SUMMARY OF CHANGES

NCI Protocol #: 10217
Local Protocol #: NCI10217
Protocol Version Date: September 25, 2024
Protocol Title: A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and Durvalumab (MEDI4736) in Patients with Advanced Solid Tumors

Informed Consent Version Date: September 25, 2024

I. PI-initiated Changes:

#	Section	Comments
1.	**Throughout**	**PI Response:** The version date has been updated throughout the protocol. **Old Text:** May 13, 2024 **New Text:** September 25, 2024

II. CTEP-issued Request for Rapid Amendment (RRA)

#	Section	Comments
1.	**ICD Page numbers**	"Pg 30 of 29" Please correct all page numbers. **PI Response:** Page numbers were corrected.

Research Study Informed Consent Document

Study Title for Participants: Testing the combination of the anti-cancer drugs copanlisib, olaparib, and durvalumab (MEDI4736) in patients with advanced solid tumors with selected mutations.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: 10217, A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and Durvalumab (MEDI4736) in Patients with Advanced Solid Tumors (NCT#TBD)

Overview and Key Information

What am I being asked to do?

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

We are asking you to take part in this research study because you have an advanced solid tumor.

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:

Can we lower the chance of your advanced cancer growing or spreading by using a doublet combination of copanlisib and olaparib, or a triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736)?

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

What is the usual approach to my advanced solid tumor?

The usual approach for patients who are not in a study is treatment with surgery, radiation, or chemotherapy drugs which are FDA-approved. Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

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

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

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

If you decide to take part in this study, you will either get the study drugs copanlisib and olaparib in a doublet combination, or you will get the triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736), until your disease gets worse or the side effects become too severe.

After you finish the study treatment, your doctor will continue to follow your condition every 3 to 6 months via phone calls for up to 2 years, and will set up clinic visits as needed, in order to watch you for side effects and cancer progression.

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 you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

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

- Diarrhea
- Nausea
- Tiredness
- High blood pressure (which may cause headaches, dizziness, or blurred vision)

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

Benefits

There is some evidence in people with another cancer that individual treatment with either copanlisib, olaparib, or durvalumab (MEDI4736) can shrink or stabilize cancer, particularly if the cancer has a change in genes in the DNA Damage Response (DDR) pathway, or genes in the PI3K pathway, but we do not know if the doublet combination, or the triplet combination will have the same effect in people with your type of cancer. It is unlikely that the doublet combination, or the triplet combination will help you live longer. This study may help the study doctors learn things that may help other people in the future.

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

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

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

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

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

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

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (National Cancer Institute [NCI]). The study sponsor is the organization who oversees the study.

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

What is the purpose of this study?

The purpose of this study is to test the safety of the treatment with the copanlisib and olaparib doublet combination, and the copanlisib, olaparib and durvalumab (MEDI4736) triplet combination. This study tests different doses of each combination treatment to see which dose is safest for people and to better understand the side effects that may happen with each drug combination. There will be about 108 people taking part in this study.

Another purpose of this study is for the doctors to learn if and how your genes can influence how you respond to these specific drug combinations.

What are the study groups?

This study has a screening step. The purpose of this step is to test your tumor to find out if it has a specific change in DDR pathway genes, or in the *PIK3CA* or *PTEN* gene. If it does and you meet all the study requirements, then we can assign you to treatment based on these changes. If we find that your tumor does not have the genetic changes that are needed for this study, then your doctor will discuss other options for your care.

There are two parts in this study, a dose escalation part and a dose expansion part. Your doctor will tell you which part you are in.

In the dose escalation part of this study, different people will get different doses of the study drugs copanlisib and olaparib as a doublet combination or different doses of the drugs copanlisib and olaparib with a fixed dose of durvalumab (MEDI4736) as a triplet combination. Patients will be selected at random for either the doublet or triplet combination.

The first 6 people taking part in this study will get the lowest doses of the doublet combination of copanlisib and olaparib. If the drugs do not cause serious side effects, the next group of people in the study will get higher doses. If the copanlisib and olaparib doublet combination of drugs do not cause serious side effects, durvalumab (MEDI4736) will be added to form a triplet combination. The doses will continue to increase for every new group until people have serious side effects that require the dose to be lower. Once the dose for the study is found, the dose escalation is stopped.

