CONSENT FOR CANCER RESEARCH

Project Title: Phase 2 Study of ONC201 in Neuroendocrine Tumors
Sponsor: Investigator Initiated Trial (Dr. Peter M. Anderson)
(drug supplier): Oncoceutics
IND#: [redacted]

Principal Investigator(s): Peter M. Anderson MD, PhD
P: [redacted]**; cell** [redacted]

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC).

What is the usual approach to my cancer?
Standard therapies include drugs (chemotherapy), surgery to remove tumor from your body, and radiation (high energy to kill cancer cells in a specific area where the radiation beam is focused).

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:

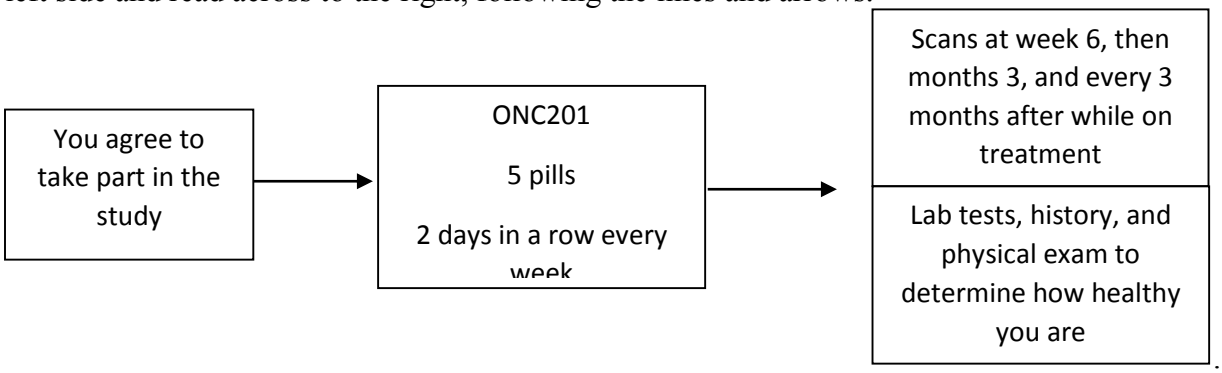
- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer. For example: comfort/palliative care

Why is this study being done?
The purpose of this study is to learn if a new drug, ONC201 can make tumors become smaller or go away completely. We also want to learn if ONC201 can prevent new deposits of cancer from appearing in new places in your body (metastases).

ONC201 is an investigational (experimental) agent and seems to have few side effects in advanced cancers. Since your neuroendocrine tumor(s) should have a molecule that binds ONC201 drug at high levels, this study will try to see if ONC201 treats neuroendocrine tumors like yours.

What are the study groups?
All people in this study are adolescents or adults and have been diagnosed with recurrent or metastatic neuroendocrine tumors
All study participants will get the same study intervention. The ONC201 study drug will be given by mouth on two consecutive days each week until your disease gets worse, you no longer have clinical benefit or the doctor no longer thinks it is in your best interest.

To find out what will happen to you during this study read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in this study?
After the initial visit and screening studies, you will learn if you can be part of the study and when treatment can start. You will receive the ONC201 drug until your disease is worse (progression) at two consecutive time points or until you no longer have clinical benefit, whichever comes first. After you finish, your doctor will continue to watch you for side effects and see if you get new disease or whether you improve.

How many people will take part in the study?
This study is being done at Cleveland Clinic and 36 patients are expected to be enrolled.

What extra tests and procedures will I have if I take part in this study?
The exams, tests, and procedures you will have are part of the usual approach for your cancer. Additional blood samples for research (2 Tablespoons at each time point) will be collected before dose #1, at the week 6 visit and at the month 3.

Before you begin the study:
You will need to have the following blood tests and scans to find out if you can be in the study:

- Blood tests for checking blood counts, kidney and liver function (2 Tablespoons)
- Monitoring of blood pressure and pulse
- CT (Computed tomography) or MRI scan to measure tumor size
- PET-CT or PET-MRI to learn where cancer is in your body

Neither you nor your health care plan/insurance carrier will be billed for the investigational drug, ONC201 that will be used for this study or the Clinical Research Unit stay, but you will be financially responsible for all other charges (blood tests, radiologic tests, hospitalizations, and clinic visits.

