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Consent to Participate in Research

Sponsor / Study Title: Phase II Trial Evaluating the Safety and Efficacy of Atezolizumab in Combination with Cabozantinib for the Treatment of Metastatic, Refractory Pancreatic Cancer

Protocol Number: 2108097176

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Summary of the Research

This is a consent form for participation in a research study. Your participation in this research study is voluntary. It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to ask questions before making your decision whether or not to participate.

You are being asked to take part in this clinical research study because you have advanced pancreatic cancer that has been previously treated and is now resistant to treatment. If you join this study, you will receive cabozantinib with atezolizumab.

This study is paid for by Exelixis Pharmaceuticals Inc. Dr. Rachna Shroff has disclosed an outside interest in Exelixis. This interest has been properly disclosed to the University of Arizona and reviewed in accordance with its conflict of interest policies.



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Cabozantinib is an oral anticancer drug which is approved in the United States and in other countries, including those in the European Union, 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 currently being studied to treat patients with multiple cancer types including your type of pancreas cancer.

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 pancreatic cancer or for use in combination with atezolizumab. More than 3,000 patients with cancer have been treated with cabozantinib in clinical trials.

To date, cabozantinib has been generally well tolerated in pancreas cancer patients at doses at or above the doses used in this study.

Atezolizumab is a drug that is given by intravenous (IV) infusion (delivered into your vein) and is approved by the FDA and other health authorities worldwide and is commercially available for the treatment of small cell lung cancer and bladder cancer. Atezolizumab is not approved for treatment of liver cancer.

This study is sponsored by the University of Arizona Cancer Center and is conducted by the study doctor listed on page 1 of this consent form and the University of Arizona Cancer Center. The pharmaceutical company Exelixis will be funding this study. Exelixis will pay your study doctor and/or the study site to cover their costs of conducting this study. If applicable, your study doctor will disclose to you any financial links or other interests that he/she may have to Exelixis.

Your participation in this study is entirely voluntary. Please take your time to decide whether to take part in this study. Your study doctor and this document will help explain how this study will be done. Please review this document carefully, ask questions about things you do not understand, and discuss it with your family and friends as you see fit. Do not sign and date this form unless you understand what the study is about and the risks and possible benefits of participating. If you decide to take part in this study, you will sign and date this document and thereby give your consent to participate. You may change your mind at any time during the course of the study.

Why is this study being done?

The purpose of this study is to find out if cabozantinib with atezolizumab is effective in treating advanced pancreatic cancer in those who have previously received treatment. This study will also examine how well people with previously treated advanced pancreatic cancer tolerate treatment

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with the combination of cabozantinib with atezolizumab. This study will also explore the immune effects of cabozantinib with atezolizumab in patients with previously treated advanced pancreatic cancer.

What will happen if I take part in this study?

If you choose to take part in this study, you will first have screening tests to see if you meet the study requirements. If you meet all the study requirements, you will receive the following treatment:

- Cabozantinib 40 mg: Two tablets 20 mg once daily by mouth
- Atezolizumab: 1200 mg infusion delivered into your vein every 3 weeks

How long will I be in this study? When may participation in the study be stopped?

Your participation in this study begins when you first give your consent by signing and dating this form. When you and your study doctor determine it is appropriate, you will begin taking study treatment. You may continue to receive study treatment as long as your study doctor feels you continue to benefit from continued use, you do not have medically unacceptable side effects, and your study doctor judges your condition to be appropriate for this study. You may also stop taking study drug(s) for your own reasons. Even after you stop taking study drug(s), you may continue to undergo study procedures or may be asked to take part in other follow up activities. Your participation in the study will end when you have stopped taking study drug(s) and you have completed all study procedures and follow up activities.

You also have the right to end your participation in the study at any time by withdrawing your consent. Further details on your options for stopping study drug(s) and other study activities are provided later in this consent form. In addition, the Sponsor, regulatory authorities, or the ethics committee may decide to stop this study at any time without consent from you or your study doctor.

It is estimated that you will take study drug(s) for approximately 1 to 6 months, but receiving the study treatment for longer than 6 months is a possibility. Your study doctor will continue to follow up with you to see how you are doing after you stop taking study drug(s). Afterwards, your study doctor may request that you return to the study site for additional tumor assessments or his/her staff will contact you every 12 weeks to follow your health status and any anti-cancer treatments you may have begun after you stop taking study drug(s).

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How many people will take part in this study?

About 29 eligible subjects will take part in this study.

How do I take the study drug(s) and when would I stop?

You will receive atezolizumab at the clinic by intravenous (IV) infusion delivered into your vein on Study Treatment Day 1 and then every 3 weeks thereafter. The infusion will be given for a period of approximately 60 minutes each time. After the IV administration of the first dose of atezolizumab in the clinic, you will wait for at least 1 hour before and after taking cabozantinib.

You will take all other doses of cabozantinib at home once daily, with a full glass of water (8 oz.; 240 mL). You should take cabozantinib at approximately the same time every day, preferably before going to bed. You will need to fast (with the exception of water) for at least 2 hours before and 1 hour after taking cabozantinib. If you miss a dose of cabozantinib by more than 12 hours, do not make up the missed dose. Take the next dose of cabozantinib at the next regularly scheduled time.

Further Instructions on Taking Study Drug Supplied as Pills

Remember to tell your study doctor if you miss taking any doses. Do not change the amount of any study drug(s) you take unless you are told to do so by your study doctor. You should never open, split, crush, or chew pills; they should be swallowed whole. If you vomit the study drug, do not take any additional doses to make up for the vomited medication. Remain on the planned dosing schedule. As some citrus fruits may increase levels of study drugs in your blood, you should not eat grapefruit, Seville oranges (also known as bitter oranges), star fruit, or products made with these fruits (including juice, jams, or sweets) while you are on this study. If you would like more information on why you should avoid these fruits, ask your study doctor. All leftover study drug and empty packages must be returned to the study center at the next visit.

