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University of Washington
Fred Hutchinson Cancer Center

Consent to take part in a research study:

A Phase 2 Trial of the CDK4/6 Inhibitor Abemaciclib in Patients with Advanced and Refractory Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors (GEP NETs)

Principal Investigator: David Zhen, MD
Fred Hutchinson Cancer Center
University of Washington
206-606-2038

Emergency number (24 hours): 206-598-6190

We invite you to join this research study.

We are inviting you to join this research study because you have a type of cancer called neuroendocrine tumor that affects the gastrointestinal tract or pancreas and the neuroendocrine tumor has spread to other parts of your body. Your cancer may have come back after getting treatment or has gotten worse while being treated.

Research is not the same as treatment or medical care. The purpose of a research study is to collect information and answer scientific questions.

You do not have to be in the study. You are free to say "yes" or "no", or to drop out after joining. If you say "no," you would have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change. We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make an informed decision about joining this study.

Up to 37 people will take part in this study. You will be asked to attend visits every other week in the first 2 cycles, then a visit on Day 1 of each cycle. Each cycle is about 28 days. During these visits, you will meet with a provider who will conduct a physical exam, ask you questions about your general well-being and quality of life and if you have had a side effects (good or bad) from the study product. You will also have routine blood tests to make sure that you are safe. You will be allowed to continue taking the study drug until images of your cancer show that you are not benefiting from the study treatment or if you have side effects that are unsafe.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the

study. If you join this study, we will give you a signed copy of this form to keep for future reference.

Study Purpose

We are doing this study to find out how a drug called abemaciclib works in subjects who have gotten treatment for their gastrointestinal (GI) neuroendocrine tumors but did not do well or got worse.

Abemaciclib (also called VERZENIO) is a type of drug that blocks the cancer cell from making more cells that would help make the tumor grow. It has been studied in the MONARCH2 trial and approved by the US Food and Drug Administration (FDA) to treat people who have hormone receptor-positive breast cancer that has grown or spread to other parts of the body. In one clinical trial of breast cancer patients, 132 subjects took 200mg of abemaciclib by mouth, twice daily. About 20% of participants' cancer responded to the study drug for about 8 months.

This study will test abemaciclib in GI neuroendocrine tumors. In the United States, the FDA has not approved the use of abemaciclib to treat this type of cancer. This means that the drug is investigational for patients with GI neuroendocrine tumors.

This study will collect information about the following:

- how your cancer responds to the study treatment,
- if the study drug is safe,
- if there are certain markers that can predict response to the study drug.

Tests, Procedures and Study Visits

Screening Visit (Before Treatment)

Before you can start the study, the study doctor and study staff will talk to you about the study. Then we will ask you to sign this form if you want to join this study. After signing this consent form, the study will begin with a screening visit. The purpose of this visit is to find out if you meet all the requirements to take part in this research study. We have to do most of the tests and procedures within 14 days of your first dose of study drug, but we can use previously collected tissue and scans to see if you will qualify to enter the study.

We will conduct the following tests and procedures:

- Physical exam
- Blood pressure, pulse, oxygen saturation, respirations, height, weight (vital signs)
- Current activity level and ability to perform daily tasks
- Review of your medical history, current conditions and medications
- Blood tests for the following:
    - To see how your organs are functioning and the levels of minerals in

your blood
    - To count your blood cells
    - To see how your blood clots
    - To make sure you don't have Hepatitis B or C
    - To measure your tumor markers
- Scans of your tumor(s) using computed tomography (CT) or magnetic resonance imaging (MRI)
- Genetic test and protein staining on your cancer tissue, either from a sample that has been stored or a fresh biopsy
- Women who are able to get pregnant will have a pregnancy test

It is possible that after the screening tests are reviewed, you will not be able to take part in this study. If this is the case, the study doctor will tell you what happened. They will discuss other treatment options with you, if available. In some instances, you may be able to re-screen.

