ID: UMCC 2020.007	Cabozantinib in Patients With Advanced Hepatocellular Carcinoma With Child Pugh Class B Cirrhosis After First-Line Therapy	NCT04497038

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THE STUDY

Study title: Phase 1/2 Trial to Evaluate Cabozantinib in Patients with Advanced Hepatocellular Carcinoma with Child Pugh Class B Cirrhosis after First-Line Therapy

Company or agency sponsoring the study: The University of Michigan along with support from Exelixis, Inc.

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):

Principal Investigator: Vaibhav Sahai, MBBS, MS, Department of Internal Medicine, University of Michigan
Co-Principal Investigator: Neehar Parikh, MD, Department of Internal Medicine, University of Michigan
Site Principal Investigator: Thomas Enzler, MD, PhD, Department of Internal Medicine, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. All information in this form is important. This form contains information that will help you decide whether to join the study. All information in this form is important. Take time to carefully review this information. After you finish, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your friends, family, or other doctors about your participation in this study. If you decide to take part in this study, you will be asked to sign this form. Before you do, be sure you understand what the study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor, Michigan or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying the use of a new drug in small numbers of people to learn about its safety, tolerability and its effect on your body at certain doses as a treatment for Advanced Hepatocellular Carcinoma with Child Pugh B cirrhosis after First-Line Therapy. Researchers want to understand how the drug works in your body and how your body will react to it. This study will be using the drug cabozantinib. You will take cabozantinib by mouth. Others procedures that will take place throughout the course of the study include physical exams, blood draws, scans of your cancer, urine collection (females) along with other items listed later in this document. Your health-related information and biospecimens (blood and tissue) will be collected for this research study.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to

join the study. For this study, a brief list of some of most commonly seen risks may include weakness, diarrhea, hypertension, nausea, vomiting, loss of appetite, blisters, rash, or pain in hands or feet and changes to the way things taste. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but may benefit others in the future by helping people to live longer or improve the quality of life.

We expect the amount of time you will participate in the study to vary depending on how your disease responds to the study intervention and if you have any major side effects and could be up to three years.

You can decide not to be in this study. Alternatives to joining this study include receiving standard of care treatment for this disease, taking part in a different study, receiving palliative care, or having no treatment.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This is a Phase I/II study which means that the goals are to see if the investigational drug cabozantinib is safe as well as whether it is effective in improving outcomes. The first part of the study will try to find out what effects, good and/or bad, this drug has on you and your cancer, and to find a dose to use in the second part of the trial.

Hepatocellular carcinoma (HCC) is the 3rd leading cause of cancer related death worldwide. Patients with advanced hepatocellular cancer with Child-Pugh B cirrhosis, that is unable to be removed with surgery, have no options for treatment based on current guidelines and available evidence.

The purpose of this study is to determine the safety and effectiveness (how well the drug works) of cabozantinib in the management of HCC in this patient population.

On January 14, 2019, the Food and Drug Administration approved cabozantinib for patients with advanced HCC with Child-Pugh A who have been previously treated with sorafenib. This approval was based on the CELESTIAL clinical trial that looked at cabozantinib versus placebo in 707 patients with HCC, and the patients taking cabozantinib showed an increase in overall survival versus the patients who received placebo. The patients in the CELESTIAL study had mild liver impairment (Child-Pugh Class A) so this study will be considered research as it is looking at how well cabozantinib works in HCC patients with moderate liver impairment (Child-Pugh Class B)**.**

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Adult men and women with hepatocellular carcinoma that cannot be treated with surgery, transplant, or ablative therapies (therapies that destroy abnormal tissue without destroying the tissue).

There are many other inclusion and exclusion criteria which the doctors will use to determine if you can participate in this study. It is important that you discuss your full medical history and all of your medications with your doctor.

3.2 How many people are expected to take part in this study?

A total of approximately 32 subjects at several institutions will take part in this study, including approximately 10 from the University of Michigan**.**

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

The study team will explain the research study and answer any questions you have about the study. If you want to participate in the study, the study team will request you sign the consent form prior to any activities that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Many of the procedures that will be performed during the study, including routine blood tests, tumor evaluations (radiology scans), physical examinations, vital signs (blood pressure, heart rate, breathing rate, and temperature) and measurement of height and weight, would normally be done as part of your standard of care regardless of study participation. However, some of these may be done more frequently as a result of your participation in this study. Administration of the study drug, tissue and some blood sample collection and analysis are solely for research purposes. Tests and procedures that are done more often than your regular medical care because of your study participation and that are solely for research purposes will be identified below. The study staff will inform you of the types of tests and procedures you have to undergo during the study.