Stopping Study Treatment

If you become ill during the study, if your cancer gets worse, or if you experience severe or intolerable side effects from any study medication, you may have to stop taking one or both of the study drugs, even if you would like to continue. Your study doctor may discuss this with the Sponsor. Your study doctor or the Sponsor may also decide that you should stop taking study drug(s) if it is believed to be in your best interest, or if you do not follow all of the study instructions described by the study doctor.

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You have the right to stop taking the study drug(s) at any time for any reason, and you do not have to give the reason. Discontinuing the study drug(s) will not affect your standard medical care.

If you decide to stop participation in study activities or you withdraw from the study, you will no longer receive study drug(s).

Are other drugs or treatments allowed while on this study?

Cabozantinib or atezolizumab may interact with other drugs. This means that the study drug(s) may change the levels of other drugs in your blood, or other drugs may change the levels of the study drug(s) in your blood. Before you start and while you are taking the study drug(s), you must tell your study doctor about any other drugs you are taking including prescription drugs, over-the-counter medications, vitamins, nutritional supplements, herbal medications, and alternative treatments. You should also talk to your study doctor about any vaccinations you have had recently. Talk to your study doctor before you get any vaccinations or start any new drug or treatment. While on this study, other cancer treatments are not allowed. Normal supportive and medical care is allowed while you are participating in the study.

What are my responsibilities if I take part in this study?

If you join this study, it is your responsibility to:

- Keep your scheduled office visits with the study doctor. If you can't go to one of your planned office visits, you will need to reschedule the visit.
- Have several tests and procedures for routine care and for research purposes.
- Take your study drug(s) as instructed by the study doctor and staff.
- Keep all study drug(s) away from children and pets. Study drug(s) should be stored at room temperature.
- Return any leftover study drug(s) and empty packages at each study visit.
- Contact your study doctor immediately if you are not feeling well.
- Tell your doctor about all medications that you are taking.
- Follow birth control requirements while you are taking study drug(s) and for at least 5 months after you stop taking study drug(s).
- Keep track of when you take the study medication in a diary that will be given to you. You will need to bring the diary to each study visit.

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What types of tests and procedures will I have on this study?

There are required tests and procedures for all subjects on this study; some are part of the routine care of patients with cancer, though they may be conducted more often because this is a research study, and some are for research purposes only. The tests done for research purposes only may help doctors learn how cabozantinib and atezolizumab impact the immune response in patients, but the results of these tests are not expected to benefit you directly or alter your treatment. Therefore, these results will typically not be shared with you, and they will not be included in your medical record or chart.

In order to participate in this study, you must have confirmed advanced pancreatic cancer either based on cells in your tumor that was collected previously (archival tumor tissue) or imaging of your tumor. If you do not have a histology report confirming pancreatic cancer based on cells in your tumor and your pancreatic cancer cannot be confirmed by a scan, you will be asked to provide a fresh tumor sample.

All patients will be requested to provide a fresh tumor sample when beginning the study. Procedures to collect these tumor samples are called biopsies. When you undergo the biopsy, your study doctor will discuss the risks with you in detail, and you will be asked to sign a separate consent form provided by the institution doing this procedure. This biopsy will be used for research. If it is not possible to collect a fresh biopsy, the study team will request to use your archival tissue for research analysis.

In addition to being asked to undergo a biopsy at the beginning of the study, you will also be asked to have another tumor biopsy that will be collected approximately 9 weeks after the first dose of study drugs. You may also be asked to provide an optional tumor biopsy if your cancer gets worse. The tumor sample will be used to evaluate the effects of the study drug(s) on your tumor cells. At the end of this form, you will be asked to check a box to show whether or not you agree to provide the optional samples. You will be instructed to stop taking your tablets of cabozantinib for 5 days before your biopsy, and you may not start taking them again until you have completely healed (at least 10 days). Your study doctor will discuss these instructions with you and can answer any questions or doubts about the procedure and the treatment interruption.

Tumor samples will also be used to study how DNA, genes, proteins, and other molecules in your tumor can affect response to study drug(s). The tumor biopsy samples will also be used to establish a cancer organoid model in the laboratory. Organoids are three-dimensional spheres grown from cancer tissues that mimic the structure and function of the cancer in a petri dish. Organoids will be generated from your tumor biopsy tissue.

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If you join this study, you will have imaging scans to see how well your tumor responds to the study drugs. You will also have blood draws in addition to other procedures to assess safety. Blood draws will also be used to isolate immune cells to see how cancer cells interact with the body's immune system.

If you decide to participate in this study, you will be giving your study doctor permission to send all of the samples you agree to have taken, as well as scans of your tumor and the results from examinations, questionnaires, tests and procedures done as part of the study, to the sponsor or designee. Every effort will be made to protect your identity and to prevent the results of genetic tests from being linked back to you.

The required tests and procedures for this study, including volumes for blood samples, are shown in the following table (Table 1), and further details about the tests are provided below it. Not all the tests shown below will be performed at every study visit; the table at the end of this document summarizes when you will have each test (Table 2).