Treatment

We will ask you to come to the clinic for study assessments. When you come to the clinic, we will perform tests and procedures to see how the study drug affects you. If you are able to take part in the study, we will give you enough study drug to take for a whole cycle (28 days). We will give you a dose of 200 mg, which is a standard dose. Each dose should be taken at least 12 hours apart.

We will ask you to keep a diary of when you take your study drug. You will need to bring your completed diary to your visits on Day 1 of each cycle. The study staff will contact you shortly after you start your study drug to make sure you are taking the correct dose and to answer any questions you may have.

The study doctor may lower or stop your study treatment if you have side effects that are uncomfortable or unsafe. If you are told to stop taking your study drug, the study doctor and staff will give you instructions about what to do.

During Cycles 1 and 2, you will come to the clinic on Day 1 and Day 15 and have some of the tests and procedures listed below. After Cycle 3, we will only ask you to come to the clinic every 28 days.

Tests and Procedures

- We will review your medical history, including your cancer history.
- We will do a physical examination. It will include an exam of major body systems and recording your weight. Your height will be measured at screening.
- We will collect blood for safety tests. We will test your blood to look at how your organs and glands are functioning, and how well you are producing

blood cells.

- We will collect blood for tumor markers. We will test these samples as they might give us information about how your cancer is responding. We will collect a sample before you get any study drug so that we can compare the results. *There are some foods and medications that you cannot have before we collect these samples. We will tell you how to prepare to have these samples collected.*
- We will ask you how you are feeling and if your level of activity has changed.
- We will review any medications that you take, including over-the-counter drugs, vitamins, and herbal products.
- We will look at places where your tumors are. We will use one of the tests described below. Your study doctor will decide which test is best for you.
    - Computed Tomography (CT) Scan: This test uses a small amount of radiation (x-ray) to take pictures of the inside of your body. It can show a cross section, like a thin "slice" of your body, or it can show the body tissues and structures in "3-D". For this test, the study doctor or staff may give you a contrast dye injected into a vein with a needle and by mouth. The study doctor or staff can tell you more about the contrast dye.
    - Magnetic Resonance Imaging (MRI) Scan: This test uses powerful magnets and radio waves to make pictures of body tissues and structures. During an MRI, you must lie on your back in the MRI scanner without moving. The inside of the MRI scanner is a tight space. You may have a contrast dye injected into a vein with a needle. The study doctor or staff can tell you more about the contrast dye.

Tissue Samples

At screening, the study doctor or staff will ask if you can provide a sample of your tumor tissue (cancer cells from your body) that was collected from a surgery or biopsy that you already had. This is called "archival tissue".

We will test this tissue to see what genes are "on" or "off" in the cancer cells. Genes are made of DNA and tell cells what to do by making proteins and enzymes. These genes might help to determine the response of the cancer cells to the study treatment. Also, the tissue will be tested for protein markers to see if they may help predict responses to treatment.

If you have already had genetic testing of your cancer, we may request to review the results.

If you do not have prior tissue on file, or you do not want us to request and study your archival tissue, it is optional. We will have you mark your choice about this optional tissue collection at the end of this form.

Stopping Treatment

Subjects can continue the study treatment until one of the following events:

- Your cancer grows or gets worse.
- You have side effects that you cannot tolerate, or you have a side effect that is related to the study treatment and does not resolve within 3 weeks of stopping the study drug.
- You cannot complete the tests and procedures needed for the study.
- You decide you don't want to continue with the study treatment.
- Your study doctor does not think that it is a good idea for you to keep taking the study drug or thinks another treatment would be better. The study doctor will ask you to stop the study drug if you get pregnant.
- The study is stopped by a regulatory authority or the sponsor.

When you stop taking the study drug, we will need to complete some tests and procedures to make sure that you are safe after about 30 days after stopping the drug.

