PATIENT INFORMATION AND CONSENT DOCUMENT

TITLE: A Phase 1 Evaluation of the Safety and Tolerability of Niraparib in Combination with Everolimus in Advanced Gynecologic Malignancies and Breast Cancer

PROTOCOL NO.: TNE001
WIRB® Protocol #20171364

SPONSOR: Avera Cancer Institute

INVESTIGATOR: Casey Williams, PharmD, BCOP
Avera Cancer Institute
1000 East 23rd Street
Sioux Falls, SD, 57105

PHONE NUMBER: 605-322-3211 (24-hours)

Summary

You are being invited to participate in a medical research study. This document gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study. You are being invited to volunteer since you may meet the requirements for enrollment into this study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled.

Please take time to review this information carefully. After you have finished, you should talk to the research team about the study and ask them any questions you have. You may also wish to talk with family, friends or family doctor about your participation in this study. If you decide to participate, you will be asked to sign this document. You will be given a signed copy of the consent document to take home and keep for your records. Before you sign this document, be sure you understand what the study is about, including the risks and possible benefits to you.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- The decision to join or not join the research study will not cause you penalty or loss of benefits to which you are otherwise entitled.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- After reading the consent and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.

- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

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.

What is the purpose of this research study?

You are invited to participate in this research study because you have been diagnosed with an advanced gynecologic malignancies or breast cancer. Your cancer has either grown back (relapsed) or has never gone away after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, and/or targeted therapy.

The purposes of this research study are:

- To determine if your tumor gets smaller after treatment with niraparib and everolimus
- To determine if specific molecular changes in the genetics of your tumor make you more likely to respond to the combination of niraparib and everolimus

Niraparib is a study drug that has been approved by the FDA for certain diagnoses. Niraparib belongs to a category of drugs called PARP inhibitors, which have the potential to selectively kill cancer cells by affecting the DNA repair mechanisms. Niraparib has been developed to address DNA repair defects, and has shown to be effective in previous studies.

Everolimus is an FDA approved anti-cancer therapy drug that is used to treat multiple types of cancer including breast cancer. Everolimus works by blocking signaling pathways that are important in the growth of cancer cells. Everolimus is currently not approved in gynecologic malignancies. Niraparib and everolimus have not been previously studied in combination and their combination is investigational.

Giving niraparib and everolimus together may be effective in treating some cancers. The dose-finding portion of this study has been completed and our investigators have found the highest tolerated dose combination.

How long will I be in the study?

You may stay on study as long as you are not having bad side effects and as long as your tumor is not getting worse. After you stop treatment, you will continue to be followed for up to five years.

How many other people will be in the study?

It is expected that up to 24 people will take part in this study at the Avera Cancer Institute.

What am I being asked to do?

Before any study procedures can be performed, you must sign this informed consent document. You will need to have the following exams, tests or procedures to find out if you are able to be enrolled into this study. Some of these exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study.

Screening Period
The following must take place within 28 days before entering the study:

- Medical history– a discussion of your past and present health issues, including a discussion of your cancer history and treatments, and any medications you have taken in the past 30 days and are taking currently
- Demographic information – collecting information regarding your date of birth, race, gender, and ethnicity
- Vital Signs – this includes your temperature, blood pressure, pulse, and oxygen saturation
- Blood tests – this will include routine laboratory tests in addition to a lipid panel, and a test that will examine your chromosomes to determine your risk for developing a blood disorder called myelodysplastic syndrome
- Serum (blood) pregnancy test (if applicable) – this will be done for females that are of childbearing potential, and will need to be performed less than 72 hours prior to the first dose of study drug.
- Tumor assessment – either a Computerized Tomography (CT) scan or Magnetic Resonance Imaging (MRI). If you have already had a tumor assessment within 28 days then you will not need to repeat this.