In the dose expansion part of this study, the highest dose with manageable side effects of the doublet combination of copanlisib and olaparib will be given to 30 more people. Additionally, the highest dose with manageable side effects of the triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736) will be given to 30 more people. This will help study doctors better understand the side effects that may happen with each drug combination.

Treatment schedule: You will either get copanlisib through a vein in your arm three times in each cycle (on the first, eighth, and fifteenth day), or two times in each cycle (on the first and fifteenth day only). Your study doctor will tell you how often you will get copanlisib. You will get olaparib as a tablet twice a day, each day. You may also receive durvalumab (MEDI4736) through a vein in your arm on the first day of each cycle beginning in Cycle 2, in addition to copanlisib and olaparib. Each cycle lasts 28 days. See the study calendar for more information.

You will be able to get additional doses of the study drugs, as long as you are getting clinical benefit. This combination of drugs is not approved by the FDA for treatment of your disease.

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:

1. Blood counts done weekly during the first cycle of treatment.
2. Thyroid testing (as a blood test) done every third cycle from Day 1 of Cycle 1.
3. Physical exams done weekly during the first cycle.
4. An electrocardiogram (ECG) before you begin the study, within 1 hour of your first dose of study treatment on Day 1 of Cycle 1, again within a few hours after this dose, and at any time deemed necessary by your physician.
5. An echocardiogram (ECHO) before you begin the study and at any time deemed necessary by your physician.

This study will use genetic tests that may identify changes in the genes in your DNA. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer. Your previous testing results will be used to determine if you have a change in three specific genes: *DDR*, *PIK3CA*, or *PTEN*. If you have not undergone testing, a piece of tissue from your previous surgery will be used for the test. If a piece of tissue is not available from your previous surgery, we will perform a biopsy to obtain tissue. The study doctors do not know if changes in your genes will determine your response to treatment (with either the doublet or triplet combination)

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, then your study doctor may discuss your options with you. If the changes in your genes were inherited, the changes could also affect the health of your family members.

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:

- Researchers will study the result further to decide if it may be medically important to you or your relatives.

- 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.
- 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.
- You will require another genetic test to confirm the results. This test must be paid for at your own expense.
- 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.

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. DNA sequencing is the analysis of all or part of your DNA. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. 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.

Research Studies

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. Some of these procedures are mandatory for inclusion in the study, others are optional. For more details on these optional studies, see the section "Optional sample collections for known laboratory studies and/or storage for possible future studies," below.

You will need to have mandatory blood samples collected during this study.

For the dose escalation part of the doublet combination only, this will occur 8 to 11 times depending on the number of days you receive copanlisib treatment.

If you get copanlisib three times in each cycle (on the first, eighth, and fifteenth day), 11 blood samples will be taken:

- Cycle 1, Day 8
    - Before you receive copanlisib

    - 30 minutes after you receive copanlisib
    - 55 minutes after you receive copanlisib
    - 1 hours after you receive copanlisib
    - 3 hours after you receive copanlisib
    - 5 hours after you receive copanlisib
    - 7 hours after you receive copanlisib
    - 23 hours after you receive copanlisib
- Cycle 1, Day 15
    - Before you receive copanlisib
    - 30 minutes after you receive copanlisib
    - 55 minutes after you receive copanlisib

If you get copanlisib two times in each cycle (on the first and fifteenth day), 8 blood samples will be taken:

- Cycle 1, Day 15
    - Before you receive copanlisib
    - 30 minutes after you receive copanlisib
    - 55 minutes after you receive copanlisib
    - 1 hours after you receive copanlisib
    - 3 hours after you receive copanlisib
    - 5 hours after you receive copanlisib
    - 7 hours after you receive copanlisib
    - 23 hours after you receive copanlisib

For the dose escalation part of the triplet combination only, this will occur 17 times on six days during this study. Here is a list of when the blood samples will be taken:

