Informed Consent Form

Study Title for Study Participants: Testing cobimetinib given with atezolizumab immunotherapy in patients with advanced lung cancer that is resistant to immune-checkpoint immunotherapy

Official Study Title for Internet Search on http://www.clinicaltrials.gov: 10166 A Phase 2 Study of Atezolizumab and Cobimetinib in PD-1/PD-L1 Inhibitor Resistant or Refractory Non-Small Cell Lung Cancer (NCI Protocol #10166)

What is the usual approach to my lung cancer?

You are being asked to take part in this study because you have non-small cell lung cancer. You have already been treated with immunotherapy and your disease is now growing. People who are not in a study are usually treated with chemotherapy, though the specific options will depend on the type of lung cancer you have and the treatment you have already received.

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 chemotherapy
- 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 test any good and bad effects of the combination of study drugs called cobimetinib and atezolizumab. Cobimetinib and atezolizumab could shrink your cancer but it could also cause side effects. Researchers hope to learn if the study drug will shrink the cancer by at least 30% compared to its present size. Cobimetinib has already been FDA-approved to treat other cancers. Atezolizumab has already been FDA-approved to treat lung cancer but it is not known if it is effective after already receiving immunotherapy. There will be about 48 people taking part in this study.

What are the study groups?

All study participants will receive the same study drugs and doses. The first study drug, atezolizumab, is given by vein (IV) once every 4 weeks. The second study drug, cobimetinib, is taken daily by mouth as a tablet for 3 weeks followed by 1 week off; the 4-week cycle then repeats itself.

If you take part in this study, the Patient Study Drug Tablet diary will be provided. The diary provides instructions on how to take the cobimetinib tablets and a form to record when you have taken the tablets.

The first group of patients have lung cancer with a DNA change (a mutation) in a gene called KRAS. If there is at least one tumor response lasting six months or more, the study drugs will be tested in the next group of patients whose lung cancer does not have a KRAS mutation.

How long will I be in this study?

There is no set limit on the duration of treatment. You will receive atezolizumab and cobimetinib until the study doctor feels that your cancer is worsening, there is some illness or condition that would make it unsafe to continue on the study, you experience unacceptable side effects, or you decide to withdraw from the study. After you finish atezolizumab and cobimetinib, your doctor will continue to watch you for side effects and follow your condition for 90 additional days. This will initially be at an in-person clinic visit but future follow-up may be by phone.

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 tests and procedures that you will need to have if you take part in this study.

Before you begin the study:

- MUGA scan or echocardiogram
- Electrocardiogram
- Eye exam (every 2 months for 1 year, then every 6 months while on cobimetinib)
- Biopsy of tumor

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 tests. They are not part of the usual approach for your type of cancer.

During the study:

- You will be asked to maintain a Patient Study Drug Tablet diary of each dose of cobimetinib. The diary will be returned to clinic staff at the end *[or beginning]* of each cycle (every 28 days).
- Biopsy of tumor (week 4 of cycle 1)
- Blood will be collected for research. This will be in addition to blood collected for normal monitoring during therapy. This blood for research will be less than two tablespoons and will not be collected at every visit.

About Mandatory Biopsies
Small pieces of cancer tissue removed by surgery (biopsies) will be taken for the study before you begin study drug and again after the third week of treatment. These samples are required in order for you to take part in this study because the research on the samples is an important part of the study. The research biopsy is done in a similar way to biopsies done for diagnosis. The biopsy specimen will be studied to see if the new treatment changes the immune cells that are found within the tumor.

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.

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.
Neither you nor your health care plan/insurance carrier will be billed for the collection of the biopsy that will be used for this study.

There is an optional biopsy that can be done if your cancer shows signs of progression, or growth. This biopsy is not required but may provide important information about your cancer to the research study. If you decide not to have this optional biopsy, you may still participate in the study.

If there is extra tissue remaining from a biopsy done before one of your prior therapies and it is not needed for any other purpose, it may be collected for research purposes. This is not required for participation in the study. This is discussed in the section on optional studies."