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Table 1: Tests and Procedures

Tests and Procedures	Purpose of Test	
	Routine	Research
Informed Consent for Research		√
Physical Examination: A complete or a medical condition-focused physical examination that will include measurement of your weight and height at the screening visit	√	
Vital Signs: To measure your body temperature, blood pressure, heart rate, and breathing rate	√	
Electrocardiogram (ECG or EKG): To measure the electrical activity of your heart	√	
Health Status: To record how well you are able to complete daily activities	√	
Blood Tests (blood samples taken throughout the study at various time points as described in the Schedule of Visits, Tests, and Procedures at the end of this document.		
To measure your blood counts (about 1/7 tbsp. [2 mL] each)	√	
To measure the natural chemicals in your blood (about 1/5 tbsp. [3 mL] each)	√	
To measure the status of Hepatitis B and C disease (about 1/2 tbsp. [7 mL] each)	√	
To measure how well your blood clots (about 1/7 tbsp. [2 mL] each)	√	
To assess the function of your thyroid gland (about 1/4 tbsp. [4 mL] each)	√	
Pregnancy Test: For women who can become pregnant (about 1/5 tbsp. [3 mL] each)	√	
To isolate immune cells (about 1 and 1/3 tbsp. [20mL each])		√
Urine Tests: To measure the natural chemicals in your urine and to determine if your kidneys are functioning normally	√	
Tumor Samples: Fresh biopsy to evaluate effect of study drug on the tumor and to develop organoids		√
Tumor Scans: By one or more of the following methods: CT or MRI	√	

Biomarkers tests: Biomarker tests on your blood samples will be required to see how the study drug(s) affects your body and cancer and to help identify biomarkers that may predict response to study drug(s). The blood tests and biopsies, which are types of biomarker test, in this study are for research purposes, and may be used to characterize certain genes that may be impacted by

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these treatments as well as to understand the immune cell changes that happen during treatment. The biomarker research tests in this study are **not** the same as traditional genetic tests which look for diseases that can be passed on to your children or inherited from your parents. Traditional genetic testing and genetic counseling are **not** part of this study. The biomarker test samples may also be used for other research, such as improving existing methods and studying the effects of study drug that may be important for understanding pancreatic cancer. Individual results will not be shared with you or your study doctor. Any information obtained will not be put in your medical record. This research will not change the care you receive but may be useful to future patients treated with the study drugs.

Photos and biopsy: If you develop a skin rash during the study, your doctor may ask for your permission to take photos of the rash and/or obtain a skin biopsy. Your doctor will explain these additional procedures to you. The information from the photo and/or biopsy will be used to learn more about your rash and may be used for publication.

The photos and biopsy information may be shared with the Sponsor and its designees as described in Section **Error! Reference source not found.** ('Will my medical information be kept private') of this consent form. The photos will not disclose your identity. All identifying information will be removed or blackened out.

The table at the end of this document summarizes when you will have each test.

Schedule of Visits, Tests, and Procedures

Before you can begin any screening or study procedures, you must sign and date this consent form. This research study consists of three periods: a Pre-Treatment Period/Screening, a Study Treatment Period and a Post-Treatment Period.

Screening Period: You will have screening tests done as described in the table at the end of this form (Table 2). Some tests done as part of your routine care before you signed this informed consent document can be used as screening tests if allowed by your study doctor and the University of Arizona Cancer Center. After you have completed all screening procedures and met all eligibility criteria, you will be assigned to one of the three study treatment groups. You will then begin the Study Treatment Period.

Study Treatment Period: You will have tests done as described in the table at the end of this form (Table 2). You will have study visits every 3 weeks until the end of the Study Treatment Period. Your study visits may be more frequent if needed to monitor side effects that may occur.

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Post-Treatment Period: After you and your study doctor have decided you should stop taking study drug(s), you will return to the clinic after approximately 30 days and then again at 100 days after deciding to stop study drug(s) for follow-up visits unless you have withdrawn consent to participate in the study. You will have tests done as described in the table at the end of this form (Table 2).

Extended Follow-up: After your disease has worsened, or after you have stopped taking the study drug(s) permanently (whichever is later), you may have one more tumor assessment.

After it is decided that you will no longer need to undergo study assessments, the study staff will contact you by telephone approximately every 12 weeks to see how you are doing and if you have received another anticancer treatment.

What benefits can I expect from being in this study?

Taking part in this study may improve, worsen, or have no effect on your health. By taking part in this study, you will have close monitoring of your health condition by blood tests and other evaluations during clinic visits. Your cancer may improve from your participation in this study, but this cannot be guaranteed. Information from this study will help doctors learn more about the study drugs that could help future patients.

What risks, side effects or discomforts can I expect from being in the study?

Your study doctor will let you know which of these tests and procedures you will have and can explain them in more detail.

Many of the tests in this study, like MRI or CT, are regularly done as a part of standard treatment for patients with your type of cancer. However, these tests may be done more frequently while you are on this study. CT scans use ionizing radiation to form pictures of your body. For one CT scan, the amount of radiation that you will be exposed to is about the same as 8 years of natural exposure. Exposure to ionizing radiation carries a slight risk of damage to cells or tissues. Your study doctor can explain these tests and any additional risks to those described below:

- **CT scan:** A CT scan is non-invasive but involves exposure to radiation. There is a potential risk of radiation exposure from CT scans; this risk is considered small. Sometimes, an intravenous (in the vein) contrast dye is given with a CT scan. This contrast dye is iodine based. A person who has allergies is more likely to have an allergic reaction to the dye. This reaction may be mild, such as skin rash or hives, to severe, such as breathing difficulties or shock. You will be closely monitored and treated should an allergic reaction occur. A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. You should discuss any

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history of allergies or concerns with your study doctor. You may also experience discomfort related to lying still in an enclosed space for a prolonged period of time. The study staff will provide additional instructions to you prior to performing the procedure.

- **MRI**: Having an MRI (Magnetic Resonance Imaging) scan involves lying still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your study doctor. Your study doctor may give you a medication to make you feel more comfortable.

