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University of Washington
RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	A Phase 1/2 Study of Neoadjuvant Cabozantinib in Combination with Radiation Therapy for Sarcomas of the Extremities
PROTOCOL NO.:	Fred Hutch IRB # CC10051
FUNDING SOURCE:	Exelixis 210 E. Grand Avenue South San Francisco, CA 94080
SPONSOR-INVESTIGATOR:	Lee Cranmer, MD, PhD, FACP 825 Eastlake Avenue E., LG-350 Seattle, Washington 98109 United States
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STUDY-RELATED PHONE NUMBER(S):	Lee Cranmer, MD, PhD, FACP 206-606-7439 Roxanne Moore, Assistant Director 206-606-6425 (Office Hours) romoore@seattlecca.org Oncology Fellow On-Call 206-598-6190 (24 hours)

Emergency (24-hour) phone: Call the Fred Hutchinson Cancer Center at 206-606-7400 Monday through Friday from 9 am to 5 pm. At all other times call the paging operator at the University of Washington Medical Center at 206-598-6190 and ask the operator to page the oncology fellow on call.

Important things to know about this study.

We invite you to participate in a research study. The purpose of this research is to determine the safety and effectiveness of cabozantinib in combination with radiation therapy in individuals with sarcoma of the extremities, for whom treatment with radiation followed by planned surgical resection (removal of tumor) is planned.

People who agree to join the study are able to receive treatment for up to about 4 ½ months. The study involves taking cabozantinib orally, once daily, over a 21-day cycle. You will receive standard-of-care radiation treatment starting after your first week of cabozantinib. Radiation treatment generally lasts between 4 and 6 weeks. While on study, we will draw your blood for tests, perform scans to measure your disease, and perform cardiac assessments. We will also ask you if you would like to donate your extra tissue for future studies.

We do not know if cabozantinib would help treat high-risk soft tissue sarcomas of the extremities and could even make your condition or disease worse. Cabozantinib could cause side effects such as diarrhea, fatigue, decreased appetite, nausea, weight decreases, changes in the skin on your hands or feet (hand-foot syndrome), vomiting, constipation, high blood pressure, changes in the way things taste, changes in the voice, weakness, shortness of breath, and others. The potential risks of taking cabozantinib are described further below in this form.

You do not have to join this study. You can choose to receive standard methods to treat high-risk soft tissue sarcomas of the extremities, instead of participating in this study. 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.

Following below 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.

We invite you to join this research study.

We invite you to join this research study because you have high-risk soft tissue sarcomas of the extremities and are intended to receive radiation therapy followed by a surgical resection. For the phase 1 portion, up to 12 people will join this study. For the phase 2 portion, there will be up to 34 additional patients.

Research is not the same as treatment or medical care. The purpose of a research study is to 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.

Why are we doing this study?

We are doing this study to examine the antitumor activity of cabozantinib with radiation therapy in subjects with soft tissue sarcomas of the extremities which would otherwise be treated with radiation therapy alone. This combination is investigational, which means it has not been approved for use by the Food and Drug Administration (FDA). This study is made up of two parts, Phase 1 and Phase 2.

The first part of this study, the Phase 1 portion, is the dose-escalation phase. The objective of this phase is to determine how much cabozantinib can be given safely in combination with radiation. Subjects will be treated at different doses of cabozantinib in combination with radiation therapy. This is done to determine the maximum tolerated dose of cabozantinib in combination with radiation. There will be different dosing groups of cabozantinib, receiving a dose level that is predetermined for each group. Subjects that join in the beginning of the study may receive a lower dose than subjects who join at a later date. Based on the presence of effects (either good or bad), the dose level can be escalated (raised) or de-escalated (reduced) accordingly. Your study doctor will watch carefully for any side effects.

Once the recommended dose is determined in the Phase 1 portion, the Phase 2 portion of the study will begin. In this part, additional subjects will be enrolled and assigned to the recommended dose level determined in Phase 1. The objective for the Phase 2 portion is to evaluate the effects (good or bad) of cabozantinib in combination with neoadjuvant (prior to surgery) radiation therapy treating subjects with soft tissue sarcomas of the extremities. Neoadjuvant means that this treatment happens before a planned surgery. Your study doctor will watch carefully for any side effects.

