Official Title:	A Phase 2 Trial of Cabozantinib and Pembrolizumab in the First-Line Treatment of Advanced Hepatocellular Carcinoma
NCT number:	NCT04442581
Document Type:	Informed Consent Form
Date of the Document:	May 13, 2021

University of Washington
Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance

Consent to take part in a research study:

A Phase 2 trial of cabozantinib and pembrolizumab in the first-line treatment of advanced hepatocellular carcinoma

Principal Investigator: Kit Wong, M.D. University of Washington; Fred Hutchinson Cancer Research Center. 206-606-7349

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

Important things to know about this study.

You are invited to participate in a research study because you have been diagnosed with advanced hepatocellular carcinoma (HCC), a type of liver cancer. The purpose of this research is to find out if the study drugs cabozantinib and pembrolizumab, given together, are effective for this type of cancer.

If you agree to join the study, the study involves the following parts:

- Medical Screening Evaluation
- Study Treatment
- End of Treatment Visit
- Long Term Follow-up

Study treatment includes a daily dose of cabozantinib taken orally and an IV infusion of pembrolizumab every 3 weeks.

We do not know if cabozantinib and pembrolizumab, would help treat advanced liver cancer. Cabozantinib and pembrolizumab, could cause side effects such as diarrhea, hypertension, abnormal liver tests, endocrine effects, and skin rash

You do not have to join this study. You can choose to receive standard methods to treat your cancer 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 treatment 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 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 advanced HCC. Up to 29 people will join this study.

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 find out if cabozantinib (XL184) and pembrolizumab (KEYTRUDA®), given together, are effective for the treatment of HCC.

The study drug cabozantinib is an oral anticancer drug that is approved in the United States to treat patients with certain types of advanced kidney cancer (renal cell carcinoma) and to treat liver cancer in patients who have previously been treated with sorafenib. Cabozantinib is considered an investigational drug because it is experimental and not approved by regulatory authorities (including the US Food and Drug Administration [FDA]) to treat advanced liver cancer in patients who have not received previous treatment or for use in combination with pembrolizumab. Pembrolizumab is approved to treat hepatocellular carcinoma after a treatment of sorafenib has failed.

The study drug pembrolizumab is considered an immunotherapy, as it may help your immune system fight cancer. Pembrolizumab has been approved by the United States Food and Drug Administration (FDA) to treat certain types of advanced skin cancer, head and neck and non-small cell lung cancer, and stomach cancer. Pembrolizumab is also used to treat some types of solid tumor cancers that have mutations in genes involved in DNA repair.

In this study, we want to learn the effects of cabozantinib given with pembrolizumab in people with advanced HCC carcinoma. If you join this study, we would give you both study drugs and watch carefully for any side effects.

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

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

Medical Screening Evaluation

To confirm you meet the medical requirements for this study, the screening procedures for this study include:

- A thorough review of your medical history within the prior 10 years, including
    - smoking history
    - any medical conditions or diseases you may have, and
    - any medications you may be taking now or have used within 28 days before starting the study
- Physical examination, including weight
- Vital signs (Blood pressure and pulse, respiratory rate, oxygen saturation, temperature, height.)
- Assessment of your overall general health (performance status)
- Blood tests to evaluate:
    - Routine blood work to measure blood cell counts, to determine how well your blood clots, and to measure thyroid, kidney and liver functions.
    - The level of alpha-fetoprotein (AFP) in your blood; AFP is a protein produced by the liver and is used to help detect, diagnose and monitor liver cancer.
    - Presence of hepatitis B and/or C viruses (HBV and/or HCV).
        - NOTE: the study doctor may have to report any positive results from your HBV and/or HCV test to your state's health department, depending on the regulations in your state. If you do not want results from your blood test(s) reported to your state's health department, you should not consent to be in this study.
- Electrocardiogram (ECG): A research test to measure the electrical activity of your heart
- Pregnancy test, if you are a woman of child-bearing potential. This will be done using a small sample of blood, within 14 day of your registration on the study.
- CT scan or MRI to assess your tumor, if one was not performed as part of your standard clinical care within 28 days prior. The scan of your chest, stomach and pelvis allows the study doctor to measure the size and location of your tumor(s).
    - CT scan (an x-ray linked to a computer that provides pictures of the inside of your body) or
    - MRI (radio waves and a powerful magnet, linked to a computer, to take pictures of the inside of your body)
- Confirmation of diagnosis of HCC from previous tumor biopsy or imaging test.
    -
        - Archival tumor tissue will be requested, if available, to study biomarkers, which may help to predict who may respond to

treatment. If archival tissue is not available, an optional research biopsy may be performed if safe and feasible.