During the study you must:

- Follow the instructions you are given.
- Come to the study center for your visits with the study doctor.
- Tell the study doctor or study staff about any changes in your health and/or medications you are taking.
- Tell the study doctor or study staff if you want to stop being in the study at any time.

Before starting the study:
Some exams, tests, and procedures will be required to find out if you can be in this study. If you have had some of them recently, they may not need to be repeated. The screening tests and procedures do not have to be completed in one day and you are allowed to take breaks if you have multiple procedures in one day.

The following tests and procedures will be performed during screening and/or at one or more study visits. Refer to the study calendar below for information about which procedures will be performed at certain study visits.

- **Medical history**: including any past treatments, surgeries, infection and autoimmune diseases.

- **Medications**: It is important that you tell your doctor about all of the medications that you have been taking, including over the counter medicines, vitamins or herbal treatments.

- **Physical exam/Vital Signs**: including measurement of your height, weight, blood pressure, heart rate,
- respiratory rate and temperature.

- **Performance status**: Your ability to perform day to day activities and care for yourself

- **Routine blood tests** (approximately 2 teaspoons): will be drawn for tests to check blood counts, chemistry, health and blood markers for cancer

- **Pregnancy test**: (urine or blood – approximately 1 teaspoon): if you are a woman able to have children

- **Scans of your cancer**: these could include Computed tomography (CT) of the chest, CT or magnetic resonance imaging (MRI) of the upper and lower belly. The scans will be sent to a central location in a coded format.
    - o A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.
    - o A MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie down on a narrow bed which will slide into a tunnel that is 6 feet long by 22 inches across and is open at each end. You will be asked to lie quietly for about one hour, during which time you will hear a loud machine-like noise. A MRI scan takes about an hour and a half to complete.

- **Blood for Research**: About 4 teaspoons of blood will be collected at each visit listed below. Samples will be collected at the following time points. This is for research purposes.
    - o Pre-treatment: Cycle 1 Day 1
    - o On-Treatment: Cycle 4 Day 1
    - o Post-Treatment: End of Treatment (EOT)

- **Blood for Pharmacokinetics (PK):** About half a teaspoon of blood will be collected at each visit listed below. This is for research purposes.
    - o Week 3 Predose: Cycle 1 Day 15
    - o Week 5 Predose: Cycle 2 Day 1
    - o Week 7 Predose: Cycle 2 Day 15
    - o Week 9 Predose: Cycle 3 Day 1

- **Toxicity evaluation**: You will be asked about any side effects or illnesses you experience.

- **ECG:** an electrical tracing of your heart rhythm
    - o Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity

- **Tumor tissue**: Your doctor will check to see if you have enough stored tissue sample of your tumor that was collected previously and submit to study for research analysis. If you do not have enough stored tissue, you will not be asked to undergo a fresh tissue biopsy prior to starting treatment.
    - o If there is a biopsy done after completion of study treatment the tissue will need to be shared with study team.

Study Intervention:
If you qualify to participate in the study based on the results of the screening tests and procedures, you will return to the study doctor's clinic.

You will take cabozantinib by mouth every day.

Below are general rules for taking cabozantinb:

- Take without food (Do not eat at least 2 hours before and at least 1 hour after taking the medication).
    - Swallow whole (do NOT chew, crush or cut the capsule)
    - The medication SHOULD NOT be ingested if broken, cracked or otherwise not intact
- If you miss a dose, take it later only if it is within 12 hours of when the missed dose should have been taken. Do NOT make up the missed dose if it's after 12 hours of when your missed dose should have been taken

If you experience adverse events, you may have to stop taking the study drug and if you recover from your adverse event, you may be able to restart the study drug.

You will continue to receive the study intervention for up to two years as long as you are tolerating the treatment and your disease hasn't progressed.

Follow-up:

If you stop the study intervention for any reason you will be asked to return for end of treatment visit 30 days after your last dose of study intervention.