What research tests, procedures, and treatments are done in this study?

Before you can receive study treatment, we will perform tests to find out whether you can participate in the study. This part of the study is called screening.

After qualifying for this study, you will take cabozantinib by mouth, once daily, in a 21-day cycle, plus radiation therapy. You can continue therapy until you complete radiation therapy, disease progression, unacceptable side effects, or until you have received a total of 6 cycles of cabozantinib therapy.

You will take cabozantinib for one week prior to your radiation therapy. You will continue to take cabozantinib during your radiation therapy, and may continue after completion of radiation therapy if your imaging scan (CT/MRI) shows that you have at least stable disease. In total, you may complete up to 6 cycles (about 4 ½ months) of cabozantinib therapy prior to your scheduled surgery.

If you join this study, we would do these tests and procedures:

Screening Evaluations

We will perform screening evaluations for all subjects to determine study eligibility. These evaluations must be obtained at least 28 days prior to enrollment. Your baseline imaging assessments may be completed on a separate date than the rest of your screening evaluations in order to have them be as close to initiation of protocol therapy as possible.

We will complete the following procedures during the screening period:

- Demographics (date of birth, sex, race, and ethnicity)
- Physical examination including assessment of your general well-being (called an Eastern Cooperative Oncology Group or ECOG score)
- Prior/concomitant medications and procedures evaluation: all medications you have taken and procedures completed within 28 days prior to signing this informed consent document
- Vital signs (temperature, systolic/diastolic blood pressure, respiration rate, and pulse)
- Height and weight collection
- 12-lead electrocardiogram (ECG) single tracing
- Left ventricular ejection fraction (LVEF, by echocardiogram or MUGA), a measure of how well your heart is pumping your blood through your body
- Adverse event assessment
- Lab tests: blood chemistry, complete blood count (CBC) + differential, complete urinalysis with microscopic evaluation, urine protein/creatinine ratio (UPCR), pregnancy test (women who are able to have children), HIV, hepatitis B surface antigen, hepatitis C antibody, fasting lipids, thyroid function
- CT or MRI scan to measure the amount of disease in your body. This must be done within the 28-day screening period, but preferably should be done as close to enrollment as possible
- Archival tissue collection (optional)

Once it is determined that you meet all the eligibility criteria for the study, you will be enrolled onto the study. Subjects should begin study treatment within 14 days of being enrolled.

Treatment Period

The treatment period begins once you take your first dose of the study drug, cabozantinib.

Cabozantinib must be taken on an empty stomach. You will not be able to eat for at least 2 hours before and at least 1 hour after you take cabozantinib. You will need to take your dose at about the same time every day. If you miss a dose, the dose may be taken later only if it is within 12 hours of when the missed dose should have been taken. Do not take a missed dose if you are within 12 hours of the next dose. If you vomit the dose after taking it, skip the dose and resume the next day at the regularly scheduled time. We will provide you with a dosing diary to mark when you take each dose of cabozantinib.

Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. You will need to avoid grapefruit, grapefruit juice, Seville oranges, and their products while you are taking cabozantinib.

Please store the study drug at a controlled room temperature, away from direct sunlight or appliances/items that give off heat. Do not leave the study drug in a hot, unventilated car for a long period of time.

Day 1 Assessment

We will perform the following assessments on Day 1 of each cycle, unless otherwise specified:

- Physical examination
- Concomitant medication and procedures evaluation
- Vital signs (weight, temperature, systolic/diastolic blood pressure, respiration rate, and pulse)
- ECOG performance status
- CBC with differential
- Clinical chemistry panel including fasting lipid panel and thyroid function tests
- Serum pregnancy test (women who are able to have children)
- ECG
- Urinalysis with microscopic evaluation
- Adverse Event assessment

We may not have to repeat some tests listed above on Day 1 if your screening tests are taken within 72 hours of Day 1.