An intravenous (in the vein) contrast dye is given with an MRI. Some people can have allergic reactions to the dye put in their veins for these tests. The allergic reactions can cause itching or rash. More serious allergic reactions can cause difficulty breathing, dangerously low blood pressure, or kidney damage. Some patients with kidney disease may have a severe reaction of skin thickening, joint pain and/or swelling, and in rare cases, lung and heart problems and even death.

MRI uses powerful magnets to make images. Therefore, people with certain metal implants, such as pacemakers, should not have an MRI. If you have an implant or any metal in your body, please check with your study care doctor to know whether you can have an MRI or not. For people without metal implants, there are no known health risks associated with exposure to the magnet. As images are taken, a loud banging noise is 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.

- **Blood Samples**: Side effects of having your blood taken may include pain, redness, swelling, and/or bruising where the needle enters the body. Rare instances of fainting, excess bleeding, blood clotting, or infection have occurred.
- **Electrocardiograms (ECGs)**: To perform the test, adhesive patches (electrodes) will be placed on your skin to record your heart's activity. If results from one test are abnormal, the test may be repeated. You may feel some discomfort when the technician removes the adhesive patches after the procedure, similar to pulling off an adhesive bandage. The adhesive patches can also cause skin irritation or rash in some patients.
- **Tumor Biopsy**: The risks or side effects involved with a tumor biopsy may include bruising, discomfort, and bleeding after the procedure. There are potentially life-threatening risks associated with this procedure, depending on the location of your tumor.



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What are the possible risks or side effects from taking cabozantinib alone?

Your study doctor and study staff will monitor you closely for side effects. Even with frequent blood tests and other examinations, taking drugs such as cabozantinib involves risks, and some side effects cannot be predicted. Side effects can range from mild to severe and life-threatening. Many side effects will get better when you stop taking the drug, but some may be long lasting or may never go away. Side effects may even cause death. You should tell your study doctor or study staff immediately about any side effects that you have or about any change in how you feel while on this study.

If you have side effects from study treatment that includes cabozantinib, your dose of cabozantinib may have to be reduced, or you may have to stop taking cabozantinib and wait until you feel better before you start again. If any side effect is severe or intolerable despite medical management, you may have to permanently stop taking cabozantinib.

Effects of Cabozantinib (XL184) in Humans

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
-

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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

- Weight loss
-

Common Side Effects That Occurred greater than or equal to 1% but less than 10% of Cancer Patients (greater than or equal to 1 in 100, but less than 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
 - 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
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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

- 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 greater than or equal to 0.1% but less than 1% of Cancer Patients (greater than or equal to 1 in 1000, but less than 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
 - 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 tables below. These events occurred in studies of cabozantinib given alone.

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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 study 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 or equal to 0.1% of Cancer Patients (greater than or equal to 1 in 10000, but less than or equal to 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
 - Blood vessel inflammation associated with possible bleeding, bruising, and/or rash
 - Brain dysfunction caused by brain swelling
 - Cancer of the mouth or skin
 - Damage to the outermost surface of the eye
 - Enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall
 - 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
-

What are the possible risks or side effects from taking atezolizumab?

Your study doctor and study staff will monitor you closely for side effects. You should tell your study doctor or study staff immediately about any side effects that you have or about any change in how you feel while on this study. If you have side effects from atezolizumab-containing treatment, your study doctor may delay atezolizumab treatment and wait until you feel better before you start again. If any side effect is severe or intolerable, your study doctor may decide to permanently stop treatment with atezolizumab.

Effects of Atezolizumab in Humans

Atezolizumab is designed to increase the number of immune system cells in your body that can fight cancer. These cells may cause inflammation within the tumor, as well as in normal tissue (immune-related side effects). Therefore, by taking atezolizumab, you may develop a condition where there is inflammation against a part of your own body (an autoimmune condition).

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The side effects described in this section are known to be associated with atezolizumab.

**Very Common Side Effects Known to be Associated with Atezolizumab
(Occurs in More Than 10% of Patients)**

- Fatigue
 - Joint pain (arthralgia)
 - Lack of energy (asthenia)
 - Decreased appetite
 - Diarrhea
 - Shortness of breath (dyspnea)
 - Urinary tract infection
 - Cough
 - Itching of the skin
 - Nausea
 - Fever
 - Rash
 - Vomiting
 - Muscle and bone pain (myalgia, musculoskeletal pain and bone pain)
 - Back pain
 - Headache
-

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**Common Side Effects Known to be Associated with Atezolizumab
(Occurs in 1%–10% of Patients)**

- Chills
 - Difficulty swallowing (dysphagia)
 - Increase in liver enzymes, which may indicate inflammation of the liver
 - Allergic reaction or intolerance to medication (hypersensitivity)
 - Decreased level of potassium in blood (hypokalemia)
 - Decreased level of sodium in blood (hyponatremia)
 - Low blood pressure (hypotension)
 - Underactive thyroid gland (hypothyroidism)
 - Inflammation of the nose and throat (nasopharyngitis)
 - Inflammation of the intestines (colitis)
 - Decreased oxygen supply in body resulting in shortness of breath (hypoxia)
 - Flu-like symptoms
 - Infusion-related reaction
 - Inflammation of the lungs (pneumonitis)
 - Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia)
 - Inflammation of the liver (hepatitis)
 - Stomach area pain (abdominal pain)
 - Inflammation or buildup of fluid in the sac that surrounds your heart, which can affect the heart's function (pericardial disorders)
 - Dry mouth
 - Dry skin
 - Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine
 - Increased blood sugar level (hyperglycemia)
 - Mouth and throat pain (oropharyngeal pain)
 - Arthritis
 - Low white blood cell count (neutropenia)
 - Nerve damage in the hands or feet (peripheral neuropathy)
-

