SUMMARY OF CHANGES – Consent

NCI Protocol #: 10042
Local Protocol #: 2000021123
Protocol Version Date: 03/27/2023

Protocol Title: A Phase II trial of Osimertinib (AZD9291) with or without bevacizumab in patients with EGFR mutation positive NSCLC and brain metastases

Informed Consent Version Date: 03/27/2023

I. CTEP Request for Rapid Amendment (RRA) dated February 28, 2023:

#	Section	Change
1.	All	Updated Version Date

2.	Risk Profile Osimertinub	The condensed risk profile has been modified
		• Added New Risk:
		  • Rare: Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions
		• Increase in Risk Attribution:
		  • Changed to Occasional from Also Reported on Osimertinib Trials But With Insufficient Evidence for Attribution (i.e. Added to the Risk Profile): Constipation; Cough; Tiredness
		• Decrease in Risk Attribution:
		  • Changed to Occasional from Common: Diarrhea; Sores in the mouth which may cause difficulty swallowing; Dry skin; Rash
		  • Changed to Also Reported on Osimertinib Trials But With Insufficient Evidence from Occasional (i.e. Removed from the Risk Profile): Nose bleed; A hole or tear in the skin which may cause pain
		  • Changed to Also Reported on Osimertinib Trials But With Insufficient Evidence from Rare (i.e. Removed from Risk Profile): Change in heart function

Study Title for Study Participants: Testing AZD9291 (osimertinib) with or without bevacizumab in patients with EGFR mutation positive lung cancer that has spread to the brain

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Phase II trial of AZD9291 (osimertinib)with or without bevacizumab in patients with EGFR mutation positive NSCLC and brain metastases

What is the usual approach to my lung cancer?

You are being asked to take part in this study because you have EGFR (Epidermal Growth Factor Receptor) mutation positive lung cancer that has spread to the brain. Some lung cancers have mutations (changes in the genetic material of the tumor) that can help physicians decide the best treatment for their patients. One particular type of mutation is called the EGFR mutation. When a patient with advanced lung cancer is found to have an EGFR mutation, the standard treatment for that stage of the disease currently involves the use of an oral (by mouth) therapy called an EGFR inhibitor (targeted therapy) that targets the mutation. In order to be eligible for the study, your tumor must be confirmed to have an EGFR mutation (or a standard-of-care optional blood test can be used as an alternate to tissue testing for the EGFR mutation) with cancer growing in the brain. People who are not in a study are usually treated with radiation to the brain, targeted therapy, chemotherapy, or a combination of these therapies. These treatments may shrink the tumor or stop it from growing for several months or more. Osimertinib (aka AZD9291) following radiotherapy to the brain is the usual care for some patients with your type of cancer and your doctor can explain if this may be best for you.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

If you choose to participate, you will be told of any significant new findings that develop during the course of your participation in this study that may affect your willingness to continue to participate.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using bevacizumab along with AZD9291 (osimertinib) to using the targeted therapy, AZD9291 (osimertinib) alone. The addition of bevacizumab to the usual AZD9291 (osimertinib) could shrink your cancer 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.

Another purpose of this study is for researchers to learn if their EGFR mutational status or other markers such as certain genes, proteins, or other substances in their cancer (biomarkers) can help predict which patients will respond better to the study drugs combined or AZD9291 (osimertinib) alone.