Study Treatment Overview
If you meet the study requirements during the screening period, you will be treated with cabozantinib and pembrolizumab in 3-week treatment cycles. A cycle is 21 days. You will receive the following treatment regimen beginning on Day 1 of your first Cycle.

- Cabozantinib: 40mg daily by mouth
- Pembrolizumab will be administered intravenous (through the vein or IV) every 3 weeks, on Day 1 of each cycle.

Cabozantinib Instructions

- Cabozantinib must be taken daily on an empty stomach. You must not to eat for at least 2 hours before and at least 1 hour after taking cabozantinib.
- Take your cabozantinib dose at approximately 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.
    - The missed dose should not be made up if it is within 12 hours of the next scheduled dose.
- Cabozantinib tablets should be swallowed whole with at least 8 ounces of water. The tablets should not be crushed. Grapefruit, grapefruit juice, Seville oranges, star fruit, and their products should be avoided.

Cabozantinib Drug Diary

You will receive a Cabozantinib Drug Diary to record the date and time of each dose of cabozantinib taken. Study staff will give you a new diary on the first day of each Cycle.

Day 1 of Each Cycle (every 3 weeks)
For Day 1 of each Cycle, the following assessments will be performed prior to each pembrolizumab treatment:

- Physical examination, including weight
- Vital Signs (Blood pressure and pulse, respiratory rate, oxygen saturation, and temperature)
- Assessment of your overall general health (performance status)
- Review of any medications you are taking or have taken since your last visit or changes to medications in addition to the study treatment
- Review of any side effects or other medical problems you have had since your last visit
- A new Cabozantinib Drug Diary provided by study staff. Bring previous drug diary for collection by study staff.
- Blood collection for:
    - Routine blood work to measure your overall health, blood cell counts, to determine how well your blood clots, and to measure thyroid, kidney and liver functions.
    - Research blood on Cycle 1 Day 1 and Cycle 2 Day 1.

    If your alpha-fetoprotein (AFP) level, the protein used to help detect and monitor liver cancer, was higher than normal during Screening, it will measured on Day 1 of Cycle 4 and every 3 cycles, thereafter.

For Cycle 1 Day 1, tests completed within 7 days prior do not need to be repeated.

ECG will be performed for research at Cycle 3 and repeated every 2 Cycles.

Cycle 1 Day 8 Assessments
On Day 8 of your first Cycle, health assessments and research blood collections will be performed:

- Physical examination, including weight
- Vital Signs (Blood pressure and pulse, respiratory rate, oxygen saturation, and temperature)
- Assessment of your overall general health (performance status)
- Review any changes to medications you are taking in addition to the study treatment
- Review of any side effects or other medical problems you have had since your last visit
- Research blood collection

Cycle 1 Day 15 Assessments
On Day 15 of your first Cycle, health assessments and routine blood collections will be performed:

- Physical examination, including weight
- Vital Signs (Blood pressure and pulse, respiratory rate, oxygen saturation, and temperature)
- Assessment of your overall general health (performance status)
- Review any changes to medications you are taking in addition to the study treatment
- Review of any side effects or other medical problems you have had since your last visit
- Blood collection for routine and research blood work to measure your overall health.

CT/MRI scans on Treatment
A repeat CT or MRI will be performed every 9 weeks (every 3 cycles, beginning with Cycle 4). This allows your tumor to be measured and evaluated.

If there is evidence your cancer has worsened (disease progression) and you continue study treatment, a repeat scan will be performed 4 weeks later to further evaluate your tumor.

End of Treatment Visit
An End of Treatment Visit will occur approximately 30 days after your last dose of cabozantinib or pembrolizumab (whichever is later). If you begin a new anti-cancer therapy sooner, the End of Treatment Visit will be scheduled before the first dose of your new therapy. The following will be performed or collected at the end of treatment visit:

- Physical examination, including weight
- Vital Signs (Blood pressure and pulse, respiratory rate, oxygen saturation, and temperature)
- Assessment of your overall general health (performance status)
- Review any changes to medications you are taking
- Review of any side effects or other medical problems you have had since your last visit
- Blood collection for routine and research blood work to measure your overall health, blood cell counts, to determine how well your blood clots, and to measure thyroid, kidney and liver functions.
    - If your alpha-fetoprotein (AFP) level was higher than normal during Screening, it will be monitored and tested as part of routine care, as well as at the End of Treatment visit.
- Review of your most recent CT/MRI imaging

How long would you stay in this study?