1. Baseline
    1. Before you receive copanlisib
2. Cycle 1, Day 15
    1. Before you receive copanlisib
    2. 30 minutes after you receive copanlisib
    3. 55 minutes after you receive copanlisib
    4. 1 hours after you receive copanlisib
    5. 3 hours after you receive copanlisib
    6. 5 hours after you receive copanlisib
    7. 7 hours after you receive copanlisib
    8. 23 hours after you receive copanlisib
3. Cycle 2, Day 1
    1. Before you receive durvalumab
    2. 50 minutes after you receive durvalumab
4. Cycle 3, Day 1
    1. Before you receive durvalumab
    2. 50 minutes after you receive durvalumab
5. Cycle 4, Day 1

1. Before you receive durvalumab
2. 50 minutes after you receive durvalumab

6. Cycle 5, Day 1
    1. Before you receive durvalumab
    2. 50 minutes after you receive durvalumab

You will need to have several tumor biopsies: up to three tumor biopsies for the doublet combination, or up to four tumor biopsies for the triplet combination. Here is a list of when each tumor biopsy is planned, and whether it is mandatory or optional:

For the dose escalation part of the study:

- For the triplet combination, there will be up to four tumor biopsies throughout the study:
    - Biopsy before you begin study drugs (*i.e.*, pre-study) for inclusion into the study (mandatory)
    - Day 15 of cycle 1 (mandatory)
    - Day 15 of cycle 2 (optional)
    - End of treatment or at disease progression (optional)

For the dose expansion part of the study:

- For the doublet combination, there will be up to three tumor biopsies throughout the study:
    - Biopsy before you begin study drugs (*i.e.*, pre-study) for inclusion into the study (mandatory)
    - Day 15 of cycle 1 (mandatory)
    - End of treatment or at disease progression (optional)
- For the triplet combination, there will be up to four tumor biopsies throughout the study:
    - Biopsy before you begin study drugs (*i.e.*, pre-study) for inclusion into the study (mandatory)
    - Day 15 of cycle 1 (mandatory)
    - Day 15 of cycle 2 (optional)
    - End of treatment or at disease progression (optional)

The study biopsies take small pieces of cancer tissue from your body. These are like the biopsy you had that helped diagnose your cancer. Genetic material (DNA, RNA), along with protein and immune cells will be obtained from your tumor and blood samples. They will be used to evaluate changes in your DNA, RNA, and protein that may occur during treatment, and may indicate if you will or will not response to 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. If there is not enough tissue left over from your biopsy, your study doctor will need to do another biopsy to get this tissue. This tumor sample will be taken before you begin the study drugs.

You will not receive the results of this research testing. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsies at the hospital or clinic where the biopsies are done.
If there is any leftover specimen, it may be stored for biobanking and later use. This will be discussed in the section under "Optional studies."

A patient study calendar is attached at the end of this document. It shows how often these tumor biopsies and blood sample collections will be done.

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

General Risks

If you choose to take part in this study, there is a risk that the treatment with the copanlisib and olaparib doublet combination, or the copanlisib, olaparib, and durvalumab (MEDI4736) triplet combination may not be as good as the usual treatment for your cancer in 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 doublet combination of copanlisib and olaparib or the triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736) 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 6 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

As part of this study, we are also studying a genetic test. The test is designed to find out if your tumor has the genetic changes that are needed for this study. If it does, we will assign you to a study group based on the genetic changes in your tumor.

Because this genetic test is still being studied, there is a risk that the test results may be wrong. If the test results are wrong, you may be included in this study even though it may not offer the best treatment option for you. Or, you may not be included in this study even though it may offer a good treatment option for you.

Biopsy Risks
Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

If there is any leftover specimen, it may be stored for biobanking and later use. This will be discussed in the section under "Optional studies."

Blood Draw Risks

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

Side Effect Risks

The copanlisib and olaparib doublet combination, or the copanlisib, olaparib, and durvalumab (MEDI4736) triplet combination 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:

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

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

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

This study is looking at a doublet combination of copanlisib and olaparib, and the triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736). This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

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

Possible Side Effects of Copanlisib dihydrochloride

If you choose to take part in this study, there is a risk that the copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) 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 copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) 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.