After you complete the study intervention visit you will have an office visit, or be contacted by a member of the study team every 3 months for up to 2 years from when you stopped the study intervention.

See the table below for a summary of the study intervention and procedures.

Study Calendar							
Procedures	**Screening**	**Cycle 1**		**Cycle X**		**EOT Visit**	**Follow-Up Every 3 months +/- 1 week**
		Day 1	**Day 15**	**Day 1**	**Day 15**		
Informed consent	X						
History, physical Examination	X	X		X		X	
Weight, height	X	X		X		X	
Vital signs (heart rate, temperature, etc.)	X	X	X	X		X	
Toxicity evaluation by		X	X	X			

your physician							
Scans with tumor measurements	X			Every 8 weeks			
12 lead ECG	X						
Follow-up every 3 months for survival							X
Routine blood tests							
CBC with differential, CMP	X	X	X	X			
Tumor marker (AFP)		X		X		X	
PT/INR, PTT	X						
TSH, Free T4 and T3		X		X			
Routine urine tests							
Pregnancy test (blood or urine)	X						
Urine protein creatinine ratio		X		X			
Research procedures							
PK blood			X	X	X		
Research blood		X		X		X	
Tumor tissue collection, if available	X						X
Study drug administration		X	X	X			

EOT, end of treatment; ECG, electrocardiogram; CBC, complete blood count; AFP, alpha-feto protein; PT, prothrombin time; INR, international normalized ratio; PTT, partial thromboplastin time; TSH, thyroid stimulating hormone; PK, pharmacokinetics.

Research Samples Stored for Future Use:

We will keep some of your research blood and tissue samples, as well as medical information (such as gender, race, and how your cancer responded to the treatment, etc.) so that we may study them in future research. The future research may be similar to this study or may be completely different. Your samples would be kept at the University of Michigan. Samples will be stored indefinitely or until they are used up.

By taking part in this study, you are giving us your permission to use your blood, tissue and medical information for future research. Even if you give us permission now to keep some of your blood, tissue and medical information, you can change your mind later and ask us to destroy it. Keep in mind, however, that once we have analyzed your blood and tissue, we may not be able to take the information out of our research.

We may share your blood, tissue and medical information with other researchers, so that they can use it in their research and evaluations of how the study regimens function in the body with the overall aim of helping future patients. No identifiable information that could be directly linked to you will be provided. Their research may be similar to this study or may be completely different. Once we have shared your blood, tissue and medical information with other researchers, we will not be able to get it back.

You will not find out the results of future research on your blood and tissue samples. Allowing us to do future research on your blood, tissue and medical information will not benefit you directly.

The University of Michigan, the investigators or a collaborating researcher may benefit financially from future

research on your blood, tissue and medical information.

Loss of Confidentiality

Your samples will be coded however there is a risk of loss of confidentiality of your information. If your samples are provided to research collaborators the following information may be made available: your diagnosis and treatments, the time the samples were collected in relation to your study regimen, your disease status, and demographic data (for example gender, race, age, etc.). Please ask the Study Doctor or Study Nurse if you would like to know more about how your information will be protected.

4.2 How much of my time will be needed to take part in this study?

The initial screening visit will take approximately 2-5 hours. Each study visit is expected to take approximately 4-6 hours. Patients will be followed every 3 months via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment.

4.3 When will my participation in the study be over?

The maximum time you will be in the study can be up to 3 years, but will depend on how your disease responds to the study intervention and how well you tolerate the study intervention. After you stop taking the study intervention you will be asked to come back for an end of treatment visit and the study team will follow you via telephone or an office visit every 3 months for up to 2 years from when you stopped taking the study intervention, or 3 years after the first date you started the study intervention. Your participation may end sooner if you decide to no longer participate, your study doctor feels it is in your best interest to stop your study participation, your disease progresses or the study is ended. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your regular physician first.

4.4 What will happen with my information and/or biospecimens used in this study?
Your biospecimens and collected information may be shared with Exelixis, Inc.

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The drug used in the study may cause certain side effects and discomforts. You may have all, some, or none of the known side effects. There is also a risk that other rare or unknown side effects may occur. Your doctors and nurses will check you closely for side effects, and may give you medicines or other treatments to stop or reduce some of these effects. Some side effects may go away soon after the study medication is stopped, but in some

cases, side effects may be serious, long lasting, and/or permanent. There is even a chance that a side effect may cause death. If you have any side effects, it is important that you report them to your study doctor or research staff.