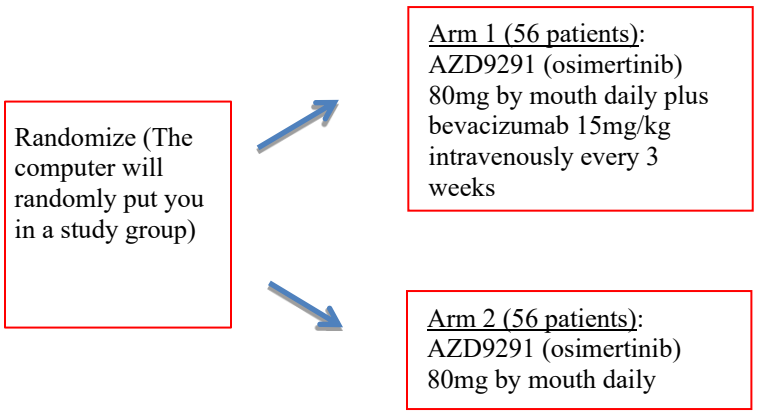
Both of the drugs in this study, AZD9291 (osimertinib) and bevacizumab, have been approved for use by the United States Food and Drug Administration (FDA) for patients with lung cancer, however, the way the drugs are being used in this study is investigational. AZD9291 (osimertinib) is currently FDA approved for patients with advanced EGFR mutation positive lung cancer who have previously failed an EGFR target therapy and for patients who have not been previously treated for their lung cancer. Bevacizumab is currently FDA approved for patients with lung cancer in combination with chemotherapy. AZD9291 (osimertinib) is investigational in this study since it is not approved alone for your type of lung cancer that has spread to the brain. The combination of AZD9291 (osimertinib) and bevacizumab has not been approved for commercial use.

About 112 people will take part in this study at several sites around the United States.

What are the study groups?

You will be "randomized" into one of the study groups (called "Arms") described below. Randomization means that you are put into a group by chance, like the flip of a coin. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have a one in two chance of receiving AZD9291 (osimertinib) and bevacizumab, and one in two chance of receiving AZD9291 (osimertinib) alone. This is done by chance because no one knows if one study group is better or worse than the other.

Another way to find out what will happen to you during the study is to read the chart below. Start reading on the left and read towards the right, following the lines and arrows.



If you are in Arm 1, you will receive AZD9291 (osimertinib) 80mg daily by mouth and bevacizumab 15mg/kg through an IV infusion every three weeks.

If you are in Arm 2, you will receive AZD9291 (osimertinib) 80mg daily by mouth.

You will be asked to complete a medication diary recording when you took AZD9291 (osimertinib) each day, and you should bring the diary with you to each clinic visit along with the AZD9291 (osimertinib) bottle with any unused pills. If you are in Arm 1, you will also receive bevacizumab. Bevacizumab will be given as an IV infusion once every three weeks. The first dose of bevacizumab will be given over 90 minutes. If there are no reactions, the second dose can be given over 60 minutes. If there are no reactions, then all bevacizumab can be given over 30 minutes. If you do have a reaction, your study doctor may decide to give the bevacizumab over a longer period of time.

How long will I be in the study?

You will receive study drugs until your cancer no longer responds or you have side effects that you require you to stop taking the study drug(s). After you are finished taking AZD9291 (osimertinib) with or without bevacizumab, the study doctor will ask you to visit the office for follow-up exams. If you stopped taking the study drug(s) because of unacceptable side effects, your study doctor may need to follow up with you until your side effects have resolved.

After you stop receiving study drug, the study team will contact you periodically to collect information. This will continue for the rest of your life until you withdraw consent or the study is stopped. After the study you will be asked to speak with your study doctor about other treatment options for your cancer.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra exams, tests, and procedure that you will need to have if you take part in this study.

Before you begin the study:

You will need to have the following exams, tests or procedures to find out if you can be in the study.

- Informed consent
- Electrocardiogram, which is a test that checks the electrical activity of your heart
- Echocardiogram (a test used to evaluate the pumping action of your heart)
- Evaluation of how you are functioning on a daily basis
- Urine or blood pregnancy test if you are capable of getting pregnant
- Blood samples for biomarkers
- Tumor biopsy (i.e. a small piece of cancer tissue removed from the body)

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra exams, tests, and procedures. They are not part of the usual approach for your type of cancer.