Risk Profile for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CAEPR Version 2.3, April 2, 2023)

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

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving copanlisib dihydrochloride (BAY 80-6946 dihydrochloride), from 4 to 20 may have:
• Anemia which may require blood transfusion • Sores in the mouth which may cause difficulty swallowing • Nausea, vomiting • Fever • Bruising, bleeding • Loss of appetite • Pain • Damage to the lungs which may cause shortness of breath • Rash

RARE, AND SERIOUS In 100 people receiving copanlisib dihydrochloride (BAY 80-6946 dihydrochloride), 3 or fewer may have:
• Change in the heart rhythm • Swelling and redness of the skin • Itching

Possible Side Effects of Olaparib

If you choose to take part in this study, there is a risk that the olaparib (AZD2281) 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 olaparib (AZD2281) 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.

Risk Profile for Olaparib (AZD2281) (CAEPR Version 2.6, June 5, 2023)

COMMON, SOME MAY BE SERIOUS In 100 people receiving olaparib (AZD2281), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Pain • Diarrhea, nausea, vomiting • Tiredness • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving olaparib (AZD2281), from 4 to 20 may have:
• Bloating, constipation, heartburn • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Cold symptoms such as stuffy nose, sneezing, sore throat • Infection which may cause painful and frequent urination • Infection, especially when white blood cell count is low • Dizziness, headache • Changes in taste • Cough, shortness of breath • Rash

RARE, AND SERIOUS In 100 people receiving olaparib (AZD2281), 3 or fewer may have:
• Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Cancer of bone marrow caused by chemotherapy • Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require transfusions • Damage to lungs which may cause shortness of breath • Blood clot

Possible Side Effects of Durvalumab (MEDI4736)

If you choose to take part in this study, there is a risk that the durvalumab (MEDI4736) 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:

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

The durvalumab (MEDI4736) 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:

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:

5. If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
6. Your study doctor will work with you to treat your side effects.
7. 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.

Risk Profile for Durvalumab (MEDI4736) (CAEPR Version 2.5, February 29, 2024)

COMMON, SOME MAY BE SERIOUS In 100 people receiving durvalumab (MEDI4736), more than 20 and up to 100 may have:
• Cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving durvalumab (MEDI4736), from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain in the muscles, joints • Diarrhea, nausea, vomiting • Swelling of the body • Tiredness, fever • Infections. Infections can be severe and involve jaws and fatty tissues • Loss of appetite • Painful urination • Shortness of breath • Changes in voice • Increased sweating Durvalumab (MEDI4736) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems 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. • 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. • Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Skin: itching; rash, patches of light skin color

RARE, AND SERIOUS In 100 people receiving durvalumab (MEDI4736), 3 or fewer may have:

- Pain and swelling of thyroid
- Reaction during or following a drug infusion which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Durvalumab (MEDI4736) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems include but are not limited to:

- Damage to blood cells that may cause bruises and bleeding
- Blood clots in small blood vessels, which may cause kidney failure, fever, and confusion
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body or abnormal heartbeat
- A condition with high blood sugar (diabetes) which leads to tiredness, frequent urination or excessive thirst which may require treatment with insulin
- 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
- Damage to the pancreas which may cause belly pain and hospitalization
- Problem of the muscle (myositis), which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nervous system that can cause weakness and paralysis, which may include: numbness, tingling of hands and feet, and may also cause problems with breathing
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion
- 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
- Severe skin reactions with blisters and peeling which can involve mouth and other parts of the body

Additional Drug Risks

The study drug could interact with other drugs, including antibiotics such as clarithromycin, certain foods (such as grapefruit juice), or herbal preparations (such as St. John's wort). 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.

What are my responsibilities in this study?

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

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.
- Use two forms of contraceptive in combination if sexually active.

Reproductive Responsibilities:

1. **For women:** Do not get pregnant or breastfeed while taking part in this study. Do not breastfeed for at least 1 month after treatment with the study drugs.
2. **For men:** Do not father a baby while taking part in this study, or donate sperm for three (3) months following the last dose of your study drugs.
3. **For all:** If sexually active, you must agree to use TWO highly effective forms of contraception in combination. This should be started from the signing of the informed consent form and continue throughout the period of taking study treatment and for at least six (6) months after the last dose of study drugs, or you must totally and truly abstain from any form of sexual intercourse. Tell your study doctor right away if you think you or your partner have become pregnant during the study or within 6 months after your last dose of study drugs.

Acceptable Birth Control Methods:

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

This use of contraception must continue for the total duration of the trial and for at least 6 months after the 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.
- the cost of getting study drugs ready and administering them.