During the Treatment Phase
If the exams, tests and procedures show that you can be in the study, you will return to your study doctor's office for the following exams, tests, and procedures at the following time-points during the time you are receiving treatment:

Day 1 of each cycle (each cycle is 28 days):

- Physical exam including vital signs
- ECOG status – an evaluation of how well you perform normal daily activities
- Review any medications you are taking
- Review medication diary – you will be asked to keep a medication diary for the niraparib and everolimus and review this with the study staff at each visit
- Monitoring of any side effects – each time you speak with the study staff you should let them know about any side effects you are having and/or health issues you have had since the last visit
- Routine laboratory tests
- Completion of questionnaires about symptoms you may be experiencing as well as your quality of life

Days 8, 15, and 22 of cycle 1 only (each cycle is 28 days):

- Physical exam including vital signs

- Monitoring of any side effects – each time you speak with the study staff you should let them know about any side effects you are having and/or health issues you have had since the last visit
- Routine laboratory tests

Treatment Plan
Investigators have found the highest tolerated dose of everolimus and niraparib that can be given together without bad side effects.

You will take everolimus 5mg by mouth on Mondays, Wednesdays, and Fridays. You will take niraparib 100mg by mouth every day.

Study Day	1	2	3	4	5	6-28
Everolimus 5mg	X		X		X	Continue on MWF
Niraparib 100mg	X	X	X	X	X	X

The treatment will be given in cycles where each cycle lasts 28 days.

End of Treatment
After you stop treatment with everolimus and niraparib, you will have the following tests performed:

- Blood tests – this will include a lipid panel and a whole blood sample that may be used to determine risk for developing myelodysplastic syndrome.
- Monitoring of any adverse events that you are experiencing
- Completion of questionnaires about symptoms you may be experiencing as well as your quality of life

Post-Study Assessments
The following assessments will also take place after you stop the study:

- Monitoring of any adverse events that you are experiencing for 30 days following the last dose of drug
- Survival assessment will occur every 8 weeks for at least 5 years. This can usually occur by gathering information from your medical chart but it may be necessary for a person involved in this research study to contact you.

What are the possible risks or discomforts?

As with all research studies, the study treatment and study procedures may involve unknown risks. Any medication can have temporary or permanent side effects that may or may not be expected.

A phase I study looks at how common and serious side effects can be for each patient. In a phase I study, some patients could have very serious side effects and could die as a result of these side effects.

Everyone taking part in this study will be watched very carefully for any side effects, however providers don't know all the side effects that may happen. Side effects may be mild or very

serious. Side effects may go away soon after you stop taking everolimus and niraparib, but it is always possible that some side effects will be long lasting or may never go away. Patients are watched carefully and treatment will be stopped if bad side effects develop. Known potential side effects for each drug are listed below:

Everolimus

The most common side effects (greater than 10% occurrence) noted in previous studies:

- Peripheral edema (swelling in legs, feet, hands)
- High blood pressure
- Fatigue
- Headache
- Rash
- Increased cholesterol and triglycerides
- Increased blood sugar
- Diarrhea
- Mouth sores
- Taste changes and/or loss of appetite
- Low hemoglobin
- Low platelet count
- Low white blood cell count
- Liver function test abnormalities that could indicate liver damage
- Cough
- Pneumonitis (inflammation of the lining of the lungs)
- Increased risk of many types of infections

1-10% occurrence:

- Poor wound healing
- Chest pain
- Rapid heart rate
- Heart failure
- Blood clots
- Numbness and/or tingling in fingers and/or toes
- Hair loss
- Muscle spasm
- Renal function test abnormalities that could indicate renal damage

Less than 1% occurrence:

- Increased risk of opportunistic infections
- Risk of angioedema with concomitant use of ACE inhibitors
- Kidney failure that could lead to death
- Hepatitis B reactivation

Niraparib

Niraparib has been studied in more than 1902 patients in TESARO clinical trials. Niraparib capsule is marketed as ZEJULA® and is approved to treat adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in the United States and in Europe. Niraparib is currently being studied as a single medication and as a combination therapy within a variety of cancer clinical studies.