Day 8 Assessment

We will perform the following assessments on Day 8 of Cycles 1-3 only:

- Physical evaluation
- Vital signs (weight, temperature, systolic/diastolic blood pressure, respiration rate, and pulse)
- Urinalysis with microscopic evaluation
- Concomitant medication and procedures evaluation
- ECOG performance status
- CBC with differential
- Clinical chemistry panel (Day 8 assessments do not include fasting lipid or thyroid studies)
- Adverse Event assessment

Day 15 Assessment

The following assessments will be performed on Day 15 of Cycles 1-3 only:

- Physical evaluation
- Vital signs (weight, temperature, systolic/diastolic blood pressure, respiration rate, and pulse)
- Concomitant medication and procedures evaluation
- ECOG performance status
- CBC with differential
- Urinalysis with microscopic evaluation
- Clinical chemistry panel (Day 15 assessments do not include fasting lipid or thyroid panel)
- Adverse Event assessment

Response Assessment

We will perform CT or MRI scans at the following times while you are on study:

- Within 28 days prior to enrollment
- Every 12 weeks from your first scan until 1 year after you start protocol therapy (Cycle 1, Day 1), your disease comes back, you withdraw your consent, the end of study, or death – whichever occurs first.

Your study doctor may decide to perform an unscheduled scan at any time if they suspect your disease has gotten worse or if they believe your disease has come back.

End of Treatment Visit Assessment

After your last dose of cabozantinib, we will perform an End of Treatment (EOT) visit within 7 days. This is a safety follow-up visit that will include the following procedures:

- Physical examination
- Concomitant medication and procedures evaluation
- Vital signs (weight, temperature, systolic/diastolic blood pressure, respiration rate, and pulse)
- ECOG performance status
- CBC with differential
- Clinical chemistry panel including fasting lipid panel and thyroid function tests
- Serum pregnancy test (women who are able to have children)
- ECG
- Urinalysis with microscopic evaluation
- Adverse Event assessment

- Archival tumor collection (optional, for patients undergoing clinical surgical resection)

30-Day Follow-Up Visit Assessment

We will perform a 30-day follow-up visit about 30 days after your last dose of cabozantinib. This is an additional safety follow-up visit that will include the following procedures:

- Physical examination
- Concomitant medication and procedures evaluation
- Vital signs (weight, temperature, systolic/diastolic blood pressure, respiration rate, and pulse)
- ECOG performance status
- Clinical chemistry panel including fasting lipid panel and thyroid function tests
- ECG
- Adverse Event assessment

Long-Term Follow-Up

We will continue to monitor your disease status and any subsequent anticancer therapy information status after you come off active treatment. We will either complete a chart review or contact you by telephone every 12 weeks from your last dose of study drug for one year after starting cabozantinib therapy, or until your disease comes back, you withdraw consent, the study closes, or death – whichever is earliest. This will include a physical exam and imaging assessment.

Thereafter, we will follow you every 6 months for up to 3 years since starting cabozantinib therapy, or until your disease comes back, you withdraw consent, the study closes, or death – whichever is earliest.

Schedule of Assessments

Assessments	**Baseline Screening**	**Treatment Phase Cycle 1-3** 21-day (3-week) Cycles Days			**Treatment Phase Cycle 4+** 21-day (3-week) Cycles Days	**End of Treatment Visit**	**30 Day Safety Follow-Up Visit**	**Survival Follow-up** Every 12 weeks after last visit for 3 years
		D1	D8	D15	D1			
Informed Consent	X							
Medical History	X							
Hepatitis and HIV Screen	X							
Urinalysis with micro	X	X	X	X	X	X		
Urine Protein/Creatinine Ratio	X							
Thyroid Function Tests	X	X			X	X		
Pregnancy Test	X	X			X	X		
Cardiac Assessment (Echo or MUGA)	X							
12-lead electrocardiogram	X	X			X	X	X	
Physical Exam (including vital signs, height at screening, ECOG, and weight)	X	X	X	X	X	X	X	
Blood Chemistry and Complete Blood Count	X	X	X	X	X	X	X	
Lipid Panel (fasting)	X	X			X	X	X	
Optional Tissue Sample	X					X		
CT or MRI Assessment	X	Every 12 weeks (±2 weeks)						
Cabozantinib		Daily						
Radiation Therapy		Administered per standard of care. Typically you will get 4-6-week radiation course after you take cabozantinib for 7 days.. Radiation therapy will start within 7 days of Cycle 1 Day 8.						
Adverse Event Assessment	X	Continuous from Cycle 1 Day 1 through 30 days follow-up.						
Survival/Long Term Follow-up								X

How long would you stay in this study?