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:

- Research tumor biopsies.
- Research blood sampling.
- The biopsy for testing for genetic changes in *PIK3CA*, *PTEN*, or *DDR* genes at the beginning of the study.

You and/or your insurance provider will not have to pay for the study drugs copanlisib, olaparib, and durvalumab (MEDI4736) 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 drugs now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.

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

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

1. You will not be asked if you agree to take part in the specific future research studies using your health information.
2. You and your study doctor will not be told when or what type of research will be done.
3. You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases,

employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

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

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call (*insert name of organization or 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. ^

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 your cancer in the future. The results will not be added to your medical records and you will not know the results.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this optional study. 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 optional study for any reason, you can still take part in the main 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 your tumor tissue and blood for research on evaluating the changes in your DNA and RNA that occur during treatment. Researchers will obtain genetic material (DNA and RNA) from both your tumor cells and your blood. Your DNA and RNA will be used for genomic sequencing, which is sequencing of all or part of your DNA. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems. Researchers hope to find potential "biomarkers" (changes present in tumor tissue that predict how patients with your type of cancer may respond to current or future treatments). This optional study may improve the ability to select future treatments or treatment combinations for others in the future. This optional study will not affect the cancer treatment or approach that you receive.

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

Unknown future studies

If you choose to take part in this optional study, samples from your previous blood samples and tumor biopsies will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Nationwide Children's Hospital in Columbus, Ohio, and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

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

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

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional study?

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

- If you are enrolled in the dose escalation part of the study, a sample from the tissue that was collected at the time of your biopsy or surgery to remove your cancer will be sent to the biobank. Specifically, mandatory tissue biopsies will be collected at baseline and Cycle 1 Day 15, with an optional biopsy at disease progression (whichever comes first) for the doublet combination. For the triplet combination, tissue biopsies will be collected at baseline, Cycle 1 Day 15, with optional biopsies at Cycle 2 Day 15, and at disease progression. (whichever comes first).
- If you are enrolled in the dose expansion part of the study, a sample from the tissue that was collected at the time of your biopsy or surgery to remove your cancer will be sent to the biobank. For the doublet combination, mandatory tissue biopsies will be collected at baseline and Cycle 1 Day 15, with an optional biopsy collected at disease progression. For the triplet combination, mandatory biopsies will be collected at baseline and at Cycle 1 Day 15, with optional biopsies collected at Cycle 2 Day 15 and disease progression (whichever comes first).
- Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
- Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
- Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional study/storage collection?

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

2. Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
3. 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.
4. 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/
5. Because it may be possible to re-identify de-identified genomic data, even if access to data is controlled and data security standards are met, confidentiality cannot be guaranteed, and re-identified data could potentially be used to discriminate against or stigmatize participants, their families, or groups. In addition, there may be unknown risks.

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. Only your study doctor and a few study researchers will have access to the master list linking the code numbers to names. The biobank and the genomic sequencing laboratory will receive your samples with the following information only: your sample code number; your age, race/ethnicity, and gender; your type of cancer; any previous treatments you received for your cancer; and the treatment you will receive for this current study.
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. The researchers must be trained in the handling of private information. Any researcher who wants to study your stored samples and genetic information must apply and be approved to do so.
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 study/storage collection?

You will not benefit from taking part.

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

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

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

What if I have questions about this optional study/storage 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

Samples for unknown future studies:

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

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

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

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Study Calendars

Attachment 1: Copanlisib and Olaparib Doublet Combination

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				End of treatment or Disease Progression	Off Study Evaluation
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Copanlisb[A]		X	X[M]	X		X	X[M]	X		X	X[M]	X			
Olaparib[B]		X----------X													
Pre-study procedures including informed consent, demographics, and medical history	X														
Physical exam, vital signs, and general well-being[C]	X	X	X	X	X	X	X[M]	X		X		X		X	X
Blood draw to measure how well your thyroid gland is working [O]	X	X								X[O]					
Height	X														
Weight	X	X	X	X	X	X	X[M]	X		X		X			X
Blood draws for complete blood count and general health status[D]	X	X	X	X	X	X	X[M]	X		X		X		X	X
Urinalysis[E]	X														
Side effects evaluation		X----------X													
Medical imaging scans for tumor measurements[F]	X	Tumor measurements will be repeated every 8 weeks (after 2 cycles)													
Tumor markers[N]	X	X				X				X				X	
Pregnancy test[G]	X	X				X				X				X	X
Blood draw to test how well one's diabetes is controlled	X[J]	X[J]								X[J]				X[J]	X[J]
Electrocardiogram (ECG)[H]	X	X													
Echocardiogram (ECHO)	X														
Blood draw to study treatment assignment interactions[I]			X[M]	X											