Niraparib single drug therapy has resulted in the following side effects

Very Common (greater than 10% occurrence):

- Low platelet count (helps blood to clot)
- Low hemoglobin (red blood cells) that causes anemia
- Low white blood cell count (helps fight infection)
- Low neutrophil count (another type of white blood cell that helps fight infection)
- High blood pressure
- Heart palpitations
- Painful and frequent urination (urinary tract infection)
- Shortness of breath
- Runny or stuffy nose
- Cough
- Headache
- Dizziness
- Weakness
- Fatigue
- Insomnia
- Joint pain
- Back pain
- Stomach pain (abdominal pain)
- Indigestion
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Decreased appetite

Common (less than or equal to 10% occurrence):

- Infection from low white blood cell counts
- Bronchitis (inflammation of the lining of the bronchial tubes in your lungs)
- Fast heart beat (tachycardia)
- Swelling of lower legs and feet (peripheral edema)
- Muscle pain
- Rash
- Weight loss
- Depression

- Feelings of worry, nervousness or unease (anxiety)
- Inflammation of the eye (conjunctivitis)
- Nose bleeds
- Sore, red mouth (stomatitis)
- Swelling or irritation of the lining of the mouth, throat, esophagus, stomach or intestines (Mucosal inflammation)
- Altered sense of taste
- Dry mouth
- Increased sensitivity of the skin to sunlight
- Decrease in potassium in the blood (hypokalaemia)
- Kidney function test abnormalities (blood creatinine increase), that could indicate kidney damage
- Liver function test abnormalities that could indicate liver damage (aspartate aminotransferase [AST] increased, alanine aminotransferase [ALT] increased, gamma-glutamyl transferase [GGT] increased)
- Other abnormal labs (alkaline phosphatase [ALP] increased)

Uncommon Occurrence (less than or equal to 1% occurrence)
- Fever with low white blood cell count (febrile neutropenia)
- Decrease in number of all types of blood cells (pancytopenia)

Rare Occurrence (less than or equal to 0.1% occurrence):
- Severe life-threatening infection due to low white cell counts (associated with low blood pressure and possible organ failure (for example, heart, kidney and/or liver) (neutropenic sepsis)
- Severe increase in blood pressure (hypertensive crisis)
- A brain condition with symptoms including seizures, headache, confusion, and changes in vision (posterior reversible encephalopathy syndrome [PRES])

In addition to the above, the side effects below were reported by patients who were prescribed niraparib by their doctors:
- Allergic reaction (hypersensitivity, including anaphylaxis)
    - Life-threatening allergic reaction (such as difficulty breathing, rash, localised swelling, such as tongue, throat or lips) (anaphylaxis)
- Confusion (confusional state)
- Disorientation
- Seeing or hearing things that are not really there (hallucination)
- Impaired concentration, understanding, memory and thinking (cognitive impairment)
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing (non-infectious pneumonitis)

<u>Side Effects Requiring Immediate Medical Attention:</u>
The side effects listed below require **<u>IMMEDIATE MEDICAL ATTENTION OR ADVICE</u>**.
Call the study doctor right away if you have any of these side effects:
- Allergic reactions can be life-threatening. Symptoms may include difficulty breathing, shortness of breath, low blood pressure (feeling lightheaded, dizziness), tingling around the mouth, rash.

- Low platelet counts may increase your risk of bleeding and bruising. Bleeding may require urgent medical attention, including a transfusion (receiving blood or blood products by vein).
- Low red blood cell counts may make you feel tired or short of breath and symptoms may require a blood transfusion.
- Low neutrophil counts may be associated with infection, sometimes severe and life-threatening.
    - Symptoms of severe life-threatening infection may include:
        - Fever, feeling of low blood pressure (lightheadedness, dizziness), decreased urination, rapid pulse, rapid breathing or shortness of breath
- High blood pressure (hypertension) including severe increase in blood pressure (hypertensive crisis) has been reported with the use of niraparib. If you have pre-existing hypertension, the physician will determine if your blood pressure is adequately controlled before starting niraparib treatment.
    - Symptoms of a severe increase in blood pressure may include:
        - Blurry vision, headache, nausea, vomiting, confusion, passing out, seizures, weakness or numbness on one side of body or in one arm or leg and/or difficulty talking (symptoms of a stroke), trouble breathing, chest pain, pain in the upper or lower back, urine that is brown or bloody
- A rare neurological side effect named Posterior Reversible Encephalopathy Syndrome (PRES) has been associated with treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