If you join this study, you may be treated with cabozantinib and pembrolizumab for a maximum of 2 years. If one of the study drugs needs to be discontinued for adverse events, treatment with the remaining study drug may continue.

As confirmed above, your End of Treatment Visit will occur approximately 30 days after your last dose of cabozantinib or pembrolizumab (whichever is later). After that, study staff will follow-up with you by phone every 4 months for up to 3 years.

Your study doctor could take you out of this study at any time. This would happen if:

- There is evidence your cancer has worsened (disease progression) unless certain criteria are met including:
    - Patient is tolerating treatment
    - Patient is receiving clinical benefit from ongoing treatment
    - Disease progression is asymptomatic and does not pose a risk
    - Patient has stable ECOG performance status
    - Treatment beyond progression will not delay intervention to prevent disease progression
- Your health changes and the study is no longer in your best interest
- You are not able or willing to follow study procedures
- New information becomes available.
- 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 could not be removed from the study records.

Long-term follow-up means keeping track of someone's medical condition for a long time. If you join this study, we will contact you by phone every 4 months for up to 3 years to see how you are doing.

If you came off the study for adverse events, every 4 months we would ask your doctor to send a copy of your medical records to follow your disease status. We would also collect information about your subsequent anti-tumor therapy and request copies of restaging scans. This information will help us learn whether the study treatment has long-term effects in hepatocellular carcinoma.

Long-term follow-up would occur for up to 3 years from the date you start treatment. You do not have to be in long-term follow-up. You could say "yes" or "no". Either way, you could still join this study. If you drop out of the study, you would be asked if we could call you by phone every 4 months to see how you are doing.

If you choose not to join long-term follow-up, you would not be contacted regularly, and we would not ask your doctor to send medical records, but we might still need to contact you for some other reason.

What are the side effects (risks)?

In this part of the consent form, we describe possible side effects or risks from participating in this study, including study tests and treatments. Cabozantinib and pembrolizumab 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 would tell you if we discover new side effects that could affect you.

This form lists side effects of *individual* drugs. Other side effects could occur when we use these drugs *together*.

Here are important points about side effects:

- 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.

Side effects may be mild or very serious. Tell the study doctor if you notice or feel anything different. The study doctor may be able to treat some side effects or adjust the study drug(s) to try to reduce side effects.

Side Effects of Cabozantinib (XL184)

In studies of cabozantinib given alone, side effects related to cabozantinib have been reported in patients with many different types of cancer. The following is a comprehensive list of side effects reported as related to cabozantinib:

Very Common Side Effects that Occurred in greater than or equal to 10% of Cancer Patients (greater than or equal to 1 in 10) Treated with Cabozantinib Alone

- 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
- Change in 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 That Occurred ≥ 1% but < 10% of Cancer Patients (≥ 1 in 100, but < 1 in 10) Treated with Cabozantinib Alone

- Abnormal thickening of the outer layer of the skin
- Change in the feeling of touch
- Cough
- Bleeding, including bleeding from 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 or 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
- Dermatitis acneiform, a type of acne
- Dehydration
- Difficulty swallowing
- Dizziness
- Dry mouth
- Dry skin
- Fever
- Fungal infections including mouth, lung, and other locations

Common Side Effects That Occurred ≥ 1% but < 10% of Cancer Patients (≥ 1 in 100, but < 1 in 10) Treated with Cabozantinib Alone

- 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 extremities
- 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 That Occurred ≥ 0.1% but < 1% of Cancer Patients (≥ 1 in 1000, but < 1 in 100) Treated with Cabozantinib Alone

- 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
- Abscesses (infected cavities filled with pus)
- Blood clot in an artery
- Chest discomfort originating from the heart
- Clouding of the lens in the eye that affects vision
- 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

Uncommon Side Effects That Occurred ≥ 0.1% but < 1% of Cancer Patients (≥ 1 in 1000, but < 1 in 100) Treated with Cabozantinib Alone
• Respiratory failure • Seizure • Stroke / mini-stroke • Tear or inflammation in skin that lines the anus • Uncoordinated movements

Side effects that occurred in less than 0.1% of patients (less than 1 out of 1000) but were considered medically important or severe or life-threatening and rarely fatal are listed in the table below. These events occurred in studies of cabozantinib given alone. If you are at the clinical site and notice any signs or symptoms of the side effects listed below, check with the staff in the clinic immediately; if you are no longer at the clinical site, call your doctor or go immediately to the nearest hospital.