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				End of treatment or Disease Progression	Off Study Evaluation
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Tumor biopsy and sample collections	X			X[K]				X[K]						X[L]	

A. Copanlisib will be given intravenously (IV) at the assigned dose 3 times (Days 1, 8, and 15) in each 28-day cycle, or 2 times (Days 1 and 15) in each 28-day cycle.

B. Olaparib will be taken at the assigned dose twice a day for each 28-day cycle.

C. Before treatment begins, and more frequently if clinically indicated.

D. Blood draws may be increased to every two weeks, depending on treatment assignment. Additional blood draws will occur if clinically indicated. Patients receiving warfarin will require additional assessments.

E. Urinalysis will be performed within 7 days of Day 1 of Cycle 1.

F. Medical imaging scans will be acquired at the end of Cycle 2 and at the end of every 2 cycles thereafter (e.g. Cycles 4, 6, 8, *etc*.). For patients on the study for more than 1 year, imaging scans will occur every 3 cycles.

G. Blood will be drawn, or urine requested, from women of childbearing potential to test for pregnancy. If your test is positive, you will stop receiving the study treatment immediately.

H. An electrocardiogram (ECG) will be performed pre-study, 1-hour before treatment begins on Cycle 1, Day 1, within a few hours after study treatment on Cycle 1, Day 1, and as clinically indicated.

I. Blood will be collected (only collected from patients who participate in the doublet escalation part of the study):
- At Cycle 1, Day 8: before copanlisib IV infusion, and ,30 minutes (post start), 55 minutes(5min pre-end infusion), 1 hours, 3 hours, 5 hours, 7 hours, and 23 hours after copanlisib IV infusion (only for participants who get copanlisib three times in each cycle)
- At Cycle 1, Day 15: before copanlisib IV infusion, and 55 minutes after copanlisib IV infusion.

J. HbA1c testing is required on Day 1 of every three cycles starting from Cycle 4 (4, 7, 10, *etc*.). It is also required at the end of treatment (EOT) visit [this testing is not required if the previous test was performed within 4 weeks preceding the EOT visit]. HbA1c testing is also required approximately 3 months after EOT visit.

K. If the Cycle 1 Day 15 Copanlisib dose is not given, this biopsy should be performed at Cycle 2 Day 15 (within 24 hours after Cycle 2 Day 15 copanlisib administration), otherwise no biopsy will occur at Cycle 2 Day 15.

L. This tumor biopsy is optional.

M. Only for participants who get copanlisib 3 times in each cycle.

N. If relevant to your cancer type, tumor markers will be collected periodically to track your response to the treatment taken.

O: Performed at pre-study, on Day 1 of Cycle 1, and every third cycle thereafter, beginning at Cycles 4, (*e.g.*, Cycles 7, 10, 13, *etc.*).

Attachment 2: Copanlisib, Olaparib, and Durvalumab (MEDI4736) Triplet Combination

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				End of treatment or Disease Progression	Off Study Evaluation
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Copanlisb[A]		X		X		X		X		X		X			
Olaparib[B]		X----------											X		
Durvalumab (MEDI4736)[C]						X				X					
Pre-study procedures including informed consent, demographics, and medical history	X														
Physical exam, vital signs, and general well-being[D]	X	X	X	X	X	X	X	X		X		X		X	X
Height	X														
Weight	X	X	X	X	X	X	X	X		X		X			X
Blood draws for complete blood count and general health status[E]	X	X	X	X	X	X	X	X		X		X		X	X
Urinalysis[F]	X														
Side effects evaluation		X----------											X		
Medical imaging scans for tumor measurements[G]		Tumor measurements will be repeated every 8 weeks (after every 2 cycles)													
Tumor markers[P]	X	X				X				X				X	
Pregnancy test[H]	X	X				X				X				X	X
Vital signs (before, during and after IV infusion)		X				X				X[I]					
Blood draw to test how well one's diabetes is controlled	X[M]	X[M]								X[M]				X[M]	X[M]
Electrocardiogram (ECG)[J]	X	X													
Echocardiogram (ECHO)	X														
Blood draw to measure how well your thyroid gland is working	X	X								X[I]					
Blood draw to check for bleeding disorders or a blood clotting disorder[K]	X														
Blood draw to study treatment assignment interactions[L]				X		X				X					