Depending on what phase of the trial you are in, you may be in the study for up to about 4 ½ months of study treatment, with follow-up lasting up to 3 years. Your participation will be stopped if you experience an unacceptable side effect, you no longer wish to participate, the whole study is stopped, or your study doctor feels that it is in your best interest to stop.

You may stop participating at any time without penalty or loss of benefits. However, if you decide to stop participating in the study, we encourage you to talk to your study doctor and your regular doctor first so that you may discontinue safely.

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 could not be removed from the study records.

What are the side effects (risks)?

In this part of the consent form, we describe the side effects we expect from the tests and treatments in this study. Cabozantinib could cause side effects we do not know about yet. We carefully watch everyone in the study for side effects.

If you join this study, we will tell you if we discover new side effects that could affect you.

This form lists side effects of the study drug cabozantinib. Other side effects could occur when we use cabozantinib in combination with radiation therapy.

Side effects may be mild or very serious. Medicines could be given to help lessen side effects. Many side effects go away soon after you stop taking cabozantinib. In some cases, side effects can last a long time or never go away. There also is a risk of death.

CABOZANTINIB

Very Common Side Effects

Seen in greater than or equal to 10% (≥ 1 in 10) Cancer Patients Treated

- Abdominal pain
- Alteration of thyroid function tests
- Blisters, rash, or pain in hands or feet
- Changes in blood tests used to monitor the liver, which may indicate liver damage
- Changes in the voice
- Changes to the way things taste
- Constipation

- Diarrhea
- Fatigue
- Hair color changes or hair loss
- High blood pressure
- Inflammation of mucus membranes
- Loss of appetite
- Mouth and throat sores or swelling
- Nausea
- Rash
- Vomiting
- Weakness
- Weight loss

Common Side Effects

Seen in greater than or equal to 1% but less than 10% of Cancer Patients (≥ 1 in 100, but < 1 in 10)

- Abnormal thickening of the outer layer of the skin
- Change in the feeling of touch
- Cough
- Bleeding, including bleeding from the stomach or intestines which may look like coffee grounds or black sticky bowel movements and bleeding within the brain
- Blood clot in a large vein, usually in the leg
- Blood clot that travels from a vein to the lung
- Confusion and disorientation
- Decreased amounts of red blood cells (anemia), which may cause feelings of tiredness or shortness of breath
- Decreased amounts of calcium or sodium in the blood
- Decreased or increased amounts of potassium in the blood
- Decreased amounts of magnesium in the blood
- Decreased amounts of phosphorus in the blood
- Decreased level of albumin in the blood
- Decreased platelet counts, which increases the risk of bleeding or make bleeding more difficult to stop
- Decreased white blood cell counts, which may increase chances of infection
- A type of acne called dermatitis acneiform

- Dehydration
- Difficulty swallowing
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Fungal infections including mouth, lung, and other locations
- Hemorrhoids and bleeding hemorrhoids
- Headache
- Increased amounts of pancreas enzymes in the blood, which may indicate damage to the pancreas
- Increased levels of bilirubin in the blood, which may indicate complications with the liver
- Increased levels of creatinine in the blood, which may indicate complications with the kidneys
- Mouth or throat pain
- Muscle spasm
- Muscle weakness
- Pain in a joint or muscle
- Pain in the extremities (arms and legs)
- Protein in the urine, which may indicate kidney damage
- Shortness of breath
- Stomach acid coming up from the stomach into the esophagus
- Swelling of the limb(s)
- Ulcer
- Upset stomach or indigestion

Uncommon Side Effects

Seen in greater than or equal to 0.1% but less than 1% of Cancer Patients (≥ 1 in 1000, but < 1 in 100)

- Abnormal electrical activity in the heart that could cause a potentially serious change in heart rhythm
- Abnormal opening between two organs or from an organ to the outside of the body
- Infected cavities filled with pus (abscess)