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 drugs 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 drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and 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 Atezolizumab (MPDL3208A):

Risk Profile for Atezolizumab (MPDL3280A) (CAEPR Version 2.5, November 18, 2024)

COMMON, SOME MAY BE SERIOUS In 100 people receiving atezolizumab (MPDL3280A), more than 20 and up to 100 may have:
• Tiredness • Infection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving atezolizumab (MPDL3280A), from 4 to 20 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Difficulty swallowing • Fever • Flu-like symptoms including body aches • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • Loss of appetite • Pain in back • Cough, shortness of breath, stuffy nose • Itching, acne, rash Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting • Pain in belly • Pain or swelling of the joints • Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

RARE, AND SERIOUS In 100 people receiving atezolizumab (MPDL3280A), 3 or fewer may have:
• Bruising, bleeding Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Heart problems including inflammation and heart failure. Symptoms and signs of heart problems may include: shortness of breath, swelling of the ankle and body.

- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst
- Swelling and redness of the eye
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Damage to organs in the body when the body produces too many white cells
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck
- Abnormal movement of the facial muscles
- Swelling of the spinal cord
- Problem of the muscle (myositis, rhabdomyolysis), including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: blisters on the skin, including inside the mouth (can be severe), rash with blisters, skin rash developing 1-8 weeks after a drug is given, which may be accompanied by fever, lymph node swelling and organ failure.
- Swelling or tenderness of blood vessels

Possible Side Effects of Cobimetinib:

Risk Profile for Cobimetinib (CAEPR Version 2.2, Marc 25, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving cobimetinib (RO5514041, GDC0973), more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Swelling of the body • Rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cobimetinib (RO5514041, GDC0973), from 4 to 20 may have:
• Anemia which may require blood transfusion • Blurred vision or blindness, visual loss • Seeing flashing lights

- Seeing spots before eyes
- Sores in the mouth which may cause difficulty swallowing
- Chills, fever
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath swelling of the face or throat
- Change in heart function
- Loss of appetite, dehydration
- Dizziness, headache
- Dry skin
- Increased risk of sunburn
- Itching, acne
- Bleeding

RARE, AND SERIOUS

In 100 people receiving cobimetinib (RO5514041, GDC0973), 3 or fewer may have:

- Damage to organs (heart, lungs) which may cause shortness of breath, swelling of ankles, and tiredness
- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- Blood clot which may cause blurred vision or blindness
- Damage to muscle which may cause muscle pain, dark red urine
- A new cancer unrelated to an earlier cancer

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: You should not get pregnant, breastfeed, or father a baby while in this study and for 150 days after the last dose of study medication. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

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 staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom CTEP 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 possible benefits can I expect from taking part in this study?

This study has only a small chance of helping you but we do not know if the study drugs are effective. This study may help researchers learn things that may help other 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).*

What are the costs of taking part in this study?

The drugs atezolizumab and cobimetinib will be supplied at no charge while you take part in this study. The cost of getting the drugs ready and administering them to you will need to be paid by you and/or your insurance provider. It is possible that the atezolizumab and cobimetinib 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.

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 sponsor and any drug company supporting the study
- 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 this study?

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).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about an optional study that 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 records and you or your study doctor will not know the results.

You will not be billed for this optional study. 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 the following study.

Optional Sample Collection for Laboratory Studies

There is an optional biopsy which would be done if your cancer were to grow during this treatment. The research biopsy is done in a similar way to biopsies done for diagnosis. The biopsy specimen will be studied to understand why the cancer grew during treatment.

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.

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.

Optional Storage of Left-Over Samples for 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.

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.

WHAT IS INVOLVED?

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

1) **A new sample of tissue will be collected if your cancer were to grow during treatment.**
2) Extra tissue from a previous biopsy will be collected if you choose to take part in the biobanking study.

3) About 1 tablespoon of blood will be collected from a vein in your arm (at baseline, C2D1, and end of treatment)
4) Your sample and some related health information will be sent to a researcher for use in the study described above.
5) 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.
6) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. However, information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) 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.
2) 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. 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.
3) 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.
4) 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.

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.

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 staff with access to the list must sign an agreement to keep your identity confidential.

3) Researchers to whom CTEP 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.

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

OPTIONAL SAMPLES FOR FUTURE STUDIES:

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

I agree to have my tissue specimens collected if the cancer shows signs of growth and I agree that my specimen sample and related information may be used for the laboratory study described above.

YES NO

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 the main study and the additional study if I circled 'yes'.

Participant's signature:_____

Date of signature:_____

Signature of person(s) conducting the informed consent discussion:_____

Date of signature:_____