Rare but Medically important Side Effects not listed above that Occurred greater than or equal to 0.01% but less than 0.1% of Cancer Patients (greater than or equal to 1 in 10000, but less than 1 in 1000) Treated with Cabozantinib Alone
• Air in the chest between lungs and chest wall • Allergic reaction • Anemia caused by destruction of red blood cells • Blocked intestines • Brain dysfunction caused by brain swelling • 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 and which can lead to serious injury to the heart and brain

Side Effects of Pembrolizumab

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in immune-related side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

VERY COMMON Side Effects of Pembrolizumab

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools (diarrhea)

- Cough

COMMON Side Effects of Pembrolizumab

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Rash
- Fever
- Back pain
- Pain in your belly
- Loss of skin color (paleness)
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

UNCOMMON Side Effects of Pembrolizumab

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone (hyperthyroidism) so you may feel:
    - anxious,
    - angry,
    - have trouble sleeping,
    - feel weak,
    - tremble,
    - sweat,
    - feel tired,
    - have loose and watery stools
- Infusion reaction, where you may feel:
    - dizzy or faint,
    - flushed,
    - get a rash,
    - have a fever,
    - feel short of breath
    - experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after,
    - or pain at the site of infusion
- Inflammation of the bowels/gut, which may cause:
    - severe pain in your belly with loose or watery stools,
    - and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itchiness, and/or

skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection.

RARE Side Effects of Pembrolizumab

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the nerves that may cause:
  - pain,
  - weakness,
  - tingling in your hands and feet, that may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis (neuropathy)
- Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat (pancreatitis)
- Inflammation of the eye (uveitis) so you may have:
  - eye redness,
  - blurred vision,
  - sensitivity to light,
  - eye pain,
  - see floaters,
  - or have headaches
- Inflammation of the liver (hepatitis) that may make you feel:
  - sick to your stomach and vomit,
  - feel like not eating,
  - feel tired,
  - have a mild fever,
  - have a pain in the right side of your belly,
  - yellow eyes and skin,
  - and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel:
  - sick to your stomach or have headaches,
  - changes in your behavior,
  - double vision,
  - few to no menstrual cycles,
  - weakness,
  - vomiting,
  - and dizziness or fainting
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause:

    - tiredness,
    - weight loss,
    - muscle weakness,
    - feeling faint,
    - joint, muscle and belly aches,
    - nausea, vomiting,
    - loose or watery stools,
    - fever,
    - salt craving,
    - and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause
    - chest pain,
    - shortness of breath,
    - and swelling of the legs (myocarditis).
    - You may experience a fast or irregular heartbeat that may cause dizziness or fainting.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to
    - change in your heart rate,
    - blood pressure,
    - body temperature,
    - and the rate at which food is converted into energy (thyroiditis)
- A condition that may make you feel:
    - weak and tired
    - and might have drooping of the eyelids, blurred or double vision,
    - difficulty swallowing,
    - slurred speech,
    - weakness in your arms and legs,
    - or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include:
    - disorientation,
    - memory problems,
    - seizures (fits),
    - changes in personality and behavior,
    - difficulty speaking,
    - weakness or loss of movement in some parts of your body,
    - and loss of consciousness
- Inflammation of the blood vessels (vasculitis)

Additionally, since pembrolizumab was approved in September 2014, the following

side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints, which may include
  - Joint pain
  - Stiffness
  - Swelling
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma.
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis), such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

Possible Side Effects of Biopsy

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising.

Rarely, an infection, moderate or major bleeding, a hole in the intestines (bowel perforation) or damage to organs next to the liver may occur. Additional side effects may be possible depending on whether and what type of numbing medication, pain medication and/or IV sedatives are used during the procedure. The doctor will review any potential side effects of these medications with you.

Risks Associated with CT Scans

The CT scans 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, water, soil, and the food you eat. Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose. There is minimal risk to your health from the amount of radiation you will receive in this study. If you have more procedures that expose you to radiation, your risk will go up. For comparison, the estimated radiation dose from each of these tests is listed below:

- CT chest: 7 mSv
- CT pelvis: 6 mSv
- 4-Phase Liver CT: 20 mSv

- CT guided biopsy: 5 mSv

There may be other risks or side effects with the procedures listed above that are unknown at this time.