During the study the following will be additional research procedures to make sure continuing ONC201 is safe and beneficial:

- Blood tests
- CT, MRI and/or PET-CT)
- Chest x-ray

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 ONC 201 may have unknown side effects:

- 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

The *ONC201 drug* used in this study may affect how different parts of your body work such as your liver, kidneys, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk you could have side effects from the study drug(s)/study approach.

Here are important points about side effects of ONC201:

- 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.
- Although to date side effects of ONC201 have been very low, testing is in an early stage and your doctor may share information what to look for as he/she learns more about ONC201

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 drug to try to reduce side effects.

Frequent (In 100 people receiving ONC 201 20 to 30 may have):

- Fatigue
- Nausea
- Headache
- Vomiting

Occasional (In 100 people receiving ONC201 10 to 20 may have):

- Decrease in the number of a type of white blood cell (lymphocytes)
- Abnormal walking
- Insomnia
- High blood sugar
- Weakness on one side of the body (Hemiparesis)

- Low red blood cells (Anemia)
- Dizziness
- Muscular weakness
- Low phosphorous in the blood (Hypophosphatemia)
- Low red blood cells (Anemia)

Less Likely (In 100 people receiving ONC201 5 to 10 may have):

- Dizziness
- Muscle weakness
- Trouble speaking (Dysarthria)
- Difficulty swallowing
- Constipation
- Increase in the blood level of liver enzymes
- Low levels of platelets
- Pain in back, arms or legs
- Impaired balance or coordination
- Low phosphorous in the blood
- Decreased appetite
- Low white blood cells (Leukopenia)
- Cough
- Trouble sleeping
- High blood pressure
- Seizures
- Weight gain
- Shortness of breath
- Diarrhea
- Nerve disorder
- Low potassium in the blood

Rare but serious adverse events that were considered related to ONC201 (In 100 people receiving ONC201, 3 or fewer may have):

- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Abdominal pain
- Small bowel obstruction
- Death
- Damage to multiple organs (kidneys, liver, lungs, other Encephalopathy
- Pneumonia
- Bleeding
- Blood infection
- Changes in thinking patterns
- Abnormal body movement

- Rash
- Bleeding in the brain or lungs
- Blood clot in the lung
- Tumor Lysis syndrome, a disease caused by cancer cells dying
- Stroke
- Trouble breathing

Adverse events that have been observed in previous clinical trials of ONC201 that were attributed by the investigator as possibly-related or probably-related to ONC201 include, but are not limited fatigue nausea, headache, vomiting, high blood sugar and low red blood cells.

When ONC201 was administered to laboratory animals at higher doses than you will receive, the following side effects were seen:

- Nausea
- Decreased appetite
- Increase of saliva
- Vomiting
- Diarrhea
- Abnormal (labored) breathing has been observed in laboratory studies, though the cause is unknown at this time
- Body tremors
- Abnormal walking or standing (gait deficiency) has been observed in laboratory studies, though the cause is unknown at this time.

Other Risks

Encephalopathy, which has been associated with the use of ONC201, is a condition that may cause altered mental state, loss of memory or cognitive ability, inability to concentrate, lethargy, and/or progressive loss of consciousness. It is recommended that you take ONC201 before sleeping, such as before bedtime and to avoid driving or use of heavy machinery while taking ONC201.

Studies in animals have shown that it may be possible that if a woman who is pregnant or breastfeeding takes ONC201 it will harm her embryo, fetus or breastfeeding infant.

Cancer research often includes biopsies, scans, x-rays that are also provided as routine care. The following describes the side effects of procedures done only for the purposes of research.

Potential Risk or Discomfort from Research Procedures

Blood samples:
In addition to the possibility of pain while blood samples are being drawn from your arm, there is

the risk of bleeding or bruising at the needle site or risk of infection. Some people may feel dizzy or light-headed after having blood drawn.

Electrocardiogram (ECG): The ECG test is a recording of the electrical activity of your heart and an ECG is generally harmless. The sticky pads (electrodes) that are placed on your chest can sometimes cause discomfort such as redness or itching. We may need to shave your chest before we attach these pads. Irritation from shaving also may occur.

The following procedures are considered part of your regular care and would be done even if you were not in the study: physical exams, routine blood tests, and CT/MRI scans.