A very rare (less than 1%) but serious side effect that may occur with niraparib is the development of a blood disorder called myelodysplastic syndrome (MDS), which typically progresses to a blood cancer called acute myeloid leukemia (AML). It is not clear from previous studies whether niraparib increases the risk for developing MDS/AML or whether other risk factors are the main cause. As a result of this potential risk, additional safety precautions and monitoring have been added to this study.

Secondary Primary Malignancy:
PARP inhibitors may also cause a new primary cancer (that is, a cancer other than the one for which you have been treated). In 2 studies comparing niraparib to placebo, the likelihood of getting a new primary cancer in patients who took niraparib was similar to those in patients who took placebo.

Reproductive risks:
You cannot participate in this study, if you are pregnant, planning to become pregnant, or are breastfeeding. Due to the effect of this drug, there could be serious harm to unborn children (or children who are breast-feeding) and it could also jeopardize the health of the mother. In addition, it is possible that harmful side effects that are not yet known could occur to both the mother and unborn or breast-feeding child. The risks to an unborn child or a nursing child from the study drug are not known.

Females:
Due to the unknown effects of this study's drug(s) on an unborn child, you understand that it is very important that you do not become pregnant during this study. Avoiding sexual activity (total abstinence) is the only certain method to prevent pregnancy. However, if you do choose to

be sexually active, you must agree to use acceptable method(s) of pregnancy prevention while in this research study and for at least 30 days after receiving study drug. Please discuss with your doctor the most appropriate method(s) of preventing pregnancy for you that also respects your cultural and religious values and traditions. If you do become pregnant, notify the study doctor and/or study staff immediately. You will be asked to withdraw from the study. The Study Doctor is required to follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished.

You must not breast-feed an infant (or store breastmilk for use) during the study and for 30 days after receiving final dose of study drug.

Males:
Due to the unknown effects of this study's drugs on a human unborn child, you understand the risk of birth defects if your partner becomes pregnant during this study. Avoiding sexual activity (total abstinence) is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use acceptable method(s) of pregnancy prevention while in this research study and for at least 90 days after receiving study drug. Please discuss with your doctor the most appropriate method(s) of preventing pregnancy for you that also respects your cultural and religious values and traditions. Inform your study doctor if you think for any reason that your partner might be pregnant.

If you agree to participate in this study, you are expected to inform your female sexual partner(s) that you are participating in a clinical research study of an investigational drug, and that the effects of the drug on sperm, an unborn baby and on a pregnant woman are unknown. If your female partner becomes pregnant while you are participating in this study or within 90 days after your last dose of Study Drug, tell your Study Doctor or study nurse right away as the Study Doctor is required to follow up and document the course and the outcome of all pregnancies. The Study Doctor may seek the pregnant woman's permission to review her medical records and the infant's medical records up to delivery, if applicable. The Study Doctor will share the information about your pregnant partner and the baby with the Sponsor to help understand the effects, if any, that the Study Drug may have on the pregnancy and maybe the child.

You must not donate sperm for 90 days after your last dose of Study Drug.

Fertility Preservation:
If you may wish to become pregnant or father a child in the future, please discuss fertility preservation options with your doctor before you begin participating in this study.

What are the possible benefits of the study?

There may or may not be direct medical benefit to you. The information learned from this study may or not benefit patients in the future.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What other choices do I have if I do not participate?

Instead of being in this study you may have the following options:

- Treatment with chemotherapy medicines
- If you have breast cancer, depending on your previous treatment, you could receive everolimus plus exemestane without being in the study.
- If you have advanced gynecologic malignancies cancer, depending on your disease status, you may be able to receive niraparib or olaparib without being in the study.
- Treatment with other experimental agents that may be available
- No further therapy, with a focus on care that will make you more comfortable

Your provider will discuss alternative options with you.