These risks will be minimized by monitoring you carefully. We will provide the usual supportive care that would be routinely given to someone with your condition. If you have side effects from the study intervention, we will make appropriate adjustments as defined by the study protocol. You may need to discontinue the study intervention if the side effects are too serious.

The known or expected risks are:

Side Effects ASSOCIATED WITH CABOZANTINIB

Very Common Side Effects that Occurred in ≥ 10% of Cancer Patients (≥ 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 acne
- 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
- 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
- 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 / mini-stroke
- Tear or inflammation in skin that lines the anus
- Uncoordinated movements

Side effects that occurred in less than 0.1% of patients but were considered medically important or severe or life-threatening and rarely fatal are listed in the tables 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 ≥ 0.01% but < 0.1% of Cancer Patients (≥ 10000, but < 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
- Enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall
- Blood vessel inflammation associated with possible bleeding, bruising, and/or rash

Risks of CT Scan
The contrast substance injected during the CT scan may cause pain, burning feeling, sweating, and rarely a serious allergic reaction that can be serious. If you know you're allergic to iodine you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated and if you're older. In addition, your thyroid function may be affected. Please inform your doctor if this is the case.

CT imaging uses ionizing radiation, which increases your risk to develop cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation. The estimated additional lifetime risk of developing a fatal cancer from a standard CT scan is approximately 1 in 2,000.

Risks of MRI Scan
Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation.

The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF). This causes a thickening of the skin, organs and other tissues, and is a rare complication in patients with kidney disease that undergo an MRI with contrast material. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

Blood tests
Blood samples will be taken from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include dizziness and fainting

Tumor tissue collection
A piece of a tumor will be collected for research, if available from prior surgery or biopsy.

- Genetic material, including DNA and RNA, will be obtained from samples, stored in freezers, and used for profiling and analyzing your cancer. Specifically, the study includes DNA sequencing of your tumor and normal cells as a comparison. The goal is to identify key changes in the genes important to cancer cells that could potentially influence clinical decision making for your cancer. However, success or clinical benefits from the profiling of your cancer DNA is not guaranteed.

- Analysis of the sequencing data will be used for research purposes, for example to discover new, unknown associations between genes and cancer. This type of research may affect the lives of future patients with cancer.

  It is possible that a mutation found in the tumor DNA is also a mutation in your normal tissue (inheritable,

or passed down in families). Since we are not testing normal tissue, we cannot tell if an abnormal gene in the tumor could also be in your normal (non-tumor) cells. Your study doctor will discuss this result with you. If your test results show that you have gene mutations that are possibly inherited, your doctor may recommend that you meet with a genetic counselor and, if warranted, undergo further genetic testing on non-tumor tissue to determine if the mutation is inherited. This type of testing is considered standard care and is not part of this study.

- As with all medical screening tests, there is a chance of a false positive or a false negative result. A "false positive" refers to the identification of a genetic change that is not present. A "false negative" is the failure to find a genetic change that indeed exists. The tests have been designed to ensure that the possibility of incorrect results is low.

Risks of Electrocardiogram (EKG) or heart trace
Small sticky pads will be stuck to your chest, shoulders and hips and a machine will measure the electrical activity of your heart. The study staff may need to clip small patches of your hair in these areas. These sticky pads may cause some local irritation and may be uncomfortable to remove.

Risks of Pregnancy
If you are a woman of child bearing potential, you must not have sexual intercourse or you must use reliable birth control throughout the study and for 4 months after the last dose of study drug. The study doctor will discuss methods of birth control with you if needed.

If you are pregnant or become pregnant or are nursing a child during the study, there may be risks to your unborn baby or nursing child. Some drugs cause premature (early) birth or birth defects. Nobody knows what all of these risks are right now.

If you become pregnant or think you may be pregnant during the study, **immediately** stop using the study drug and contact the study doctor's office immediately. You must not breast-feed an infant during the study.

Please also inform the study doctor if you become pregnant up to 4 months after the completion of the study drug.

Women of child-bearing potential (not surgically sterilized and between menarche and 1-year post menopause) and men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation (including study breaks), and for 4 months following completion of study therapy.