	Pre-Study	Cycle 1				Cycle 2				Cycle 3+				End of treatment or Disease Progression	Off Study Evaluation
		Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Tumor biopsy and sample collections[N,O]	X			X[N]				X[N,O]				X[N,O]		X[O]	

A. Copanlisib will be given intravenously (IV) at the assigned dose on Days 1 and 15 of each 28-day cycle.
B. Olaparib will be taken at the assigned dose twice a day for each 28-day cycle.
C. Durvalumab (MEDI4736) will be given IV at the assigned dose starting on Cycle 2 Day 1. The next dose will be given on Day 1 of every 28-day cycle. Durvalumab treatment will be given for a maximum of 24 months or until your disease worsens, whichever is earlier.
D. Before treatment begins, and more frequently if clinically indicated.
E. Blood draws may be increased to every two weeks, depending on treatment assignment. Additional blood draws will occur if clinically indicated. Patients receiving warfarin will require additional assessments.
F. Urinalysis will be performed within 7 days of Day 1 of Cycle 1.
G. Medical imaging scans will be acquired at the end of Cycle 2 and at the end of every 2 cycles thereafter (e.g., Cycles 4, 6, 8, etc.). For patients on the study for more than 1 year, imaging scans will occur every 3 cycles.
H. Blood will be drawn or urine requested from women of childbearing potential to test for pregnancy. If your test is positive, you will stop receiving the study treatment immediately.
I. Performed at pres-study, on Day 1 of Cycle 1, and every third cycle thereafter, beginning at Cycles 4, (*e.g.*, Cycles 7, 10, 13, *etc.*).
J. An electrocardiogram (ECG) will be performed pre-study, 1-hour before treatment begins on Cycle 1, Day 1, within a few hours after study treatment on Cycle 1, Day 1, and as clinically indicated.
K. Additional blood draws may occur if clinically indicated.
L. Blood will be collected (only collected from patients who participate in the triplet escalation part of the study):
   - At Cycle 1, Day 15: before copanlisib IV infusion, and,30 minutes (post start), 55 minutes (5min pre-end infusion), 1 hours, 3 hours, 5 hours, 7 hours, and 23 hours after copanlisib IV infusion.
   - At Cycle 2, Day 1: before durvalumab IV infusion, and 55 minutes after durvalumab IV infusion.
   - At Cycle 3, Day 1: before durvalumab IV infusion, and 55 minutes after durvalumab IV infusion.
   - At Cycle 4, Day 1: before durvalumab IV infusion, and 55 minutes after durvalumab IV infusion.
   - At Cycle 5, Day 1: before durvalumab IV infusion, and 55 minutes after durvalumab IV infusion.
M. HbA1c testing is required on Day 1 of every three cycles starting from Cycle 4 (4, 7, 10, *etc.*). It is also required at the end of treatment (EOT) visit [this testing is not required if the previous test was performed within 4 weeks preceding the EOT visit]. HbA1c testing is also required approximately 3 months after EOT visit.
N. If the Cycle 1 Day 15 Copanlisib dose is not given, this biopsy should be moved to the Cycle 2 Day 15 timepoint (within 24 hours after Cycle 2 Day 15 copanlisib administration). If this occurs, then the optional Cycle 2 Day 15 biopsy will be moved to the Cycle 3 Day 15 timepoint (within 24 hour after the Cycle 3 Day 15 copanlisib administration) otherwise no biopsy will occur on Cycle 3 Day 15.
O. The Cycle 2 Day 15 and disease progression biopsies are optional.
P. If relevant to your cancer type, tumor markers will be collected periodically to track your response to the treatment taken.