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**Rare but Potentially Serious Side Effects Known to be Associated with Atezolizumab
(Occurs in Less Than 1% of Patients)**

- Decreased production of hormones by the adrenal glands (adrenal insufficiency)
 - Diabetes
 - Overactive thyroid gland (hyperthyroidism)
 - Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis)
 - Inflammation of the pituitary gland (hypophysitis)
 - Inflammation of the heart muscle (myocarditis)
 - Inflammation of the kidney (nephritis)
 - Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome)
 - Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis)
 - Inflammation of the pancreas (pancreatitis)
 - Increase in pancreatic enzymes, which may indicate inflammation of the pancreas (increase in amylase and lipase)
 - Severe high levels of sugar and acids in the blood or urine (diabetic ketoacidosis)
 - Inflammation or damage of the muscles (myositis)
 - Reduced ability to move face muscles (facial paresis)
 - Build-up of certain white blood cells that may cause organ damage and destruction of other blood cells (hemophagocytic lymphohistiocytosis)
 - Inflammation of the spinal cord (myelitis)
 - Red, dry, scaly patches of thickened skin (psoriasis)
 - Severe skin or mucosal reactions (severe cutaneous adverse reactions)
 - Higher levels of a muscle enzyme in the blood (blood creatinine phosphokinase increased)
 - Cytomegalovirus infection
 - Inflammation in different parts of the body (sarcoidosis)
 - Swelling around tendons (tenosynovitis)
 - Inflammation of the eye (uveitis)
-

Among the side effects known to be associated with atezolizumab, the Sponsor and your study doctors would like you to pay more attention to the following:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood in stool, and pain in stomach area
- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptoms may include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal gland (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- Inflammation of the pituitary gland (hypophysitis); symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision.



Side effects that may occur at the same time include hypothyroidism and adrenal insufficiency (see above for details)

- Inflammation of the liver (hepatitis); symptoms may include yellowing of skin, pain in stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin, and dark urine
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis/facial paresis); symptoms may include weakness in the arm and leg muscles, double vision, and difficulties with speech and chewing
- Inflammation of the spinal cord (myelitis); symptoms may include pain, abnormal sensations such as numbness, tingling, coldness or burning, weakness in the arms or legs, and bladder and bowel problems. These symptoms may develop over a few hours to a few days and may sometimes progress gradually over several weeks.
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficulty walking
- Inflammation of the lungs (pneumonitis); symptoms may include new or worsening cough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat and fainting
- Inflammation of the heart sac with buildup of fluid in the sac (in some cases) (pericardial disorders); symptoms are similar to those of myocarditis and may include chest pain (usually over the front of the chest, sharp, and worsened by deep breathing and better when you sit up and lean forward in case of inflammation of the heart sac), cough, irregular heartbeat, swelling of the ankles, legs or abdomen, shortness of breath, fatigue, and fainting
- Reactions associated with infusion (events usually occurring within one day of infusion but can be delayed in onset for several days); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest



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- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain, nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue
- Inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- Inflammation or damage of the muscles (myositis, myopathies including rhabdomyolysis); symptoms may include muscle pain and weakness, urine with a dark brown or reddish color, nausea, and vomiting.
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptoms may include itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area
- Build-up of certain white blood cells (histiocytes and lymphocytes) in various organs (hemophagocytic lymphohistiocytosis), including the bone marrow, liver, and spleen, leading to their damage and destruction of other blood cells; symptoms vary depending on affected organs

Allergic Reactions

Allergic reactions may occur with atezolizumab and typically occur while it is being given into your vein or after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability. If you experience any of these symptoms, your study doctor will interrupt, or even stop, the delivery of atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

Side Effects Potentially Associated with Atezolizumab

The following are side effects that may be associated with atezolizumab:

- Development of special antibodies to atezolizumab (proteins made in the body that respond to a substance that is foreign to the body) by your immune system. If you develop these special antibodies, it may affect your body's ability to respond to atezolizumab in the future. Blood samples will be drawn to monitor for the development of these antibodies during study treatment and at your treatment discontinuation visit.

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- Potential to cause harm to a developing fetus
- Inflammation of the blood vessels that can lead to damage of different organs (vasculitis); symptoms may include fever, fatigue, weight loss, weakness, general aches and pains, rash, headache, lightheadedness, shortness of breath, and numbness
- Breakdown of red blood cells (autoimmune hemolytic anemia); symptoms may include fatigue, fever, lightheadedness, paleness of the skin, yellowing of the skin and/or eyes, weakness, and inability to do physical activity
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptoms may include severe skin or mucosal blistering, shedding, scaling, and death of the skin or mucosa

Systemic Immune Activation

In rare situations, when atezolizumab is combined with another drug that also increases your body's immune response (immune-modulating drugs), a more-than-normal (excessive) immune response can occur. Like other immune-mediated conditions, excessive systemic immune activation can cause side effects related to severe inflammation and/or generalized infection (sepsis). Several organs in your body (for example, liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms of systemic immune activation may include very low blood pressure that does not respond to standard treatment - including fluids given through the veins (intravenous fluids), high-grade fever (more than 38.5° Celsius), cough, severe shortness of breath (respiratory distress) requiring oxygen therapy and/or mechanical help (intubation), severe dizziness, confusion, weakness, decreased urination with failure of the kidneys (renal failure), significantly high levels of liver enzymes (liver failure), very low blood cell counts, and/or bleeding within the organs.

If you experience any of these symptoms, you should notify your doctor immediately as you may need immediate treatment and hospitalization. Your study doctor may give you drugs to treat these symptoms.

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Vaccinations

You should not receive live vaccines (for example, influenza, measles, mumps, rubella, varicella, etc.) or be in close contact with people who have received live vaccines while you are taking atezolizumab to reduce the risk of infection from the vaccine.