You must talk to the doctor before changing any birth control methods you have already agreed to use.

Primary forms	Hormonal forms	Barrier forms
• Tubal sterilization (tubes tied)	• Birth control pill • Hormonal intrauterine device	• Male latex condom with or without spermicide
• Partner's vasectomy	• Birth control injections (Depo-Provera)	• Diaphragm with spermicide
• Abstinence	• Vaginal rings (NuvaRing)	• Cervical cap with spermicide

- Birth control implants (Nexplanon)
- Birth control patches (Ortho Evra)
- Vaginal sponge (contains spermicide)

Any birth control method can fail. The reports of birth control failing are more frequent for female patients who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

MEN
All men must use two acceptable forms of birth control (hormonal plus barrier or 2 barrier forms) OR abstinence while taking part in the study and for 4 months after treatment has stopped because the effects on sperm are not known. Also, men should not donate sperm or semen while taking part in the study because the effects on sperm are not known.

The study doctor must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished. If you become pregnant during the study, the study doctor or his/her staff will ask to contact you and your pregnancy physician for information about the pregnancy until the child is born and may share this information with the sponsor.

Genetic Risks:
The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment
- GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:
- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You will not receive any direct personal benefits from being in this study. However, others may benefit from the knowledge gained from this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You do not have to be in this study to get treatment for your cancer. You have the option to receive other treatment for your cancer, participate in other research trials, receive other care for your disease, or choose not to receive any treatment. You should talk to your study doctor and your regular physician about each of your options and their risks and benefits before you decide if you want to take part in this study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information”.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

If you decide to leave the study early, please notify someone on the study team. They will instruct you on how to stop the study safely and you will be advised whether any additional test may need to be done for your safety.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' telephone number listed in Section 10.1.

The study drug cabozantinib will be provided by Exelixis, Inc. free of charge.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.
The pre-treatment and end of treatment biopsy are mandatory and the cost will be paid for by the study.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Enzler immediately, at 734-647-8902 (Clinic) or 734-936-4000 (Hospital Operator; 24-hour paging). The doctor will either treat you or send you to another doctor for treatment.

If taking part in the study makes you sick or causes you injury, you or your insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will be paid to take part in this study. However, to cover your travel cost, you will be eligible to receive $50 per study visit, up to 12 completed visits (up to 600 US dollars beginning with cycle 1 day 1), via gift card. Initial

request is payable at the completion of the first treatment visit, subsequent payments are based on completion of study visits. The University of Michigan will be responsible for payments. In order to process your payment, full name, completed mailing address, date of birth, and social security number will be required.

8.3 Who could profit or financially benefit from the study results?

Information obtained from this study may help the supporter Exelixis, Inc. and/or the University of Michigan learn more about the causes, risks, treatments, or how to prevent this and other health problems. In the interest of transparency, we would like you to know that Dr. Parikh has served on an Advisory Board for the sponsor of this research. Dr. Parikh is not likely to benefit financially from the results of this research.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my privacy?

The University of Michigan has rules to protect information about you. Federal and state laws also protect your privacy. Upon enrolling in this study, you will be assigned a unique identification number. All records related to the study will use this identification number instead of your name or other personally identifying information whenever possible. We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.
Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file.

You have the right to request access to your protected health information that is used or shared during this research and that is related to your study treatment or payment for your study treatment, but you may access this information only after the study is completed. To request this information, please contact the researchers listed in Section 10 “Contact Information” (below).

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.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records
- Alcohol/substance abuse treatment records
- HIV/AIDS status
- Sexually transmitted disease and/or other communicable disease status
- Genetic counseling/genetic testing records
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, Social Security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

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.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Thomas Enzler, MD, PhD
Mailing Address: University of Michigan
1500 East Medical Center Drive
C437 MIB; SPC 5843
Ann Arbor, MI 48109

Telephone: 734-647-8902 (Clinic)
Emergency Contact: 734-936-4000 (Hospital Operator – 24-hour paging)

You may also express a concern about a study by contacting the Institutional Review Board listed below.
University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

You will receive a copy of the signed and dated informed consent.

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Sig-A

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-D

Consent/Assent to collect for unspecified future research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep my specimens for future research.

_____ No, I do not agree to let the study team keep my specimens for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-G

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____