SUMMARY OF CHANGES

NCI Protocol #: 10221
Local Protocol #: NCI10221
Protocol Version Date: July 16, 2025

Protocol Title: A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Immune Checkpoint Inhibitors in patients with advanced solid tumors

Informed Consent Version Date: July 16, 2025

I. CTEP-issued Request for Rapid Amendment (Nivolumab):

#	Section	Comments
1.	**Throughout**	**PI Response:** The version date has been updated throughout the protocol. **Old Text:** October 24, 2024 **New Text:** July 16, 2025
2.	**Possible Side Effects of Nivolumab**	**PI Response:** The Nivolumab Risk Profile table was updated to version 2.6, May 14, 2025

II. Additional CTEP- requested changes:

3.	**How will information about me be kept private?**	Per the recent Executive Order regarding Defending Women (https://www.whitehouse.gov/presidential-actions/2025/01/defending-women-from-gender-ideology-extremism-and-restoring-biological-truth-to-the-federal-government/), DCTD/CTEP is making investigators aware of several changes that are being introduced to comply with this Order. CTEP is requiring that the term 'gender' in the protocol be amended so that 'gender' is replaced with the word 'sex'. **PI Response:** The changes were made as requested above.

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of an anti-cancer drug, copanlisib, to the usual immunotherapy (nivolumab) in patients with advanced solid cancers that have changes in the following genes: PIK3CA and PTEN (Trial 1).

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10221, "A Phase I/II Biomarker Driven Combination Trial of Copanlisib and Nivolumab in patients with advanced solid tumors," (Insert NCT)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. 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 cancer that has spread and for which there are no available, effective treatments; and your cancer may have a change in one of the following genes: PTEN (phosphatase and tensin homolog) or PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha).

Taking part in this study is your choice.

You can choose to take part or to not take part in this study. You can also 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 is 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 trial has 2 phases: Phase 1 and Phase 2. The Phase1 is being done to answer the following question: "How safe and tolerable is the study drug, Copanlisib, when given in Combination with Nivolumab in patients with advanced solid tumors.

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 advanced solid tumors.

Copanlisib and Nivolumab are FDA approved individually but this combination of drugs is not approved by the Food and Drug Administration (FDA) for the treatment of advanced solid tumors. This is the second time these drugs will be tested together in humans.

What is the usual approach to my advanced cancer?

The usual approach for patients who are not in a study is treatment with surgery, radiation, chemotherapy, targeted therapy or immunotherapy if approved by the FDA. Sometimes, combinations of these doses 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 get the study drugs, copanlisib and nivolumab over 24 months, until your disease gets worse or the side effects become too severe or you desire to discontinue the study.

Nivolumab will be given as an intravenous infusion over 60 minutes. Copanlisib will be given as an IV infusion over 60 minutes.

After you finish your study treatment, your doctor or research nurse will continue to follow you for at least 90 days to watch you for side effects. Your doctor or research nurse will also continue to follow your condition every 3 to 6 months by phone calls for 2 years and set up clinic visits as needed, in order to see how your cancer is doing (if it is getting better, worse or staying the same).

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer or may be greater than the side effects you would experience with each of the study drugs individually.

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

- The study drug copanlisib can increase your blood pressure. If this happens, your doctor may advise you to begin taking or increase the dose of your blood pressure medication.
- Your blood counts can decrease, increasing your risk of infections, bleeding and anemia.
- You can experience diarrhea which may become severe requiring you to be admitted to the hospital for treatment.
- You may feel sick to your stomach.
- You may experience tiredness.
- You may experience increased blood sugar.

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

Benefits

There is some evidence in animals that this treatment can shrink cancer, particularly if the cancer has a change in the PTEN gene or the PIK3CA gene, but we do not know if this will happen in people. It is unlikely that this combination of drugs 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 is 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 (the National Cancer Institute Cancer Therapy Evaluation Program). 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 do not 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 and tolerability (side effects) of the combination of copanlisib and nivolumab. In this study, this combination of drugs will be given to more people at the highest dose that was safe to use in people in the previous earlier study mentioned above. This study tests different doses of the drug copanlisib when combined with nivolumab to see which dose is safer and more tolerable for people. There will be approximately 45 people taking part in this study.

