INSTITUTE: National Cancer Institute

STUDY NUMBER: 18-C-0034 PRINCIPAL INVESTIGATOR: Alexandra Zimmer, MD

STUDY TITLE: A Phase 2 Study of ONC201 in recurrent/refractory metastatic breast cancer and advanced endometrial carcinoma

Continuing Review Approved by the IRB on 11/19/18

Amendment Approved by the IRB on 09/20/18 (C) Date posted to web: 12/01/18

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

You are taking part in the Phase II study of an investigational drug called ONC201. The main purpose of this study is to see if ONC201 will help to shrink tumors in people with certain types of breast or endometrial cancers. This study also looks at how long the tumors respond to the

treatment. ONC201 is manufactured by Oncoceutics, Inc and is not approved by the United States (U.S.) Food and Drug Administration (FDA) to treat any type of breast, or endometrial cancer, or any other type of disease. The exact mechanism of ONC201 is unknown at this time, but we suspect that it works through interrupting activity of the mitochondria (the "powerhouse" of the cell). Mitochondria are important for metabolism of all cells but cancer cells rely more heavily on mitochondria for their function than normal cells. The researchers in this study hope that by blocking the mitochondrial activity it will cause tumor cells to die, thereby shrinking tumors.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have:

- Metastatic estrogen receptor positive breast cancer OR
- Metastatic triple negative breast cancer OR
- Advanced or metastatic endometrial cancer

How many people will take part in this study?

Up to 90 people will take part in this study.

Description of Research Study

What will happen if you take part in this research study?

Before you begin the study

Certain standards (criteria) have been established to ensure that you are a medically appropriate candidate for this trial. These criteria also make sure that the results of this study can be used to help make decisions about treating other patients.

Before you begin this study, you will need to have the following exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care.

- A review of any past or current medical conditions, medicines you are taking and cancer history.
- Physical examination, including height, weight, vital signs
- Electrocardiogram (EKG – a record of your heartbeat)
- Review of your symptoms and your ability to perform your normal activities.

- Imaging Assessments – a computed tomographic scan (CT) that produces a picture of your body using a small amount of radiation and magnetic resonance imaging (MRI) that uses a magnetic field to produce an image of your body. These will be used to examine your chest, abdomen, pelvis, bones and brain.
- You will have blood drawn for:
  - routine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, and other organs are working well.
  - Tests for HIV, Hepatitis B and Hepatitis C.
- If you have not been tested for BRAC ½ mutations (for breast cancer) or for Lynch Syndrome (for endometrial cancer), a small amount of blood will be collected for genetic analysis. If you have been previously tested for these mutations, you will not need to have blood drawn for this as long as you can show the researchers the test results.
- Pregnancy serum or urine test if you are a woman who can have children.
- You will be asked to provide a pathologist's report from an accredited laboratory or sample of your tumor from a previous surgery so that we may confirm your diagnosis.

If you are eligible to participate in this trial and wish to do so, an image-guided biopsy of your tumor will be required for research purposes before you start treatment. To help researchers determine the way ONC201 works on tumor cells, an additional image-guided biopsy will be required after you have had 5 weekly doses of ONC201. If/when your tumor no longer responds to the treatment and it starts to grow, you can decide if you would like to undergo an additional image-guided biopsy so that researchers can study what made the tumors stop responding to ONC201.

Blood donation

Patients should not donate blood while participating in this study, nor for 90 days following the last dose of ONC201.

During the study

During the study, the study doctor and staff will monitor you for any side effects and monitor your cancer. You may receive supportive care to manage side effects during this study. Ask the study doctor or staff if you have questions about supportive care. Each cycle is 28 days long. You will take ONC201 weekly for a total of 4 doses of ONC201 during 1 cycle. During Cycle 1, you will receive weekly phone calls to ask about whether there have been any changes to your health and about any other medications that you may be taking.

Day 1

On Day 1, the study staff will perform a complete physical exam. They will ask if there have been any changes to your physical health and about any medications you have taken since your screening visit. They will check your vital signs and may do some routine laboratory tests. Laboratory tests that were completed within the last 4 days before Cycle 1 Day 1, will not be repeated. Blood will also be drawn for research tests to assess certain cancer markers (about 2 tablespoons). A CT scan of the chest, abdomen, and pelvis will not be repeated if you had one done within 17 days prior to the start of Cycle 1 Day 1. After signing this consent form, a CT-assisted biopsy of your tumor will be performed for research purposes before you start treatment with ONC201.