During the study:

- Blood samples will be taken to check for biomarkers (biologically derived indicators of cancer [note: the results of these studies will not affect how the study doctor manages your care]).
- Perform an electrocardiogram (ECG)
- Perform an echocardiogram
- Collect information on any signs and symptoms you have after you join the study
- Additional eye examinations, if you are experiencing visual symptoms
- Dispense the study drug and provide instructions
- Record the time of day when receiving the study drug(s) (in your medication diary)
- Evaluate how you are functioning on a daily basis

Any leftover blood or tumor material may be stored for biobanking. This will be discussed in the section on optional studies.

You should swallow 1 tablet once daily of AZD9291 (osimertinib), starting on the day you receive your new bottle(s). The tablet should be taken as whole (do not chew or crush) with water, with or without food. You should take these tablets daily around the same time every day. If you miss a tablet, you can take it within 12 hours of the usual time. If it is past 12 hours, do not take the missed tablet. You can take the tablet the next day at the regular

time. If you vomit after taking the tablet, do not make up for that by taking another tablet.

You must be willing to attend the scheduled visits. It is also important that you take the study drug as directed. Any leftover study drug that you do not take, and the container even if it is empty, must be returned at each of your visits. It is also important that you tell the medical staff about any other medication you are taking before and during the study including any over-the-counter medication, herbal/natural products or other folk remedies. There are also other medications that you should not take while taking the study drug (for example another chemotherapy, immunotherapy, hormonal therapy, as well as some other types of drugs that your study doctor will tell you about).

About mandatory samples for research:

A tumor biopsy will be taken before you begin on the study drug. For patients who have a place to biopsy in the body, this sample must be provided before you begin dosing with the study drugs or you cannot be in this study. For patients who do not have a place to biopsy in the body or who only have cancer growing in the brain, or if you have already undergone a biopsy, a biopsy may not be required. Research on the sample is an important part of this study and will be tested for mutations and proteins (such as EGFR and other mutations in the cancer, and also proteins that might be important in blood vessel growth) that may help researchers understand why certain treatments work or do not work for some patients.

At the time that your cancer starts to grow after being treated with the study drugs, your study doctor may recommend a biopsy of part of your cancer as part of your standard medical care. If this happens, a piece of the cancer will be collected for research on this study.

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place.

With your consent, blood will be collected to check your eligibility for the study as well as during the study period and following the study period. The total amount of blood that will be taken over the entire study will depend on how long you will be participating in this study.

The blood samples that you have provided during the study will be stored and will not be labelled with any information that could identify you. These blood samples will be tested by researchers in order to increase the understanding of non-small cell lung cancer and how it responds to the study drug. It is possible that this work may result in new drugs or diagnostic tests being developed. The blood samples that you have provided during the study will be stored at a secure laboratory. Samples may be kept, for up to 15 years from last patient last visit, after

which time any remaining samples will be destroyed.

You may withdraw your consent to the use of your blood samples at any time. The Study Sponsor and the Study Doctor will make sure that your blood samples are disposed of/destroyed. However, if any analysis has already been performed on the samples, the Study Sponsor does not have to destroy the results of this research.

Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Results will not be available to you or your study doctor.

Your health care plan/insurance carrier may be billed for the collection of the tumor tissue that will be used for this study since biopsy at this point in your care is considered standard.

Study Calendar

You will take AZD9291 (osimertinib) every day and may also receive bevacizumab every three weeks in this study. A three-week period of time is called a cycle. The cycle will be repeated until your cancer grows on study drug(s)or you need to stop study study drug(s) for another reason that your study doctor will explain to you. Each cycle is numbered in order. A Study Calendar that shows what will happen to you during Cycle 1 and future cycles is attached.

What possible 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 drug(s) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

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

The study drug(s) 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 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 drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go

away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:
- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

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.

