SUMMARY OF CHANGES -- CONSENT

NCI Protocol #:9984
Local Protocol #: 2000020461
Protocol Version Date: September 7, 2021

Protocol Title:
NCI# 9984: A randomized phase 2 study of cediranib in combination with olaparib versus olaparib alone in men with metastatic castration resistant prostate cancer.

Informed Consent Version Date: September 7, 2021

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with olaparib.

1) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.

I. CTEP Request for Rapid Amendment (RRA) dated August 27, 2021:

#	Section	Comments

1.	What possible risks	Updated "possible side effects for olaparib" table per RRA instructions:
		• Added New Risk:
		  • Occasional: Cold symptoms such as stuffy nose, sneezing, sore throat; Infection which may cause painful and frequent urination
		  • Rare: Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
		• Increase in Risk Attribution:
		  • Changed to Common from Occasional: Pain
		  • Changed to Occasional from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution (i.e. added to Risk Profile): Rash; Sores in the mouth which may cause difficulty swallowing
		• Decrease in Risk Attribution:
		  • Changed to Rare and Serious from Occasional: Bruising, bleeding

		• Changed to Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution from Occasional (i.e. removed from Risk Profile): Fever PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to olaparib is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

II. Additional Changes:

#	Section	Comments
2.	All	Updated Version Date in Header

THIS PAGE IS INTENTIONALLY LEFT BLANK

Study Title for Study Participants: Testing two oral drugs combination (cediranib and olaparib) compared to a single drug (olaparib) for men with advanced prostate cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

NCI# 9984: A Randomized Phase 2 Study of cediranib in Combination with olaparib versus olaparib alone in men with metastatic castration resistant prostate cancer.

What is the usual approach to my prostate cancer?

You are being asked to take part in this study because you have an advanced prostate cancer, which has recurred and grown after standard hormone therapy and additional standard therapy. People who are not in a study are usually treated with a continuous standard hormone therapy, called androgen deprivation therapy with either additional hormone therapy, chemotherapy, immunotherapy, radioisotope therapy or external radiation therapy. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

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

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

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

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using the combination of cediranib and olaparib to the use of olaparib by itself, for men with metastatic castration resistant prostate cancer.

Any of these different approaches could shrink your cancer but could also cause side effects. This study allows the researchers to learn whether giving the combination of cediranib and olaparib is better, the same, or worse than giving olaparib by itself by observing both the effect of these treatments on your cancer as well as any side effects that may be experienced.

The combination therapy of olaparib and cediranib has already been tested for safety in patients with other types of cancer. This therapy is not part of a standard approach for your cancer and is investigational. Olaparib by itself has also been tested for safety and efficacy in men with prostate cancer, but is not FDA-approved for prostate cancer. The activity of olaparib in men with prostate cancer who are not selected by a genetic test is unknown. Olaparib is FDA-approved for use in women with ovarian cancer selected by a genetic test.

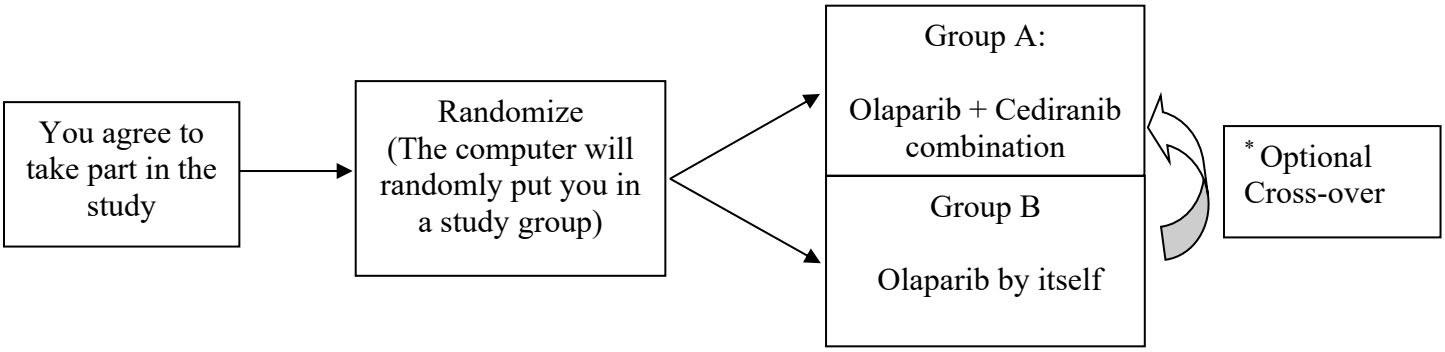
Another purpose of this study is for researchers to learn if a biomarker test is helpful to predict whether or not a patient's tumor will respond to the study drugs. A tumor biopsy tissue will be used for the biomarker test. An extra tube of blood will also be drawn for the biomarker test. Researchers do not know if using the biomarker test is better, the same, or worse than if you enrolled in this study without using the biomarker test.