ONC201 Therapy

You will receive the study drug ONC201 by mouth every 7 days of each 28-day cycle.

You will take this study drug by mouth every 7 days while you are on trial.

Day 28

On Day 28, the first treatment cycle will end. You will be asked about whether there have been any changes to your health and about any other medications you have taken. You will have a complete physical exam and have about 3 tablespoons of blood drawn for routine laboratory tests.

Cycle 2 and beyond

Some tests will be performed every cycle, some will be performed every other cycle, some will be performed every three cycles, and some will be completed in the first cycle only. You will undergo blood draws at the start of each cycle and you will have imaging studies to evaluate the effect ONC201 has on your cancer every 2 cycles (every 8 weeks). To help researchers determine the way ONC201 works on tumor cells, an additional image-guided biopsy will be performed on Cycle 2 Day 2. If/when your tumor no longer responds to the treatment and it starts to grow, you can decide if you would like to undergo an additional image-guided biopsy so that researchers can study what made the tumors stop responding to ONC201.

When you are finished taking the drugs (treatment)

You will be invited for a follow up safety visit approximately one month after the last day you take the study drug. At this visit, you will have the following tests:

- Physical exam and vitals
- Review of your symptoms and your ability to perform your normal activities.

- Routine blood tests to find out if you are anemic, have low blood counts, your blood is clotting normally and if your liver, kidneys, and other organs are working well.
- You will also be given the option for another biopsy of your tumor as well as for research labs. These tests may help researchers determine why your tumor didn't response or stopped responding to treatment.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice two effective forms of birth control before starting study treatment, during study treatment, and for at least one month after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

What tests will be done on my samples?

Your tissue (tumor and normal tissue) and blood that are collected will be used to look for specific changes in the cell signaling, DNA repair, mitochondrial, or other pathways in tumors.

This analysis could be used to develop new ways of diagnosing and treating cancer. In order to examine the tumor and normal tissue, we may use several different techniques depending on the type of tissue we collect. Also, we will look for changes of DNA damage repair markers, circulating tumor cells, and immune cells in the blood. We will study whether these changes link to your health outcomes.

When we are conducting these tests, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings." However, the analyses that we perform in our laboratory are for research purposes only; they are not nearly as sensitive as the tests that are performed in a laboratory that

is certified to perform genetic testing. Changes that we observe unrelated to our research may or may not be valid.

Therefore, we do not plan to inform you of the results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding that is believed to be clinically important based on medical standards at the time that we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results

Release of genetic information

Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

While the databases developed for this project are not open to everyone and also will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

Your individual genomic data and health information may be put in a controlled access database. This means that only researchers who apply for and get permission to use the information for a specific research project will be able to access the information. Your genomic data and health information will not be labeled with your name or other information that could be used to identify you. Researchers approved to access information in the database have agreed not to attempt to identify you.

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives.
Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

It is possible also that someone could get unauthorized access or break into the system that stores information about you. Every precaution will be taken to minimize this risk. There also may be other privacy risks that we have not foreseen. There also may be other privacy risks that we have not foreseen.

Since some genetic variations can help to predict future health problems for you and your relatives, this information might be of interest to health care providers, life insurance companies, and others. However, Federal and State laws provide some protections against discrimination based on genetic information. For example, the Genetic Information Nondiscrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent companies that sell life insurance, disability insurance, or long-term care insurance from using genetic information as a reason to deny coverage or set premiums. GINA also does not apply to members of the United States military, individuals covered by the Indian Health Service, or veterans obtaining health care through the Veteran's Administration. Lastly, GINA does not forbid insurance medical underwriting based on your current health status though the Affordable Care Act limits consideration of pre-existing conditions by insurers.

Who else besides the investigators on this study will know the results of my sample testing?

Once we obtain any of the samples listed above, the investigators take all your personal information off those samples and label them with a study code number. Only the investigators on this study know who the sample came from. The key linking your personal information with the code number is kept in a secure computer data base, with access only to the 2-3 research staff who will be discussing this study with you. Once the sample has been labeled with a code, it is sent to a variety of NIH laboratories for storage and testing. No one testing your samples will be able to link the results to you personally. Specimens obtained during your participation in this study may be sent for testing to investigators outside of NCI or the NIH. All samples will be coded to protect your privacy and no personal information will be included. Other investigators on this study will have access to limited clinical and biologic data such as age, gender and disease status.