Possible Side Effects of Bevacizumab

COMMON, SOME MAY BE SERIOUS In 100 people receiving bevacizumab (rhuMAb VEGF), more than 20 and up to 100 may have:
• High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving bevacizumab (rhuMAb VEGF), from 4 to 20 may have:
• Anemia which may require blood transfusion • Low white cell count that may increase the risk of infection • Infection, including collection of pus in the belly or rectum • Abnormal heartbeat which may cause palpitations or fainting • Pain in the belly, rectum, chest, joints, muscles, or tumor • Low appetite, constipation, diarrhea, heartburn, nausea, vomiting, or dehydration • Bleeding from multiple sites including the vagina or nose • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood, or blood in urine • Blockage of internal organs which may cause vomiting or inability to pass stool • Sores in the mouth • Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Delay in healing of wounds or spontaneous opening of wounds • Weight loss, tiredness, or dizziness • Muscle weakness • Damage to the jawbone which may cause loss of teeth • Headache • Numbness, tingling or pain in the fingers or toes • Hoarseness, stuffy nose, or cough • Dry skin • Swelling and redness of the skin • Blood clot in limbs or lungs which may cause swelling, pain, shortness of breath • Leakage of protein in the urine, which can rarely lead to damage to the kidney

RARE, AND SERIOUS In 100 people receiving bevacizumab (rhuMAb VEGF), 3 or fewer may have:
• Clots in the arteries, causing stroke (which may cause paralysis or weakness) or heart attack (which may cause chest pain or shortness of breath). This risk is significantly increased in patients who are elderly or with history of diabetes • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Bowel perforation (a tear in the bowel) that can cause pain or bleeding and require surgery to repair • A tear or hole (fistula) in internal organs such as the nose, throat, lungs, esophagus, rectum, or vagina. These conditions may cause serious infections or bleeding and require surgery to repair • Sores in the throat • Flesh-eating bacteria syndrome, an infection in the deep layers of skin • Damage to organs (bone, lungs, others) which may cause loss of motion • Bleeding in the tumor, brain, belly or lungs which may cause confusion, blood in stool or coughing up blood • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis • Redness, pain or peeling of palms and soles

Additional Notes on Possible Side Effects for Bevacizumab:
• Risk in children or adolescents: abnormal bone changes which may interfere with growth.
• Risk in pre-menopausal women: more likely to develop menopause when taking bevacizumab.

Possible Side Effects of AZD9291 (osimertinib)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Osimertinib (AZD9291), more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low

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 • Change in the heart rhythm. • Bruising, bleeding • Loss of appetite • Cough • Damage to the lungs which may cause shortness of breath • Hair loss, itching, acne, rash • Dry skin • Change in or loss of some or all of the finger or toenails

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
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body

AZD9291 (osimertinib) in combination with bevacizumab could cause a worsening of any side effect currently known to be caused by the other study drug, or the combination may result in side effects never previously associated with either study drug.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: Because the drug*(s)* in this study can possibly affect an unborn baby and infants, you should not become pregnant or father a baby or breast feed while you are on this study. Also, because AZD9291 (osimertinib) and bevacizumab can remain in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least the following amount of time:

- 6 months after your last dose of bevacizumab for men and women
- 4 months after your last dose of AZD9291 (osimertinib) for men
- 6 weeks after your last dose of AZD9291 (osimertinib) for women

It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Men and women participating in this trial should inform their treating physician immediately should they or their partner become pregnant.

Other Risks

Blood Collection and Intravenous (IV) catheter placement:
The risks of taking blood may include pain, redness, swelling and/or bruising where the needle enters your body, light-headedness and fainting. On rare occasions, local blood clot formation or infection with redness and irritation of the vein has occurred. The blood pressure cuff may cause discomfort or bruising to the upper arm. Approximately 20 mL of blood will be taken at every other cycle during your participation in this study for research purposes only.