- Blood clot in an artery
- Chest discomfort originating from the heart
- Clouding of the lens in the eye that affects vision (cataracts)
- Damage to skeletal muscle tissue
- Decreased brain function or decreased alertness and ability to think
- Decrease in all blood counts (red blood cells, white blood cells, and platelets)
- Destruction of bone tissue, in particular, bone in the jaw
- Feelings of unease or fear
- Gallstones
- Heart attack
- Heart failure
- Holes in the stomach or intestines
- Infections
- Inflammation of the intestine, appendix, gall bladder, or thin tissue lining the inner wall of the abdomen and most of the abdominal organs
- Reduced kidney function
- Liver failure
- Loss of consciousness, fainting episode
- Pneumonia and inflammation of the lungs
- Rapid heart rhythm
- Re-opening of wounds after surgery
- Respiratory failure
- Seizure
- Stroke or mini-stroke
- Tear or inflammation in the skin that lines the anus
- Uncoordinated movements

Rare but Medically Important Side Effects

Seen in greater than 0.01% but less than 0.1% of Cancer Patients (≥ 1 in 10,000 but < 1 in 1000)

- Air in the chest between the lungs and chest wall
- Allergic reaction
- Anemia caused by destruction of red blood cells
- Blocked intestines

- Blood vessel inflammation associated with possible bleeding, bruising, and/or rash
- Brain dysfunction caused by brain swelling (Posterior Reversible Encephalopathy Syndrome [PRES])
- Cancer of the mouth or skin
- Damage to the outermost surface of the eye
- Inflammation and blockage of channels that carry bile from the liver
- Severe swelling of the mouth, lips, tongue, eyes and throat, or difficulty swallowing or breathing
- Temporary paralysis of the intestines
- Throat swelling
- Very high blood pressure that comes on suddenly and quickly which can lead to serious injury to the heart and brain
- Enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall

Radiation risks

Some of the tests that you will 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, soil and the food you eat. If you live in the US, you receive about 3 millisieverts of radiation each year of this background radiation. A "millisievert" (mSv) is a unit used to measure radiation dose. The risk to your health from this level of radiation exposure is too low to be detectable and may be nonexistent. The radiation dose to your whole body from each of your scans will be about as follows:

- CT scan of the chest: 7 mSv
- CT scan of the abdomen: 8 mSv
- CT scan of the pelvis: 6 mSv

You may need to have other x-rays or scans for your care. Your doctors will explain the risks of the other x-rays or scans.

Radiotherapy risks

Common side effects from radiotherapy could include: slow or delayed wound healing after surgery, decreased bone density that could increase the risk of developing a fracture in the future, scarring in the soft tissue / skin, swelling of the treated limb/extremity (also known as lymphedema), and there is a rare risk that radiation treatments could increase the chance of developing a cancer in the future (in the area that received radiation). There are potential acute toxicities that can occur with radiation, which include dermatitis (inflammation of the skin) and pain at the site of radiation.

Reproductive risks

Chemotherapy and radiation treatments could cause sterility (unable to have children).

Taking cabozantinib may involve unknown risks to an unborn baby (embryo or fetus) or nursing infant. Therefore, you cannot join this study if you are pregnant, if you are planning to become pregnant, or if you are breast-feeding.

If you join this study, you will have to use a highly effective method of birth control from the time this form is signed until at least 4 months after the last dose of cabozantinib, if you are able to have children. If you are already using a method of birth control, you will need to check with the study doctor or a member of the study staff to make sure it is acceptable. The list below are forms of acceptable birth control:

Highly Effective Contraceptive Methods

- Hormonal contraception associated with the inhibition of ovulation (may be either combined estrogen/progestogen-containing or progestogen only)
    - Oral (pills)
    - Intravaginal
        - NuvaRing®
        - Intrauterine device (IUD) or Intrauterine hormone-releasing system (IUS)
    - Transdermal
        - Patch
    - Injectable
        - Depo-Provera
- Permanent methods
    - Bilateral tubal occlusion (procedure that blocks both fallopian tubes, which prevents eggs from getting to the uterus)
    - Partner who has had a vasectomy

Abstinence is an allowed method of contraception if used during the entire study duration and for 4 months after your last dose of cabozantinib.

If you or your partner becomes pregnant after joining this study, you will have to notify the study doctor immediately. If you become pregnant, you will no longer be able to participate in this study. We would follow-up with you throughout the pregnancy and for about 6 months after the child is born, if you consent to this.