Another purpose of this study is for the study doctors to learn if having a change in the PTEN gene or PIK3CA gene is helpful to decide who will benefit from the study drug combination. You will be allowed to participate in this study only if your tumor has been tested for a change in these genes.

What are the study groups?

All of the participants in the study will receive copanlisib and nivolumab. The doses of copanlisib and nivolumab to be received by participants in this study, are being determined in another previous study as mentioned earlier (Study number: NCI 10145). 45 patients will be treated with copanlisib and nivolumab at those doses in this study.

Treatment schedule: You will get copanlisib through a vein in your arm on the first, eighth, and fifteenth day of each cycle. You will also receive nivolumab through a vein in your arm on the first day of each cycle beginning in Cycle 2, in addition to copanlisib. Each cycle lasts 28 days. This study has 24 cycles. 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.

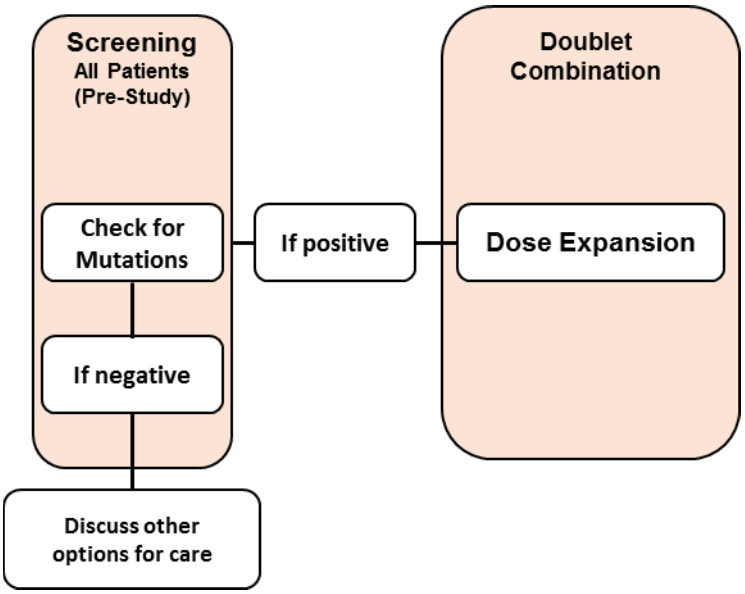
If the disease appears to be getting worse or the tumors appear to be getting larger, you may still be able to receive the study treatment if you and your doctor decide it is in your best interest. This is because sometimes the disease appears to get worse but the study treatment is actually working.

However, there are risks of continuing to receive the study treatment. For example, the disease may actually be getting worse and may reach the point that you are no longer able to receive

other treatments. You are still at risk for side effects due to the study treatment. This could also delay starting other treatments.

If you choose to receive the study treatment after the disease appears to get worse, you will continue to have study visits as described in this informed consent document.

Here is a schema of the different stages of the study:



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:

- Blood counts done weekly during the first cycle of treatment.
- Coagulation (blood clotting) tests done before you begin the study, on Day 1 of Cycle 1.
- Hepatitis B and C testing before you begin the study.
- Physical exams done weekly during the first cycle.
- Pregnancy test done before you begin the study.

- Diabetes and thyroid testing done before you begin the study, on Day 1 of every 3 cycles starting at Cycle 4 (e.g. C4, C7, C10 etc.) and at the end of treatment.
- 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.

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.

Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. 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:

1. Researchers will study the result further to decide if it may be medically important to you or your relatives.
2. The research laboratory that performed the genetic test will contact your doctor about the finding. The research laboratory, which will not have any identifying information about you, will provide your doctor with a code number assigned to your genetic test sample.
3. Your doctor will use the code number to identify you, and will then contact you about the medically important finding. Your doctor may try to contact you several times.
4. You will require another genetic test to confirm the results. This test must be paid for at your own expense.
5. If it is confirmed that there are changes found that could cause health problems, then your doctor will discuss your options with you. We strongly suggest that you also talk to a genetic counselor. Genetic counseling services must be paid for at your own expense.