Tumor Biopsy:
As with any procedure, there are risks and discomforts. You may feel some amount of pain or discomfort during a biopsy, including slight, stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness, inflammation, bleeding, swelling, and/or

infection at the biopsy site. With a tumor biopsy, there is a rare possibility of tumor cells spreading into the nearby area. If a general anesthetic is used, you will not feel pain during the procedure because you will be asleep. Your physician will explain the details of the procedure and the risks to you, depending on how the biopsy will be obtained.

Echocardiogram (ECHO):
ECHO is a noninvasive scan of the heart using sound waves. This test will be used to see how well your heart pumps blood. This test has no known risks or side effects.

Electrocardiogram (ECG):
An ECG is an electrical tracing of your heart's activity. During the procedure, you will have electrodes (small sticky patches) placed on your chest skin and wires attached to them. There may be some pulling on your skin or irritation, similar to pulling off an adhesive bandage, when the patches are removed.

There may also be side effects, other than listed above that we cannot predict. Other drugs will be given to make side effects that occur less serious and less uncomfortable. Many side effects go away shortly after the drug or procedure is stopped, but in some cases side effects can be serious, long lasting or permanent.
Note: *you will be given a drug interaction handout and wallet card as a resource for yourself, caregivers and other health care providers.*

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drugs are better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The 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.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

AZD9291 (osimertinib) and bevacizumab will be supplied at no charge while you take part in this study. The cost of getting the study drugs ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the AZD9291 (osimertinib) or bevacizumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsors and any drug company supporting the study (AstraZeneca and Genentech).
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

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.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* **at** _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ Institutional Review Board (a group of people who review the research to protect your rights) at _____*(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in. You will not get health benefits from any of these studies. 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 record and you and your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these 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 Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, any leftover tissue from your surgery or biopsy or any blood that was taken for the mandatory research studies on this trial will be saved for possible future studies. 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 the Yale Cancer Center and supported by the National Cancer Institute.

WHAT IS INVOLVED?

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

1) Any leftover tissue that was collected at the time of your surgery or biopsy and any leftover blood will be sent to the Biobank.
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 POSSIBLE RISKS?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) 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. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

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

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Yale Cancer Center staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Yale Cancer Center sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

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?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any

profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, Dr. Sarah Goldberg at 203-737-6980 who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, Dr. Sarah Goldberg at 203-737-6980.

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

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

I agree that my study doctor, or their representative, may contact me or my physician 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 Main 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 copy of this form. I agree to take part in this study.

Participant's signature _____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

Study Calendar

	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Disease Progression	Off Study
		Day 1	Day 8	Day 15	Day 1	Day 1	Day 1	Day 1	Day 1		
AZD9291 (osimertinib)[+]		X			X	X	X	X	X		
Bevacizumab[@]		X			X	X	X	X	X		
Office Visit with Physical Exam	X	X	X	X	X	X	X	X	X		X
Blood for safety laboratory tests	X	X	X	X	X	X	X	X	X		X
Electrocardiogram[#]	X				X	X		X			
Echocardiogram[%]	X							X			
CT chest/abdomen/pelvis and MRI brain[^]	X					X		X			X
Tumor biopsy[&]	X[i]									X[j]	
Blood samples for biomarkers[*]	X					X		X		X	
Eye Exam		At any time if patient experiences visual symptoms									

+ AZD9291 (osimertinib) tablets will be provided on Day 1 of each cycle for a 21-day supply.
@ Bevacizumab is only given to patients in Arm 1
# After cycle 5, electrocardiograms are obtained every other cycle (i.e. every 6 weeks) while study drug(s), or more frequently if needed.
% Echocardiogram is obtained every 3 months while on study drug(s).
^ CT chest/abdomen/pelvis and MRI brain is obtained every 6 weeks while on study therapy.
& Tumor tissue is required before starting study drug(s). It is not required at disease progression, but is requested if a biopsy is obtained for clinical purposes.
* Blood will be collected for research studies pre-treatment, every 6 weeks while on study drug(s), and at disease progression.