What are the possible risks or side effects from taking cabozantinib + atezolizumab together?

The risks and side effects of taking cabozantinib and cabozantinib plus atezolizumab together have been studied in another clinical study. So far, subjects in that study have experienced side effects listed above for either cabozantinib or atezolizumab, including diarrhea, high blood pressure, hand-foot reaction, decreased amounts of phosphorus in the blood, overactive thyroid gland, and blood clot that travels from a vein to the lung. It is possible that effects that haven't been seen with either drug alone could occur. Be sure to tell your study doctor about any symptoms you may have, so your study doctor can best determine how to treat you and whether or not you need to have your study drugs held or reduced to help you get better.

Your study doctor and study staff will monitor you closely for side effects. You should tell your study doctor or study staff immediately about any side effects that you have or about any change in how you feel while on this study. If you have side effects from cabozantinib + atezolizumab, your dose may need to be reduced, or you may need to stop taking cabozantinib + atezolizumab and wait until you feel better before you start again. If any side effect is severe or intolerable, you may have to permanently stop taking cabozantinib or atezolizumab.

What happens if I am injured because I took part in this study?

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in this consent form. However, side effects that are not currently known may happen and require care. You and/or your insurance company will be responsible for the costs of such care.

The University of Arizona and Banner-University Medical Center have no funds set aside for the payment of treatment expenses for this study.

You do not waive any legal rights by signing this form.

As with all injuries or medical issues in the study, you should contact your study doctor at the phone number on page 1 of this form and seek medical treatment when needed.

This, however, does not waive your rights in the event of negligence. If you suffer an injury from participating in this study, you should seek treatment.

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You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

If you decide to take part in this study, at any time you may stop taking study drug(s) and undergoing study procedures or you may withdraw your consent to participate in the study. Leaving the study will not affect your standard medical care.

You also have the right to learn about changes in the study or significant new findings (good or bad) such as benefits or side effects that may affect your health or willingness to continue in the study. If new information is provided to you, you will be asked to sign an updated consent form.

The University of Arizona and Banner-University Medical Center have no funds set aside for the payment of treatment expenses for this study.

What are the costs of taking part in this study?

You may or may not have additional costs as a result of your participation in this study. The pharmaceutical company Exelixis will supply the study drug atezolizumab and the pharmaceutical company Genentech will supply the study drug cabozantinib. Study procedures performed for research purposes only will not be charged to you and/or your insurance company. You will be financially responsible for your general medical care while participating in this study. This will include but may not be limited to exams, blood work, imaging, and administration of medications, to include administration of the drugs provided by Exelixis and/or Genentech if applicable. This will include any applicable co-payments and/or deductibles. Some insurance companies will not pay for services when performed in connection with a clinical trial, even when considered usual. You will be responsible for any charges that your insurance does not cover including regular co-payments and deductibles. You should check with your insurance company about the potential costs.

Will I be paid for participating in this study?

You will not be paid for participating in this study. You will not be compensated for your time or for any wages lost as a result of your participation in this study.

Will my data or specimens be stored for future research?

There may be some specimens (blood, tissue, etc.) remaining after the study is complete. These leftover samples may be used in future research to learn about preventing or treating gastrointestinal cancers. By participating in this study, you agree to the use of your leftover samples in future research.

Identifiers will be removed from the biospecimens, and after such removal, the biospecimens may be used for future research studies without additional informed consent. Organoid cultures

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may be shared with other research universities and institutions. Future research may include genetics and organoid cultures.

If you change your mind about the permission you granted for the use of your samples, you should tell your study doctor in writing that you want the samples destroyed. He/she will tell the Sponsor or designee, who will destroy the samples. If you request it, the Sponsor or designee will tell your study doctor in writing when the samples have been destroyed. It is possible that your samples might have already been used and analyzed.

By agreeing to participate in this study, you waive any claim to the blood and tissue samples (apart from being able to request that samples be destroyed, as discussed above) or any new material or processes developed through research with these samples that will be owned by the Sponsor or authorized representatives.

Other than the study site staff, no one working with your samples will know your identity, and individual results from some of the tests will not be shared with you or your study doctor, nor will they be put in your medical record.

A federal law, called the 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 generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that the sponsor will get 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 the sponsor will get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans and all employers with 15 or more people must follow this law.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance or long-term care insurance.

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1) Specimens collected in course of treatment and care:

In addition to the treatment study, researchers are also interested in studying tissue, body fluids, or other specimens that were, or may be, obtained from you in the normal course of your treatment and care. These research tests may be developed during the time you are on treatment, or years later.

2) Specimens collected in course of surgical treatment or biopsies (endoscopic or percutaneous):

You will be undergoing tumor biopsies as a part of participation in this study.

We would like to keep any of the tissue that is left over for future research. This will be stored in a central facility (called a “tissue bank”) which is located here at the University of Arizona, College of Medicine, Department of Cellular and Molecular Medicine. Your sample will be stored there permanently and will not be available for use in making health care decisions for you. At some time in the future, pieces of this stored tissue may be used by other researchers for other tests that are not known at this time. In most cases, you will not be told what your sample is being used for.

When your sample(s) is sent to the researchers, samples will be identified by a unique study code only. Researchers to whom the University of Arizona sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are. If research results are published, your name and other identifiable information will not be used.

You cannot participate in the treatment part of the study without having tissue taken prior to starting treatment, or without having tissue taken during treatment. You cannot participate in this trial if you do not participate in all blood collections.

You can participate in the treatment part of the study without participating in all tissue research studies. If you have any questions, please talk to your doctor.

Will my specimens be sold for commercial profits?