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 analyzed. 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.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only:

- You will need to have 3 mandatory biopsies and one optional biopsy for the study. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. The first biopsy will be done before you begin the study drug. If a biopsy is not possible or cannot be done safely before you begin the study drug, then your study doctor, with your consent, will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer or had surgery to remove your tumor. If a tumor tissue sample cannot be obtained by biopsy or by using left over tissue, your study doctor will let you know if you are still able to participate in the study. Two biopsies will be performed during treatment (on day 15 of cycle 1, and on day 15 of cycle 2). A biopsy will also be performed, if possible, at the point where the cancer starts growing while receiving the study treatment. This biopsy after the cancer starts growing will be optional.

- Mandatory blood samples will also be taken for the study. The first blood sample will be collected before you begin the study drug. A blood sample will be taken weekly for the first three weeks on study, on the 15th day of cycle 2, on the 1st day of cycle 4 and then on the 1st day of every 3rd cycle thereafter. Blood samples will also be taken, if possible, at the point where the cancer starts growing while receiving the study treatment (disease progression).

- Female participants will be required to be screened for pregnancy before taking part of this study.

- Participants will receive an electrocardiogram before taking part in this study to make sure your heart is healthy enough to participate in this study.

Researchers will obtain genetic material (DNA and RNA) from your tumor tissue and blood samples. Your DNA and RNA will be analyzed to evaluate changes in your DNA and RNA that may occur during treatment. Levels of different proteins will be measured in your tumor and blood including the proteins involved in fighting cancer. Changes in different cancer fighting immune cells as a result of the treatment will also be determined. This information will be important to understand why the treatment you received worked or did not work to stop the growth of your cancer. Researchers hope to find potential "biomarkers" (changes present in tumor tissue or blood that predict if current or future treatments would stop your type of cancer from growing). You and your study doctor will not get any results of this testing. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done. A non-routine blood sample will be taken before the study begins to monitor the blood glucose related to the drugs being given. There is concern that

Copanlisib may pose additional risk to participants that may have diabetes as a preexisting condition. Copanlisib may cause an increase in blood sugar. Participants will be monitored for changes in their blood sugar levels to confirm that their diabetes does increase the risk for side effects associated with copanlisib treatment.

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.

Here is a list of when the blood samples will be taken:

Here is a table showing when each blood sample or tumor biopsy will occur:

Time	Sample	Mandatory or Optional?
Baseline	Tumor biopsy/Blood sample	Mandatory
Cycle 1, Day 8	Blood sample	Mandatory
Cycle 1, Day 15	Tumor Biopsy/Blood sample	Mandatory
Cycle 2, Day 15	Tumor biopsy/Blood sample	Mandatory
Cycle 4, Day 1	Blood sample	Mandatory
Every 3 cycles after C4D1 (e.g. C7D1, C10D1 etc.)	Blood sample	Mandatory
Cycle 24, Day 1 (or at disease progression)	Tumor biopsy	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 study drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

You also may have the following discomforts:

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

The drugs 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. It is very important for you to keep using effective birth control or pregnancy prevention methods for 7 months after the last dose of the study drugs if you are a woman, and for 5 months after the last dose of the study drugs if you are a man.

This study may need to use a sample of your tissue if a biopsy cannot be obtained before starting treatment. 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 if the combination of copanlisib with nivolumab works better on tumors with genetic changes in the PTEN or PIK3CA gene. Your tumor will be tested for genetic changes in PTEN gene and PIK3CA gene before you are allowed to take part in this study. We will assign you to a study group based on the genetic changes in your tumor. However, these genetic changes will not determine the type of treatment you receive.

In this study, your tumor will also be tested for other changes in your genes. Some of these 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.

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

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

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. Also include whether or not the results will be available to the study participant or study doctor. Neither you nor your health care plan/insurance carrier will be billed for the collection of the research tumor biopsies or research blood tests.

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”.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.

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

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

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

This study is looking at a new combination of a targeted therapy copanlisib with an immunotherapy drug, nivolumab. This new 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 may 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 and Nivolumab are listed in the tables below.

Possible Side Effects of Copanlisib

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 Nivolumab

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.