Will I be paid for being in this study?

You will not be paid for being in this research study.

Will I have to pay for anything?

You and/or your health insurance company will be responsible for the cost of treatments and procedures that would be done whether or not you took part in this study. This includes the drug everolimus. It is important to understand that some insurance companies do not cover some costs (for example approved drugs used in a way different from the package instructions). If your insurance company does not cover these treatments or procedures, you will be required to pay for them.

The study drug, Niraparib, will be provided by Tesaro, the company that makes this drug. Tesaro is now owned by GlaxoSmithKline, LLC (GSK). They will provide the Niraparib at no cost to you.

Ask the study staff if you have any questions about bills, fees or other costs related to this study.

What happens if I am injured or hurt during the study?

If you have a medical emergency during the study you should go to the nearest emergency room. You may contact the study doctor or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the Avera. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the Avera Cancer Institute. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise available from the Avera Cancer Institute. If you have an illness or injury during this research trial that is <u>not</u> directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury.

When is the Study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The study doctor feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study doctor, or the Food and Drug Administration (FDA) has decided to stop the study.

You may choose to participate or not participate in this research study. You are not waiving any legal rights by agreeing to participate or participating in this study. If you decide to take part in this research study, you may remove yourself from the study at any time. No matter what decision you make about participating or stopping your participation, there will be no penalty to you and you will not lose any of your regular benefits to which you are otherwise entitled. Withdrawal will not interfere with your future care. If you no longer wish to participate, you must let us know in writing by sending a letter to:

Dr. Casey Williams
Avera Cancer Institute
1000 East 23rd Street
Sioux Falls, SD 57105

Confidentiality of Study Records and Medical Records.

Information collected for this study is confidential. However, the sponsor company, Tesaro/GSK, and the Food and Drug Administration (FDA) of the U.S. Government will receive copies of the study records. Employees of Tesaro/GSK, the FDA, and the Institutional Review Board may see parts of your medical records related to this study. Data collected and entered into the Case Report Forms are the property of Tesaro/GSK. In the event of any publication regarding this study, your identity will not be disclosed.

Who can see or use my information? How will my personal information be protected?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care.

Information about you may include information about your health and your medical care before, during, and after the study, even if that information wasn't collected as part of this research study. For example:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- All records relating to your cancer, the treatment you have received, and your response to the treatment

- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- Tesaro/GSK, the Food and Drug Administration [FDA], and other government officials may need the information to make sure that the study is done properly.
- Organizations that are funding the study may need the information to make sure that the study is done properly.
- Safety monitors or committees may need the information to make sure that the study is safe.
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.

Your health information and any research data derived from it will be stored for a minimum of ten years, at which time the need to retain it will be reviewed.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help regulatory and government officials make sure that the study was conducted properly

When does my permission expire*?*

Your permission will not expire unless you cancel it. You may cancel your permission at any time by writing to the study staff listed on the first page of this document.

Who can I call about my rights as a research subject?

If you have questions regarding your rights as a research subject, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

(An Institutional Review Board [IRB] is a committee established to review and approve research involving human subjects. The purpose of the IRB is to ensure that all human subject research be conducted in accordance with all federal, institutional, and ethical guidelines.)

- You may also call this number to discuss or report any problems, questions, complaints, or concerns you have about this research study.
- WIRB will not be able to answer some study-specific questions, such as questions about appointment times. You may also call this number if you cannot reach research staff, or you wish to talk with someone who is independent of the research team.

Consent

When you sign this document, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. If you have additional questions, concerns or complaints about taking part in this study or research-related injury, you may contact Dr. Casey Williams at 605-322-3211 (24-hours).

You understand taking part in this research study is voluntary. You may quit the study at any time without harming future medical care or losing any benefits to which you might otherwise be entitled.

I have read and understand the above information. I agree to take part in this study. I will be given a copy of this document for my own records.

Name of Subject (Please Print)	Signature of Subject	Date
Name of Person Obtaining Consent (Please Print)	Signature of Person Obtaining Consent	Date