No data or specimens will be sold for commercial profit. The information/specimens may be used in this research or other research and shared with other organizations. You will not share in any commercial value or other compensation from products developed using the information/specimens.

Will I hear back on any results that directly impact me?

You may not receive any clinically relevant results discovered about you and/or the general subject population.

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Will Whole Genome Sequencing be done with my specimen?

We are requesting your permission to perform genome and/or exome sequencing on your biospecimen, (blood and tissue samples) and link this to your medical and/or family history. Your blood and tissue samples contain genes, which are made up of DNA (deoxyribonucleic acid) which serves as the "instruction book" for the cells that make up our bodies. Sequencing genome and/or exome will determine the exact order of the base pairs (chemical letters) in your biospecimen, (blood and tissue samples).

We are requesting your permission to perform exome sequencing on your blood and/or tissue samples and link this to your medical and/or family history. Your blood and tissue samples contain genes, which are made up of DNA (deoxyribonucleic acid) which serves as the "instruction book" for the cells that make up our bodies. Sequencing exome will determine the exact order of the base pairs (chemical letters) in the tumor being studied, and blood. Your sample(s), medical and family history information will help us study how genes affect GI pathology.

If I sign this consent form, my genetic and health information will be released, with no direct identifiers, into scientific databases.

What other options are there?

You do not have to participate in this study. You may choose to:

- Get treatment or care for your cancer without being in a study. These options should be discussed with your treating physician.
- Take part in another study
- Get no additional cancer treatment
- Get comfort care. This type of care does not treat the cancer directly, but helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer.

Your study doctor will explain all of the treatment options available to you, including their benefits and risks. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits.

What other choices do I have if I do not take part in this study?

Your participation is voluntary. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The University of Arizona. If you are a student or employee at the University of Arizona, your decision will not affect your grades or employment status. You can stop your study drug(s)

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at any time, and if you do you will have choices regarding your further participation in the study:

- You may continue other study activities, including having further tests and examinations, completing questionnaires, and other study follow-up.
- You may stop further tests and examinations, but may continue to allow your study doctor to collect follow-up information for the study by contacting you or your family by phone or looking at your medical records. You may not stop tests and examinations and still continue to receive study drug(s).
- If you want to completely stop all study activities including receiving study treatment, undergoing study procedures, having follow-up calls to you or your family, and allowing the study sponsor to collect information from your medical records, you can withdraw your consent from the study.

You can discontinue study drug(s) and activities or withdraw consent without any penalty, any effect to your relationship to your doctor or the hospital, or any other impact to your healthcare. Please tell your study doctor if you are thinking about stopping study drug(s) and study activities or withdrawing consent. Your study doctor will tell you how to do so safely, evaluate any risks associated with discontinuing, and will discuss what other care and testing would be most helpful for you. Though it is recommended that you participate in a follow up visit approximately 4 weeks after stopping study treatment, you are not required to do so. If you are having side effects at the time you decide to stop study drug(s) and procedures or withdraw consent, we ask that you continue to visit your study doctor per his/her recommendation until the side effects have resolved to a safe level.

An important goal of this study is to evaluate how long subjects taking cabozantinib with atezolizumab live. By signing and dating this consent form, you agree that your survival status can be obtained by your study doctor and shared with the sponsor, even after you have discontinued study drug(s) and stopped all other study-related activities. Your study doctor (or appointed delegate) may seek to establish your survival status from your hospital records or by contacting you or your relatives as permitted by local regulations. That follow-up is anticipated to last about 72 months but may carry on beyond that time if necessary. Even in the event that you withdraw consent to study follow-up, your study doctor may still obtain this information from public records (for example, death registries and obituaries) as permitted by local regulations.

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Will my study-related information be shared, disclosed, and kept confidential?

It is anticipated that there will be circumstances where your study related information and Protected Health Information (PHI) will be released to persons and organizations described in this form. If you sign this form, you give permission to the research team to use and/or disclose your PHI for this study. Your information may be shared or disclosed with others to conduct the study, for regulatory purposes, and to help ensure that the study has been done correctly. These other groups may include:

- Office for Human Research Protections, Food and Drug Administration, or other federal, state, or international regulatory agencies
- *Banner University Medical Group and Banner Health*
- The University of Arizona (UA) and the UA Institutional Review Board
- The sponsor and/or funder supporting the study, their agents or study monitors
- Your primary care physician or a specialist taking care of your health.

If you agree to take part in this study a copy of this signed informed consent form will be saved into your electronic medical record (EMR) at Banner Health. As a result, healthcare providers and staff who are not working on this study, but who may provide you medical treatment in the future, will know that you are taking part or took part in this study.

Your PHI may no longer be protected under the HIPAA privacy rule once it is disclosed by the research team.

What study-related information and PHI will be obtained, used or disclosed from my medical record at Banner?

Information related to this research study that identifies you and your PHI will be collected from your past, present, and future hospital and/or other health care provider medical records.

The PHI you are authorizing to be used and/or disclosed in connection with this research study may include, but is not limited to, your name, address, telephone number, date of birth, government-issued identification number, and medical records and charts, including the results of all tests and procedures performed during this study.

Demographic information to be disclosed may include, but is not limited to, your name, address, phone number, or social security number.

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Your existing health records may include information related to the diagnosis or treatment of sexually transmitted disease (STD), acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV), other communicable diseases, genetic information (e.g., genetic testing), and/or alcohol and/or drug abuse. The study staff and study sponsor's monitor may see this information while reviewing your regular health records for this study, but they WILL NOT create, collect, or disclose this type of information for the purposes of this research study.

When will my authorization expire?

There is no expiration date or event for your authorization. Therefore, unless you cancel this authorization (as instructed below) this authorization will continue to be effective.