How long will your samples be stored?

The samples collected during this study will be stored for as long as the study is open. When this study is closed, we would like to keep the samples for future research. We will request your permission to do so, later in this consent.

Risks or Discomforts of Participation

As with all treatments, there are several side effects or risks from the treatment provided in this study. However, doctors don't know all the side effects that may happen with this drug, so it is

important to report any changes that you notice, even if your study team does not ask specifically about them. Side effects may be mild or severe. Your study team will give you medicines to help lessen side effects. Many side effects go away with those medicines and others may go away soon after you stop treatment. In some cases, side effects can be serious, long-lasting, or may never go away. In very rare instances, they could cause death.

What side effects or risks can I expect from being in this study?

Potential Side effects from ONC201

To date, over 70 patients have taken at least one dose of ONC201 and it has been generally well tolerated. Very few side effects have been attributed to ONC201.

Likely	**Less Likely**	**Rare but Serious**
• Fever • Fatigue (tiredness)	• Elevated Amylase • Nausea/Vomiting • Rash • Neutropenia	• Twitching • Abnormal breathing • Abnormal walking or standing • Stroke, also known as cerebrovascular accident (CVA). This is the sudden death of brain cells due to lack of oxygen, caused by blockage of blood flow or rupture of an artery to the brain. Sudden loss of speech, weakness, or paralysis of one side of the body can occur. It may have a long-term effect on brain function, and it could be fatal. At this time it is unclear if it's linked to the use of ONC201.

Tumor Biopsy

If your doctor determines it is safe we will obtain a piece of your tumor (biopsy) using a needle with minimal risk to you. You will be given local anesthesia (numbing medicine) and a sedative prior to the biopsy. The biopsy will be taken through a needle put through the skin into your tumor. Depending upon the location of your tumor, a CT scan or other imaging modality such as an ultrasound may be used to assist the biopsy. After the procedure, the nurses will watch your blood pressure and other vital signs. This biopsy is not optional and you cannot participate in this study if you do not agree to the biopsy. If the first biopsy is too difficult, you will be able to continue on the protocol without undergoing the second (required) and third (optional) biopsies. However, an attempt at the first biopsy is needed to enter this study. There are other studies at NIH which may also be options for you and which do not involve biopsies.

Risk of Radiation

This research study involves exposure to radiation from up to 3 CT scans that may be used during your tumor biopsies. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 2.4 rem, which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects. While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. It is best to avoid radiation exposure to unborn infants since they are more sensitive to radiation than adults.

Blood Sampling

Risks of blood sampling include bruising or bleeding at the needle site; rarely infection. This is treated with bandages, pressure and, if infection, antibiotic medicines. For more information about risks and side effects, ask your study team.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if treatment with ONC201 will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

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

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study, with standard chemotherapy or CDK4/6 inhibitors.
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you become pregnant
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if the study is closed for any reason

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Oncoceutics, Inc. or their designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.

- National Institutes of Health Intramural Institutional Review Board
- Qualified representatives from Oncoceutics, Inc., the pharmaceutical company who produces ONC201.

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.

We may put your research data in a large database for broad sharing with the research community. These databases are commonly called data repositories. These data repositories might or might not be located at the NIH. *The information in this database could include but is not limited to genetic information, ethnicity and sex.* If your individual research data is placed in one of these repositories*, it will not be labeled with your name or other information that could be used to easily identify you,* and only qualified researchers will be able to look at your data. These researchers must receive prior approval from individuals or committees to access the data.

Your summary genomic data is being placed in an unrestricted database, so researchers will be able to access summary information about all the participants included in the study (including you), or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or
- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

Oncoceutics, Inc. is providing the investigational agent, ONC201, for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly

for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Alexandra Zimmer, M.D., Building 10, Room 2B50A, Telephone: 240-760-6132. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative | Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian | Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian | Date | Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM NOVEMBER 19, 2018 THROUGH DECEMBER 3, 2019.

Signature of Investigator | Date

Print Name

Signature of Witness | Date

Print Name