There will be about 90 people taking part in this study.

What are the study groups?

This study has two study groups. Group A will receive the combination study drugs (olaparib and cediranib) and Group B will receive a single drug (olaparib). Olaparib will be taken by mouth twice a day. Cediranib will be taken by mouth once a day. You will receive a pill diary, which will give you the detailed instructions on how to take one or both study drugs. You must maintain the pill diary to record the time that you take the study drug(s) and must return the diary with the used pill bottles.

A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other. Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



*: the patients in Group B can choose to cross-over to Group A to receive the combination of cediranib and olaparib when your cancer gets worse.

Patients in groups A and B must continue with standard androgen deprivation therapy to maintain castrated level of testosterone. Patients in group A receiving cediranib and olaparib, will be given a blood pressure cuff and a symptom diary. Patients in group A must monitor and record blood pressure twice a day, and monitor symptoms and signs of diarrhea. The symptom diary form provides with specific instructions on how to manage these side effects and when to call your study team. Patient must bring this for the clinic visits.

How long will I be in this study?

You will receive the study drugs as long as you continue to benefit and your doctors thinks it is safe to keep you on therapy. After you finish this treatment, your doctor or the study team will be in contact with you via a phone call or review your medical record every 6 months to follow your survival status.

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

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

<u>Before you begin the study:</u>

You will need to have the following extra tests to find out if you can be in the study:

- Blood tests to make sure your thyroid is working properly.
- A urine study to check urine protein and creatinine levels. These levels will help monitor any damage to your kidneys.
- Echocardiogram to test your heart (if your doctor thinks necessary)
- Electrocardiogram to test your heart's rhythm

Your health care plan/insurance carrier will be billed for these tests that will be used for this study.

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

During the study:

- **Two research tumor biopsies:** the first biopsy will take place within 1 week before you starting the study drug(s) and the second biopsy will take place during the 4th week of the study drug. Both of these biopsies are mandatory for all participants.

  There are risks associated with mandatory research tumor biopsies. Risks include a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. If necessary, your doctor may ask you hold your study medications before and after the biopsy. You will sign a separate consent for any biopsy procedure.

- Research blood test (1 ½ teaspoon) along with the first research biopsy
- Research blood tests (1 ½ teaspoon) every 4 weeks

All of these research biopsies and blood tests are required in order for you to take part in this study because the research on these samples are an important part of the study.

If you are receiving the combination of cediranib and olaparib treatment, you will need the following extra tests and procedures.

- **Blood pressure monitoring:** You will be provided with a blood pressure monitor at no cost. You must check and record your blood pressures at least twice a day during the first 8 weeks of the therapy, or as otherwise instructed by your study doctor. This is explained in the "What are the study groups?" section and in the symptom diary, which will be provided to you at the start of the treatment.
- If your blood pressures are elevated persistently, you will need medications to lower blood pressures prescribed by your study doctor.
- Urine test every 4 weeks.
- Blood tests every 12 weeks to make sure your thyroid is working properly.