If you choose to take part in this study, there is a risk that the nivolumab 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 nivolumab 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 Nivolumab (CAEPR Version 2.6, May 14, 2025)

Special precautions Side effects of nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when nivolumab is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving nivolumab, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving nivolumab, from 4 to 20 may have:

- Anemia which may require blood transfusion
- Swelling and redness of the eye
- Pain
- Diarrhea, nausea
- Dry mouth
- Fever
- Swelling and redness at the site of the medication injection
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Bruising, bleeding
- Loss of appetite
- Pain or swelling of the joints

Nivolumab 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.
- 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.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: New or worsening cough, chest pain, shortness of breath.
- Skin: Itching; rash, blisters including inside the mouth; loss of skin pigment

RARE, AND SERIOUS
In 100 people receiving nivolumab, 3 or fewer may have:

- Swelling of arms and legs which may cause a feeling of heaviness and tightness
- Dry eye
- Sores in the mouth which may cause difficulty swallowing
- Swelling of the bowels
- Rejection of organ transplant
- Low grade skin tumor that is skin-colored or red which may cause itching

Nivolumab 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 swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss.
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage) and can lead to death. If you are considering an allogeneic stem cell transplant after participating in this study, please tell your doctor that you have received nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck, confusion, sleepiness, seizures or injury to the brain which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome).
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: Numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- 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.

Additional Drug Risks

The study drug could interact with other drugs such as antibiotics, herbal medication and anti-seizure medication. 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.

Other Risks

Your cancer will be monitored for response to treatment using CT scan which will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

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.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or after your last dose of study drug within 7 months if you are a woman and within 5 months if you are a man.

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.
- the costs of getting the study drugs (copanlisib and nivolumab) ready and giving it to you.
- your insurance co-pays and deductibles.

You and/or your insurance provider will have to pay for testing required to undergo blood glucose testing and monitoring, pregnancy testing, more frequent physical exams (as these relate to the investigational drug combination), and an electrocardiogram.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it does not 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:

- Blood tests to measure the effect of the study drugs on cells in your blood (blood will be collected at baseline, Cycle 1 Days 8 and 15, Cycle 2 Day 15, Cycle 4 Day 1, Day 1 of every 3 cycles thereafter (C7D1, C10D1 etc.), and Cycle 24 or disease progression (whichever comes first).
- Biopsies to measure the effect of the study drugs on your tumor and immune cells (biopsies will be performed at baseline, Cycle 1 Day 15, Cycle 2 Day 15, and Cycle 24 or disease progression (whichever comes first).

You or your insurance provider will not have to pay for the study drugs (copanlisib and nivolumab) 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 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 (the National Cancer Institute Cancer Therapy Evaluation Program [CTEP]).
- The 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.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research.

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we do not know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information. After the study is completed, the results will be made public by publishing in a cancer related journal and or presentation at a cancer related conference.

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, Dr. Timothy A. Yap, at 713-563-1784 or tyap@mdanderson.org.

For questions about your rights while in this study, call the The University of Texas MD Anderson Cancer Center Institutional Review Board at 713-792-2933.

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 these optional studies hope the results will help other people with you cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

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

Optional tissue and blood 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 biopsy and blood sample collection on progression of cancer, researchers will use the samples to evaluate 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. Researchers will also determine the levels of different proteins in your tumor and blood, including the proteins involved in fighting cancer. Changes in different cancer fighting immune cells as a result of the treatment will also be determined. This information will be important to understand why the treatment you received worked or did not work. Researchers hope to find potential "biomarkers" (changes present in tumor tissue or blood that predict if current or future treatments would stop the growth of your type of cancer).

This optional study may improve the ability to select future treatments or dosage 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 these tests will be done on your tissue or blood sample. 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, any of your tumor tissue or blood samples left over from planned research studies will be 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. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use. 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.

We do not know what research may be done in the future using your tumor tissue and blood samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.

- You will not get reports or other information about any research that is done using your samples.

What is involved in this optional sample collection?