The effects of fathering a child are also unknown. Men who join this study must agree to the following:

- Inform any and all partner(s) of your participation in this trial and the need to comply with contraception instructions as directed by your study doctor
- Use a male condom during heterosexual intercourse or remain abstinent for the study duration and until at least 4 months after the last dose of cabozantinib
- Female partners of male subjects should consider using effective methods of contraception until at least 4 months after the male subject's last dose of cabozantinib

- Agree to not donate sperm for the duration of the study and for at least 4 months after your last dose of cabozantinib.

Non-physical Risks

If you join this study, non-physical risks are:

- You might not be able to work.
- Results of genetic tests might be released by accident.
    - This risk is very low, because we keep personal information private. If these results became known, you could have problems from others knowing about your genetic test results. For example, the results could cause stress or anxiety in family members who learn about their own risk of developing disease, or you could have problems with insurance because of your health status.

What are the benefits?

You may or may not receive any benefit from being in this study. It is possible that you may get better, stay the same, or get worse. If you take part in this study, other people with sarcoma of the extremities may be helped in the future.

We do not know if this study would help you. The use of cabozantinib with radiation therapy in sarcomas of the extremities is still investigational, and we are trying to find the highest safe dose for this combination. We hope the information from this study will help us in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say “yes” or “no”. Your regular medical care would not change if you decide to say “no”.

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Other choices include:

- Chemotherapy
- Radiation therapy
- Hormonal therapy
- Experimental therapy or another research study
- Surgery
- No treatment

The risks and benefits of these other treatments will be explained to you by your doctor. The study doctor will answer any questions you have about these other treatments.

If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home. 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.

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
- Exelixis, the funding source for this study, 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, University of Washington, and Seattle Children's.
- US National Institutes of Health, National Cancer Institute, 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. 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. Or 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 information is used in a publication or presentation, it will be de-identified or used in a grouped manner (aggregate analysis).

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 an insurance company or employer or anyone else were authorized 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 prevent 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.

Would we pay you if you join this study?

There is no payment for being in this study.

Would you have extra costs if you join this study?

The funding source of this study, Exelixis, will provide the study drug to you free of charge. Radiation therapy will be billed to you or your insurance as a standard of care treatment. Study related medical examinations and laboratory tests that are not part of your routine care for your condition will be provided at no charge. You may have to pay for some expenses related to this study, such as transportation to the study site, parking, meals, etc. Exelixis pays the study doctor to conduct the study and covers the cost of study-related tests and procedures.

You or your insurance company will be billed in the usual way for examinations, testing, and treatments that are considered routine and required for the management of your cancer. Some examples of standard procedures include routine laboratory blood tests, x-rays, CT or MRI scans, surgeries, blood transfusions, physicians' charges, and routine medical care.

Ask your study doctor to discuss the costs that will or will not be covered by Exelixis. This discussion should include the costs of treating side effects. Examples of medications you could possibly require in addition to the study medications include antibiotics or other medications to manage side effects of treatment. Otherwise, you might have unexpected expenses from being in this study. Your health insurance company might not pay for these charges because you are in a research study. You are responsible for charges your insurance company does not pay.

You will **not** be billed for: the cost of the study medication (cabozantinib), correlative blood tests for research, tissue slides and curls from a previous biopsy, hepatitis and HIV blood screening tests, echocardiogram or MUGA test (baseline only), 12-lead ECG, lipid testing, coagulation testing (baseline only), or urine protein tests (baseline only).

If you are on a Medicare Advantage Plan, please check with your plan regarding coverage as you may be responsible for certain costs.

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.

For all other medical problems or illness related to this research, immediately contact Dr. Lee Cranmer (206-606-7439). 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

- You do not have to join this study. You are free to say "yes" or "no".
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you do not have to stay in it. You can stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.
- If you decide to drop out, you will need to tell the study doctor. The doctor will tell you about the effects of stopping cabozantinib. You and the doctor will talk about the follow-up care and testing that would help the most.

