenastat (CB-839) HCl 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 Institutional Review Board (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:

- 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.

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*).

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 this optional study 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 this optional study. If you sign up for, but cannot complete this study for any reason, you can still take part in the main study.

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

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, researchers will collect about 1 tablespoon of blood about 24 hours after your one-month visit for research on the levels of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291) in the blood. This will require one additional visit and the only purpose of this visit is for a blood test. This will give the researchers a better idea of how the two study drugs interact. 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.

What is involved in this optional sample collection?

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

1. About 1 tablespoon of blood will be collected from a vein in your arm.

2. Your sample 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. This will be performed on the second day of the second "cycle" (or Cycle 2, Day 2) of study treatment.
3. 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.
4. 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 drawing blood from your arm are brief pain and possibly a bruise.
- 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:

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 samples 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 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 learn more about the interactions of these two study drugs.

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 need my blood samples to be returned?

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. 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.

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 for main trial*) at (*insert telephone number of study doctor for main trial*).

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 study described above.

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 _____

Appendix A: Study Calendar for Protocol 10216 Consent Form

	Pre-Study	Cycle 1			Cycle 2			Cycle 3 onwards			Off Study
		D1 [A]	D15	D16	D1	D2	D15	D1	D8	D15	
Telaglenastat (CB-839) HCl[B]		X----------								----------X	
Osimertinib (AZD9291)[C]				X [D]	X----------					----------X	
Osimertinib (AZD9291)[C]		X----------								----------X	
Pre-study procedures including informed consent, demographics, medical history, and height	X										
Inclusion/exclusion criteria	X	X									
Concurrent meds	X	X			X			X			X
Physical exam, vital signs, and general well-being	X	X	X		X			X			X
Weight	X	X			X			X			X
Blood draw for complete blood count and general health status	X	X	X		X			X			
EKG[E]	X				X						X
Imaging to check heart function (sonogram and MUGA scan)[E]	X										X
Side effects evaluation	X	X	X		X		X [J]	X			
Tumor measurements	X	Tumor measurements are repeated every 8 weeks until progression.									
Pregnancy test [F]	X										
Tumor biopsy (archival)	X										
Blood draw for scientific study		X [G]	X [G]		X [G]						X [G]
Blood draw for studying drug interactions		X [H]	X [H]		X [H]	X [H, I]		X [H]			

Cycle length = 28 days

A. All days are +/- 5 days to account for patient and clinic schedules, holidays, etc.
B. Telaglenastat (CB-839) HCl will be given at the assigned dose.
C. Osimertinib (AZD9291) will be given at 80 mg PO QD and will start at either Day 16 (escalation) or Day 1 (expansion)
D. Osimertinib (AZD9291) treatment will begin on D16 of Cycle 1.
E. Repeated if necessary.
F. Pregnancy test is for women of childbearing potential.
G. Blood will be collected on Cycle 1 Day 1, Cycle 1 Day 15 (before Osimertinib (AZD9291) treatment begins), Cycle 2 Day 1, and at the time of disease progression.
H. Blood will be collected on Cycle 1 Day 1 and after the morning dose of Telaglenastat (CB-839 HCl) on Day 15. On Cycle 2 Day 1, blood will be collected after the morning dose of Telaglenastat (CB-839) HCl and Osimertinib (AZD9291). Blood will also be collected on D1 of each cycle starting with Cycle 3 onwards.
I. The C2D2 blood collection for studying drug interactions is optional.
J. Your study doctor will contact you by telephone on Cycle 2, Day 15 to assess any side effects.