We will collect the following:

- Collect your drug diary
- Conduct a physical exam
- Collect vital signs
- Ask you how you are feeling and if your activity level has changed
- Review any side effects. If you have side effects related to the study drug that are ongoing when you stop study treatment, we may need to contact you, or have you come to the clinic until the effects resolve, go back to normal, or the study doctor thinks that the effects are no longer important.
- Blood tests for the following:
    - To see how your organs are functioning and the levels of minerals in your blood
    - To count your blood cells
- Most recent tumor markers and scans of your tumor(s) using computed tomography (CT) or magnetic resonance imaging (MRI)

Long Term Follow-up

After stopping treatment, we will contact all subjects who received the study drug to see how they are doing. The study staff will contact you every 4 months for 1 year from the date you signed the original consent form.

If treatment was stopped because of side effects, we will also collect copies of your scans (CT or MRI) and the reports done during this period of follow-up to see what happens to the cancer. We can ask your regular doctor to send these to the study doctor or staff.

If you or your partner become pregnant during the study treatment, the study doctor and staff will follow the pregnancy to the outcome.

Study Length

If you join this study, you would stay in this study and receive abemaciclib until your cancer gets worse or you cannot tolerate the side effects. You will be followed for at least 1 year.

The study doctor can stop you from taking part in the study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You not able or willing to follow study procedures.
- The whole study is stopped.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information cannot be removed from the study records.

Risks and Side Effects

Treatments for cancer often have side effects. This includes some that are life-threatening. Death could happen as a result of this treatment and its side effects. There may be additional unknown risks.

If you have severe side effects from the study drug, your doctor may prescribe medications to treat the side effects. They may also choose to delay or stop future study treatments.

Very common side effects (at least 1 in 10 patients) of abemaciclib are:

- Nausea
- Diarrhea
- Vomiting
- Headache
- Feeling tired (fatigue)
- Decreased appetite
- Abdominal pain
- Decreased white blood cell count, which can make you more likely to get an infection.
- Decreased red blood cell count, which can make you feel more tired.
- Decreased platelets, which can make it harder to stop bleeding
- Body pain
- Cough
- Hard stools (constipation)
- Difficulty breathing (dyspnea)
- Dry mouth
- Inflamed sores in the mouth (stomatitis)
- Weight loss

- Creatinine increased: lab test result associated with decreased kidney function
- Hair loss
- Difficulty swallowing (dysgeusia)
- Back pain
- Dizziness
- Fever

Common side effects (at least 1 in 100 patients but more than 1 in 10 patients) of abemaciclib include:

- Increased risk of infections, like upper respiratory tract infections and urinary tract infections
- Increased liver function test results, including ALT, AST and bilirubin. This can mean that your liver is not functioning properly.
- Blood clots, which can cause your blood to stop flowing from the legs to the heart. These blood clots can also break apart and be carried to the lungs, which can cause difficulty breathing and lung damage. In rare cases, this can lead to permanent injury or death.

Uncommon side effects of abemaciclib include:

- Lung Inflammation (pneumonitis): abemaciclib may cause lung tissue inflammation. Many patients with X-ray or CT abnormalities may not develop any symptoms but some may develop mild to severe symptoms. In some cases, lung inflammation has led to death. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.

Please tell your study doctor or nurse **AT ONCE** if you have any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain or difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example, any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to have symptoms, your study doctor will ask you to come back to the clinic for more tests. These could include a physical exam, measuring your oxygen levels, blood tests, chest x-rays, and CT scans. We will watch you very closely for changes in your overall lung symptoms. If necessary, this may require hospitalization. You may need specific treatment to control pneumonitis. You may also be seen by a doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Risks Associated with Study Procedures

Risks and possible discomforts you might experience from the study procedures include:

Blood draws: A blood draw via needle may cause faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight chance of infection.

Intravenous (IV) catheter: The use of an intravenous catheter may cause pain, bruising, clotting, bleeding, leakage of study treatment solution, and possibly infection at the catheter site.