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)	206-606-7439 (Dr. Lee Cranmer) 206-606-6425 (Roxanne Moore, Assistant Director)
If you get sick or hurt in this study	206-606-7439 (Dr. Lee Cranmer) 206-598-6190 UW operator and ask to page the 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 Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-606-6226 The financial services department at Fred Hutchinson Cancer Center

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

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

Your information and tissue samples (such as 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.

During the study we may learn new information you need to know. For example, some information may affect your health or well-being. Other information may make you change your mind about being in this study. If we learn these kinds of information, we will tell you.

In addition, be aware that by agreeing to participate in this study, your information or tissue samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information or tissue samples. If you do not want your information or tissue samples to be used for future research studies without your consent, you should not participate in this study.

Your tissue contains DNA. DNA makes up the genes that serve as the "instruction book" for the cells in our bodies. By studying genes, researchers can learn more about diseases such as cancer. There are many different types of genetic tests. The testing on your tissue samples might include genetic testing called whole genome sequencing. Whole genome sequencing looks at all the known genes in your cells. This type of testing can provide useful information to researchers. It can also present risks if the test results became known to others, for example you could have problems with family members or insurance companies. There is also a risk that these test results could be combined with other genetic information to identify you.

There are two time points where we may collect additional archival tissue from you. Once during screening and a second one after you have completed study treatment. These archival tissues will only be collected if you are already having a surgery or biopsy as a part of your regular standard of care. Please indicate your choice below if you will allow us to collect this archival tissue:

☐ YES _____ ☐ NO _____
Initials Initials

We invite you to donate tissue samples for other research.

After we do tests on tissue in this study, some tissue may be left over. We invite you to donate this leftover tissue for future research. This may include genetic research.

If you join this study, you would not have to donate tissue for future research. You would be free to say "yes" or "no." Regular medical care would not change if you say "no."

If you donate tissue, it would be stored in a secure location. If we want to use your tissue for other research or share it with other scientists for research, an ethics review committee (IRB) would review the request. The IRB would decide if we need to ask you for permission to do the research.

Your donated tissue would be used only for research. This research could be done by for-profit companies. Researchers would not report their results to you or your doctors. The research results would not be included in medical records. The results would not affect your medical care.

Research with tissue might help develop new products. If these products make money, there is no plan to share the money with the participants who donate the tissue.

If you donate tissue for research, you could withdraw the donation at any time by calling Dr. Lee Cranmer at 206-606-7439. You would have no penalty for withdrawing the donation, and regular medical care would not change. We could not return donated tissue, but we might be able to destroy the donated tissue. We could not destroy tissue if it is stored or shared without any label saying who donated it. In this case, it could still be used for research.

Please read the sentence below and think about your choice. After reading the sentence, check either "Yes" or "No" box and initial next to your choice. If you have any questions, please contact your study doctor.

My remaining tumor tissue from a previous or future surgery or biopsy may be stored and used for analysis.

☐ YES _____ Initials

☐ NO _____ Initials

SUBJECT'S STATEMENT

I have read the information in this consent form (or had it read to me). All my questions about the study and my part in it have been answered. I freely consent to take part in this research study. If I sign this form, I will not lose any of the legal rights that I would otherwise have as a subject in a research study.

CONSENT SIGNATURE:

_____
Subject Name (printed):

_____ _____
Signature of Subject (18 years and older) Date

RESEARCHER'S STATEMENT

I confirm that the research study was thoroughly explained to the subject. I reviewed the consent form with the subject and answered the subject's questions. The subject appeared to have understood the information and was able to answer the following questions correctly:

1. What is the purpose of this study?
2. If you decide to be in the study, what will you be asked to do?
3. What is the possible benefit of participating in this study?
4. What are the possible risks of participating in this study?
5. If you decide not to participate in this study, what options do you have?
6. Will participating in this study cost you anything? If so, what will you have to pay for?
7. Do you have to be in this study?
8. If you decide to be in the study, can you leave the study when you want to?

_____ _____
Printed Name of Person Conducting the Informed Consent Discussion Position

_____ _____
Signature of Person Conducting the Informed Consent Discussion Date

---------- **Use this witness section only if applicable** ----------

If this consent form is read to the subject because the subject is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

_____
Printed Name of Impartial Witness

_____ _____
Signature of Impartial Witness Date

Copies to: Researcher's file
Subject
Subject's medical record (if applicable)