Do I have to sign this authorization form?

You do not have to sign this authorization. However, if you decide not to sign, you will not be able to participate in this research study; and it will not affect any non-study Banner Health medical treatment or health care, payment, enrollment in any health plans, or benefits.

What do I need to know if I decide to cancel my authorization?

After signing the authorization, you may decide to cancel your previous authorization for the research team to use your PHI. If you cancel the authorization, you will no longer be able to stay in the research study. Please note that any PHI collected before you cancel the authorization may still be used. You may revoke the authorization by contacting the Principal Investigator in writing. Contact information is under "Who can answer my questions about the study" at the end of this document.

Will access be limited to your research study record during this study?

You may not have access to the research information developed as part of this study until it is completed.

Who can answer my questions about my rights and this study?

If at any time you feel you have had a research-related injury, or for questions, concerns, or complaints about the study you may contact Dr. Rachna Shroff at 520-626-2430.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the

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Human Subjects Protection Program Director at 520-626-8630 or online at
<https://research.arizona.edu/compliance/human-subjects-protection-program>.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact Dr. Rachna Shroff at 520-626-2430.

If you have questions, concerns, or complaints about the use or sharing of your health information or would like a copy of the Banner Notice of Privacy Practices, you may contact the Banner Research HIPAA Liaison at BannerResearchCompliance@bannerhealth.com.

To cancel your authorization for access to PHI you must notify the Principal Investigator and/or Research Team in writing at the following address:

Rachna Shroff, MD
1515 N. Campbell Ave.
Tucson, AZ 85724
USA

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.

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SIGNATURE OF PATIENT

My tissue, if taken at disease progression, may be used in future research to learn about preventing or treating gastrointestinal cancers. In addition to the samples required for this study, your study doctor would like to obtain optional tumor samples from you for research purposes. They will be used to evaluate the effects of study drug(s) on your tumor cells. Your decision will not affect your treatment. If you say “No” you may still participate in the study. Whatever you decide, you can change your mind at any time. Just tell your study doctor.

Depending on your decisions, please mark the box for “Yes” or “No”.

I agree to the optional tumor biopsy taken at disease progression:

☐ Yes ☐ No

Optional Research Activity

Optional research activity is part of this project. If you choose to participate in this optional activity, your PHI shall be included for this optional activity.

By initialing the line below, you agree to allow your PHI to be used and/or disclosed for the optional Study activity referenced above.

_____ Initials

The sponsor would like your permission to keep leftover tumor samples if taken at disease progression for research that is part of this study. Reports from this research will not be given to you or your doctor and will not be put in your health record; the research will not affect your care. If you agree, you can change your mind at any time. Just tell your study doctor in writing that you want the samples destroyed.

I agree to the use of my leftover tumor samples if taken at disease progression: ☐ Yes ☐ No

Optional Research Activity

Optional research activity is part of this project. If you choose to participate in this optional activity, your PHI shall be included for this optional activity.

By initialing the line below, you agree to allow your PHI to be used and/or disclosed for the optional Study activity referenced above.

_____ Initials

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My doctor may contact me in the future to ask me to take part in more research.

☐ Yes ☐ No

Optional Research Activity

Optional research activity is part of this project. If you choose to participate in this optional activity, your PHI shall be included for this optional activity.

By initialing the line below, you agree to allow your PHI to be used and/or disclosed for the optional Study activity referenced above.

_____ Initials

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Signing the consent form

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study and I authorize the use and/or disclosure of my PHI. I am not giving up any legal rights by signing this form. I will be given a signed copy of this form.

Also, by signing this form you are authorizing and permitting uses and/or disclosures of your PHI for future research purposes (e.g., future studies) as described in this document.

Printed name of subject

Signature of subject

Date

Printed name of person authorized to
consent for subject (when applicable)

Signature of person authorized to consent for subject
(when applicable)

Date

Relationship to the subject

Investigator/Research Staff

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A signed copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent

Signature of person obtaining consent

Date

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Table 2: Schedule of Visits, Tests, and Procedures

	Pre-treatment	Treatment					Post-treatment		
	Screening/ Baseline	Week 1 Day 1	Week 4 Day 1	Week 7 Day 1	Week 10 Day 1	Week 13 Day 1 and beyond	Decision to end Treatment	30-days Post- treatment	Long-term Follow-up
Informed Consent	X								
Demographics	X								
Height	X								
Physical Examination and Weight	X	X	X	X	X	Every 3 Weeks	X	X	
Vital Signs	X	X	X	X	X	Every 3 Weeks	X	X	
Health Status	X	X	X	X	X	Every 3 Weeks	X	X	
Blood Samples (Routine)	X	X	X	X	X	Every 3 Weeks	X	X	
Urine Samples	X	X	X	X	X	Every 3 Weeks	X	X	
12-lead ECG	X	X	X	X	X	Every 9 Weeks	X	X	
Pregnancy Test	X								
MRI/CT	X				X	Every 9 Weeks			

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	Pre-treatment	Treatment					Post-treatment		
	Screening/ Baseline	Week 1 Day 1	Week 4 Day 1	Week 7 Day 1	Week 10 Day 1	Week 13 Day 1 and beyond	Decision to end Treatment	30-days Post- treatment	Long-term Follow-up
Cabozantinib Treatment		Continuously							
Atezolizumab Administration		X	X	X	X	Every 3 weeks			
Blood Samples (Research)	X				X	Every 9 Weeks	X		
Tumor Biopsy	X				X		X (optional)		
Study Treatment Compliance	X	X	X	X	X	Every 3 Weeks	X		
Survival follow-up							X	X	X
Medications	Continuously Monitored								
Side Effects		Continuously Monitored							

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