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

1. Samples of tissue will be collected from one optional extra biopsy after the cancer progresses while receiving treatment on the study. For the biopsy procedure, the study doctor will use a needle to take pieces of your tumor. This process may be repeated several times in the same appointment in order to get enough tissue. Blood will also be collected from a vein in your arm. Up to 3 tablespoons of blood each will be collected at the end of treatment or on progression of cancer.
2. 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.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to 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.
- 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.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/
- 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 sex; 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 sample collection?

You will not benefit from taking part.

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

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance for exams, tests, and procedures done for research purposes only; these include the optional biopsy, and biobanking of your specimen(s). You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, Dr. Timothy A. Yap, at 713-563-1784, 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 returned 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 sample collection?

If you have questions about the use of your samples for research, contact the study doctor, Dr. Timothy A. Yap, at 713-563-1784.

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 studies described above.

YES NO

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to learn about results from these studies.

YES NO

Samples for unknown future studies:

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

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

Contact for Medically Important Genetic Test Results

I agree that my study doctor, or someone on the study team, may contact me and my doctor if the laboratory finds a possible genetic test result that may be important to the health of me and/or my family members.

YES NO

Before you join this study, you may wish to talk with family members to see if they would like to learn of any genetic test results that may be important to their health. You have the right to decide how to handle sharing this information with your family members. However, if you were to become unable to share this information with family members due to illness or injury, or if you were no longer alive, please select and sign one of the options below on releasing genetic information to family members. Only genetic test results that may be medically important to your family members would be released.

Select and sign ONE option from below:

(1) **You have my permission** to release my genetic test results to **any and all** family members involved, in the event that I am unable to or have not survived to grant permission myself.

Participant's signature

Date of signature

Witness's signature

Date of signature

(2) **You have my permission** to release my genetic test results or stored DNA **only** to the family members listed. Please write the name of the family member(s) in the space provided below.

Participant's signature

Date of signature

Witness's signature

(3) **You do NOT have my permission** to release my genetic test results or stored DNA to any family members. I request that this information be kept private.

Participant's signature

Date of signature

Witness's signature

This is the end of the section about optional studies.

My signature agreeing to take part in the study

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

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Study Calendar for Patients on Trial 1: Combination therapy with Copanlisib and Nivolumab

	Before Study	Cycle 1				Cycle 2				Cycle 3				Cycle 4 and Onwards				At disease progression
		D1	D8	D15	D21	D1	D8	D15	D21	D1	D8	D15	D21	D1	D8	D15	D21	
Copanlisib		A	A	A		A	A	A		A	A	A		A	A	A		
Nivolumab						B				B				B				
Doctor's visit[a]	X	X	X			X				X				X				X
Temperature, heart rate, blood pressure, breathing rate	X	X	X	X		X	X	X		X	X	X		X	X	X		X
Weight	X	X		X		X		X		X		X		X		X		X
Performance status	X	X	X	X		X	X	X		X	X	X		X	X	X		X
Routine blood tests[b]	X	X	X	X		X	X	X		X	X	X		X	X	X		X
Thyroid function tests[e]		X																
Coagulation tests		X																
Hepatitis B and C testing	X																	
Urinalysis		X																
EKG, creatine phosphokinase, troponin		X				X				X				X				
ECHO	X																	
CT scans (every 8 weeks)	X									X								X

Blood draw to test how well one's diabetes is controlled[e]	X[e]																
Blood for research[c]		X	X	X				X						X				X*
Research biopsy of tumor[d]	X			X				X										X*

A: Copanlisib: given through vein weekly for 3 weeks, then 1 week off.
B: Nivolumab: given though vein every 4 weeks (starting from cycle 2).
a: Doctor's visit for physical exam and management of side effects.
b: Routine blood tests to monitor blood cell counts, hemoglobin, electrolytes, blood sugar, kidney function and liver function.
c: Blood for research studies will be collected on the 1st, 8th and 15th day of cycle 1; 15th day of cycle 2; 1st day of cycle 4; and then on the 1st day of every 3rd cycle thereafter.
d: Tumor biopsy will be obtained before study, on the 15th day of cycle 1 and on the 15th day of cycle 2.
e: HbA1c and thyroid function testing is required on Day 1 of every 3 cycles starting in 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 required approximately 3 months after the EOT visit.
*: Tumor biopsy and blood sample collection will be optional at disease progression.