The contrast dye given during a CT scan may cause an allergic reaction, in rare cases. The contrast dye also rarely can cause kidney damage, and this is more likely if you are dehydrated or have diabetes. You may experience fear of being in a narrow or enclosed space (claustrophobia) while having a CT scan.

If you have had a previous reaction to Gadolinium-based contrast agents or a history of severe allergies, please notify the operator/Study Doctor.

Risks Associated with MRI Scans

While you are in this research study, an MRI (Magnetic Resonance Imaging) scan may be used to evaluate your disease. When having an MRI scan, you will lie still on a table that slides into a tunnel slightly wider than your body.

People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tunnel. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Reproductive risks

You should not get pregnant, breastfeed or father a baby while on this study. Cabozantinib and pembrolizumab could be damaging to an unborn baby. Men must agree to use effective methods of birth control unless they are surgically sterile (vasectomy) from the time of informed consent to 120 days after the last dose of cabozantinib or pembrolizumab, whichever dose is later. Women of childbearing potential must agree to use effective methods of birth control from the time of informed consent to 120 days after the last dose of cabozantinib or pembrolizumab, whichever dose is later. Women of childbearing potential are defined as: (1) has not had an effective tubal ligation (tubes tied) or (2) has not had ovaries or uterus removed or (3) is not post-menopausal (at least 12 months since last menstrual period and not possibly due to prior chemotherapy, antiestrogens, low body weight, ovarian suppression or other reasons). Effective forms of contraception that are acceptable for this study include:

- Combined oral contraceptive pill and mini-pill
- NuvaRing®
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (IUD)
- Contraceptive patch for women <90 Kg (<198 pounds)
- Bilateral tubal occlusion (procedure creating a barrier in the fallopian tubes) or hysterectomy with bilateral salpingo-oophorectomy (removing both ovaries and fallopian tubes)
- Vasectomy (male subject or female subject's male partner)

All subjects (male or female): If you or your partner become pregnant after joining this study, you would have to notify the study doctor immediately. For female subjects who become pregnant while on this study, your participation in this study would end. You would receive counseling and follow-up throughout the pregnancy and for about 6 months after the child is born.

Non-physical risks

If you join this study, you may lose time at work or home and spend more time in the hospital or clinic than usual.

Other possible side effects

We do not know if this study would help you. We are testing cabozantinib and pembrolizumab to see if the combination of these drugs helps to treat advanced liver cancer. You might get better, but your condition could stay the same or even get worse. We hope the information from this study will help other people with advanced hepatocellular carcinoma 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: Standard Treatment, Another Research Study, No Treatment, or Comfort Care.

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.
- Kit Wong, M.D. (the Principal Investigator) and any persons or companies that are working with or for the Principal Investigator.
- Exelixis, Inc., the funding source and cabozantinib drug supplier, and their agents.
- Merck, the pembrolizumab drug supplier, 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 Research Center, University of Washington, and Seattle Cancer Care Alliance.
- 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. 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. Or a court may order study information to be disclosed. Such cases are rare.

We will not use your 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 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 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.

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?

If you join this study, you would 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 administration of pembrolizumab. There is no charge for the study drugs, cabozantinib and pembrolizumab, themselves.
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care needed because of this study.

Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for. You may be responsible for a certain amount of the charges billed to your healthcare insurer, a deductible, or have a co-pay for certain testing.

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 your study doctor. 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.

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.

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.

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 would not have to stay in it. You could 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, we would want you to tell the study doctor. The doctor could tell you about the effects of stopping cabozantinib and pembrolizumab. You and the doctor could talk about the follow-up care and testing that would be best for you.
- efore you leave the study, the doctor might ask you to continue in the long-term follow-up part of the study.

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.
- Take study medications as directed.
- Prevent pregnancy.
- Tell us about side effects.

For more information

If you have questions or concerns about this study, you can 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)	206-606-7349 (Dr. Kit Wong)
If you get sick or hurt in this study	206-606-7349 (Dr. Kit Wong)
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	The financial services department at Seattle Cancer Care Alliance at (206) 606-6226 or toll-free (800) 304-1763.

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

Signatures

Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask any questions you have;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to participate in this study.

Participant:

Printed Name	Signature	Date

If you served as an interpreter or impartial witness during the consent process, sign below to indicate you attest to the accuracy of the presentation and the participant's apparent understanding of and willingness to participate in the research.

Impartial Witness or Interpreter:

Printed Name	Signature	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	Signature	Date

Protocol: RG1007034
Current consent version date: 16Apr2021
Previous consent version date:16Mar2021
Copies to: Research file; Subject's medical record