MRI: There are risks from an MRI if you are pregnant or have one of the following: an artificial heart valve, pacemaker, metal plate, pin, or other metallic objects in your body (including gun shot or shrapnel). You may also become anxious from lying in a tight space without moving. The MRI scan does not cause any pain and does not expose you to x-ray radiation. Please let the study doctor know if you have a fear of enclosed spaces (claustrophobia).

Imaging scans (CT):
Some of the tests that you have in this research study will expose you to radiation. Everyone receives a small amount of radiation every day called "background radiation". This radiation is natural and comes from space, air, water, soil, and the food that you eat. Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose. For comparison, the estimated radiation dose from each of these tests is listed below. The risk to your health from this level of radiation exposure is likely zero.

- Head CT: 2 mSv
- Chest CT: 7 mSv
- Abdominal CT: 8 mSv
- Pelvic CT: 6 mSv

You may also become anxious from lying in a tight space without moving. Please let the study doctor know if you have a fear of enclosed spaces (claustrophobia).

Contrast dye for CT scans and MRI: Contrast dye is usually injected when you get a CT scan or MRI. The contrast dye may cause pain or burning when it is injected. It could make your kidney function get worse if you already have kidney disease or if you have not had enough liquids that day and are dehydrated. The contrast dye may also cause an allergic reaction. This could be severe and life-threatening.

Genetic research risks: The pharmacogenomics and biomarker research that may be performed using your tissue and blood samples may involve genetic testing. Procedures have been put into place to make sure that any results from genetic research cannot be linked to you. However, there is a possibility that information

from your participation in this study could negatively affect you or your family in some way if a genetic disorder were discovered.

Other Risks

Since the study drug combinations are investigational, we don't know all the risks of this treatment.

All study treatments could cause an allergic reaction. If not treated right away, this reaction could become life threatening. Get medical help and contact the study doctor **right away** if you have any of the following symptoms of a serious allergic reaction: trouble breathing, or swelling of the face, mouth, lips, gums, tongue, or neck. Other allergic reactions may include rash, hives, or blisters.

It is important that you tell us about all symptoms and side effects that you have as soon as they happen, whether you think they are caused by the study treatment or not. The phone numbers for the study team are on the first page of this document.

Pregnancy Related Risks / Use of Birth Control

Abemaciclib may cause harm to unborn babies when given to a pregnant woman. There have been no studies of these treatments in pregnant women. The effects on sperm, a pregnancy, or a nursing child are not fully known. Female patients who are able to have children must use effective contraception through treatment and for 3 weeks after the study treatment is stopped. Abemaciclib may cause injury to sperm, including infertility.

Men who have partners who are able to get pregnant must be sterile (unable to father a child) or agree to use a highly effective method of contraception during the study. They must continue to this contraception method for at least 3 weeks after their last dose of study drug.

If you are currently pregnant, planning to become pregnant, or breastfeeding a child, **do NOT** join this study.

If you are a female patient or your partner is able to have children, the study doctor will talk to you about the types of birth control that you can use while taking part in this study. They will help you select birth control methods that are the best choice for you. The study doctor will instruct you in correct use of your selected birth control methods. They will review your responsibility to use this birth control consistently and correctly at each visit.

Birth control methods, even when used properly, are not perfect. If you are a female patient or the female partner of a male patient and become pregnant during the study, or you want to stop using birth control during the study, you should tell the study doctor **immediately**. Your doctor will remove you from the study if you stop using birth control or you or your partner become pregnant.

Pregnancy Follow Up

If you are a female patient or the partner of a male patient and become pregnant during the study or within 3 weeks after finishing the study treatment, please tell the study doctor **immediately**. Please also tell the doctor who will be taking care of you during the pregnancy that you took part in this research study. The study doctor will ask if you or your pregnancy doctor is willing to give updates on the pregnancy and its outcome. If you agree, this information will be given to the study sponsor for safety monitoring.

Benefits

It is possible that your condition or health may improve because you are taking part in this study. We do not know if this study would help you. We are testing abemaciclib to see its effects on people with neuroendocrine tumors. Your participation in this research may help future cancer patients.