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

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- Olaparib, or the combination of olaparib and cediranib approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse

of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

- There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study. This could include learning about a hereditary mutation in the genes such as BRCA1 or BRCA2, which may convey a higher risk of developing certain types of cancer for you or your blood relatives. If new health information about inherited traits is found on research testing, your study doctor will let you know about this. You will then be able to choose whether or not to receive this information.

The study 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 be testing 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 points 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, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.
- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drug. This will include an information handout and a wallet card to carry with you that you may refer to or give any other medical providers as reference regarding medications or substances to avoid.
- The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drugs.
- Participants in group A will be given a symptom diary to monitor two most common side effects of cediranib, including elevated blood pressure and diarrhea. The diary provides with specific instructions on how to manage these side effects and when to call the study doctor.

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

Possible Side Effects of Cediranib

COMMON, SOME MAY BE SERIOUS In 100 people receiving cediranib (AZD2171), more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness • Loss of appetite • Changes in voice • High blood pressure which may cause headaches, dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving cediranib (AZD2171), from 4 to 20 may have:
• Pain • Constipation, vomiting • Dry mouth • Difficulty swallowing • Sores in the mouth • Infection • Bruising, bleeding • Weight loss • Dehydration • Muscle weakness • Dizziness, headache • Cough, shortness of breath, sore throat • Redness, pain or peeling of palms and soles • Blood clot which may cause swelling, pain, shortness of breath, confusion, or paralysis

RARE, AND SERIOUS In 100 people receiving cediranib (AZD2171), 3 or fewer may have:
• Anemia, kidney problems which may cause tiredness, bruising, swelling, or may require dialysis • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or hole in internal organs that may require surgery • Liver damage which may cause yellowing of eyes and skin, swelling • Non-healing surgical site • Damage to the brain which may cause changes in thinking • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Kidney damage which may require dialysis • Blood clot in artery which may cause swelling, pain, shortness of breath or change of color in extremity

Possible Side Effects of Olaparib

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 the lungs which may cause shortness of breath

Your study doctor will monitor your blood counts closely while you are on study treatment and may ask you to undergo additional tests including a bone marrow biopsy if they are concerned you are at risk for developing cancer of bone marrow.

Other effects that have been reported by other participants taking the combination of cediranib and olaparib, although it is not clear that they are related to taking both cediranib and olaparib, include muscle tear in the shoulder(s). This can cause pain and inability to lift your arm(s).

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

Reproductive risks: You should not father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. You must also agree to use adequate contraception and not to donate sperms prior to the study, for the duration of study participation, and for 3 months after completion of study drug administration. You should notify your health care team immediately if you think your partner has become pregnant for the duration of study participation, and for 3 months after completion of study drug.

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

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

Can I stop taking part in this study?

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

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

The study doctor may take you out of the study:

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

What are my rights in this study?

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

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

What are the costs of taking part in this study?

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

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

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

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

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

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

Who will see my medical information?

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

from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

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

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

Where can I get more information?

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

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

Who can answer my questions about this study?

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

ADDITIONAL STUDIES SECTION:

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

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

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

1. <u>Optional Sample Collection for Laboratory Studies</u>

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

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

If you choose to take part in the optional biopsy study, the study doctor for the main study would like to collect a tissue from a tumor biopsy when your disease progresses. The purpose of this biopsy is to understand how genes, and proteins in your tumor may have changed from before the beginning of the study treatment.

WHAT IS INVOLVED?

If you agree to take part in the Sample Collection for Laboratory Studies, here is what will happen next:

1) A sample of tissue will be collected from the optional extra biopsy. The biopsy will be performed within 4 weeks of the last dose of the study treatment or before you start the next treatment, whichever comes first.
2) Your sample and some related health information will be sent to a researcher for use in the study described above. The samples will be kept until they are used up.

WHAT ARE THE POSSIBLE RISKS?

1) For a biopsy, risks include a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

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

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

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

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

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

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

SAMPLE COLLECTION FOR LABORATORY STUDIES:

I agree to undergo a tumor biopsy to have my specimen collected and I agree that my specimen sample(s) and related information may be used for the laboratory study(ies) described above.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and 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_____