X-ray

During this study, you will have exposure to radiation from chest x-rays. This radiation exposure is not necessary for your medical care and is for research purposes only. This means that you will be exposed to small doses or amounts of radiation. The risk from this amount of radiation is less than the risk from everyday exposure to the sun. The risks of receiving very small doses of radiation are thought to be low. These risks are not actually known.
Pregnant women cannot be exposed to radiation. Women must have a negative pregnancy test before they can have an X-ray.

CT Scans

If you take part in this research, you may have one or more medical imaging studies such as a CT scan which uses some radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may not have received or will receive from other tests. The CT scan that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation." No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe being exposed to too much radiation can cause harmful side effects, including causing a new cancer. The amount of radiation that scientists think can cause harmful side effects equals more than 15 times the amount of extra radiation you would receive from being in this study. Also, scientists believe the number of people who would be at risk for developing a second cancer from being exposed to large amounts of radiation to be about 1 out of every 1,000.

Magnetic Resonance Imaging (MRI)

If you take part in this research, you may an MRI (magnetic resonance imaging and/or magnetic resonance spectroscopy). MRI uses a magnet and radio waves to make images (pictures) of the inside of the head and/or body. There have been no ill effects reported from exposure to the magnetism or radio waves used for these studies; however, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal that may cause injury to you. We will ask you about metal within your body (this includes certain dyes used in tattoos and body piercings). If there is any question about potentially

hazardous metal within your body, you will not be able to participate in this research study. We will also keep the MRI room locked so that no one carrying metal objects enters the room while you are having this scan performed. In addition, the MRI scanner makes a loud buzzing noise that could affect hearing ability. You will be provided with earplugs and assistance in their use in order to protect your hearing. You will be able to communicate with the scanner technologist using an intercom and/or signaling device. The technologist will try to help you feel as comfortable as possible in the scanner. You can ask to stop the scan and be removed from the scanner at any time by using the intercom or signaling device.
There is a very slight risk of an allergic reaction if contrast material is injected. Such reactions usually are mild and easily controlled by medication. If you experience allergic symptoms, a radiologist or other physician will be available for immediate assistance.

Non-Physical Risks:

Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

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

We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your cancer, which may give you relief from some symptoms, improve your quality of life, or prolong your survival. However, it is possible that your condition could worsen. Your participation in this study will help to obtain information about treating adults with neuroendocrine tumors.

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.

If you are responding to therapy and there are existing areas of cancer that grow, some of these areas could be treated with surgery, radiation, freezing or heating tumors. This is possible on the study (you continue to take ONC201 every week) as long are you do not develop new areas from of spread of your cancer (metastases). This is so we can determine if ONC201 can act to suppress development of new areas of cancer (metastases).

If you have new areas of cancer spread (metastases) occur while on ONC201, your doctor(s) will consider ONC201 to be ineffective and take you out of 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 ONC201.

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 requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.
- If you become pregnant.

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.

What are the costs of taking part in this study?
Your involvement in this research study is voluntary and you will not be paid for your participation.

The study agent, ONC201, will be provided free of charge by Oncoceutics, while you are participating in this study. Neither you nor your insurance provider will be responsible for the costs of the drug.

You and/or your health plan/insurance company will need to pay for all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

What happens if I am injured or hurt because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland

Clinic Institutional Review Board at (216) 444-2924.

HIPAA AUTHORIZATION

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Peter M. Anderson MD, PhD and the research study staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Oncoceutics its study monitors and representatives
- Oncoceutics collaborators and licensees (people and companies who partner with Sponsor)
- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Cleveland Clinic Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Peter M. Anderson, MD, PhD
Case Comprehensive Cancer Center
[redacted] Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, you can ask Dr. Peter Anderson, the Principal Investigator of the study, and/or research staff at [redacted]
Emergency or after-hours contact information
If you are a Cleveland Clinic patient, you should contact the page operator at [redacted] or toll free at [redacted], and ask for the medical oncologist (cancer doctor) that is on call.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB [redacted]

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on, if applicable, 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.

Signature

I have been given a copy of all 10 pages of this form.

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____
Printed Name of Participant

_____ _____
Signature of Participant or Child *(If form is used to obtain assent)* Date

Permission of Parent/Legal Guardian if patient is a minor

_____ _____
Printed Name of Parent or Legal Guardian Relationship to Participant

_____ _____
Signature of Parent or Legal Guardian Date

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____ _____
Signature of Person Obtaining Consent Date

_____
Printed Name of Person Obtaining Consent