Alternative Treatments

Instead of taking part in this study, you may choose to have treatment with other cancer drugs or treatment methods. These options may include any current standard treatment for your type of cancer. Your study doctor will talk with you about alternate treatments available for your form of cancer. They will talk with you about the risks and benefits of the alternative treatments.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor. Enrollment in this study may exclude you from other research studies.

What will my information and/or tissue samples be used for?

Your information and tissue samples (such as blood and tumor cells) will be used for the purposes of this study.

Your tissue samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

If you join this study, some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Eli Lilly and Company (the manufacturer of the study product) and their

agents.

- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer Center and University of Washington.
- Office for Human Research Protections, Food and Drug Administration, and other regulatory agencies as required.

We will do our best to keep personal information confidential. But we cannot guarantee total confidentiality. Personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. A court may order study information to be disclosed. Such cases are rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If you authorize others to see your medical record, they would see a copy of this consent form.

How is my genetic information protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect genetic information about people who join research studies.

GINA restricts access to genetic information so that it cannot be used for health insurance coverage decisions. GINA prevents health insurance companies or group health plans from

- Asking for genetic information obtained in research studies, or
- Using genetic information when making decisions regarding your eligibility or premiums

GINA *does not* help or protect against genetic discrimination by companies that sell life, disability or long-term care insurance.

Payment for Participation

There is no payment for being in this study.

Costs

If you join this study, you may have some extra costs. Your insurance company might pay these costs, but some insurance policies do not cover these costs. We could help

find out whether your insurance company would cover these costs.

The extra costs are:

- Cost of tests that are given more often than usual.
- Cost of any other medical care needed, including treatment of side effects, because of this study.

If you join this study, you or your insurance company would have to pay for the costs of standard treatment in this study.

You would **not** be billed for:

- Abemaciclib

What if you get sick or hurt after you join this study?

For a life-threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can. Please contact the study doctor as soon as possible and within 24 hours of hospital admission if possible.

For all other medical problems or illness related to this research, immediately contact David Zhen, MD at 206-606-7551. They will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

Your rights

Taking part in this study is your choice. You can change your mind and drop out (withdraw) at any time. If you do not to participate or decide to withdraw, there will be no penalty. You won't lose any benefits you receive now or have a right to receive.

The research study team will also tell you if we learn new information that could change your mind about taking part or continuing in this research study.

If you want to drop out, you need to tell the study team so that you end the study in the safest way. The study team will also talk to you about follow-up care, if needed. They will discuss the different withdrawal options and your responsibilities with you.

The study doctor may ask you to have more tests for safety reasons. You may also be asked if you would agree to take part in the follow up portion of the research study. If you agree to continue with the follow up part of the study, we will continue to collect information about your health as described above.

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.

Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of study visits and procedures.
- Takes study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you could talk to your doctor anytime. Other people you could talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	206-606-2038 (Dr. David Zhen) 206-606-7551 (Phase 1 Research Program)
If you get sick or hurt in this study	206-598-6190 (Dr. Zhen or Oncology Fellow on-call)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-606-1113 (Patient Finance, FHCC)

Emergency number (24 hours): 206-598-6190

Please read the following statement, mark your choice, and write your initials.

Optional tissue samples:

1. I agree to allow samples of my tissue to be collected for research testing for this study.

   ☐ Yes _____ (subject's initials)

   ☐ No _____ (subject's initials)

Signatures

Subject: If you have read this form (or had it read to you), asked any questions, and agree to participate, please sign:

_____

Participant (age 18+) / Printed Name

_____ _____

Participant (age 18+) Signature Date

Witness: If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

_____

Witness or Interpreter / Printed Name, Signature, and Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

_____

Person obtaining consent signature / Printed Name,

_____ _____

Person obtaining consent Signature Date

Current version date: 25Aug2022
Previous version date: 29Apr2022
Copies to: Subject
Subject Medical Record