CONSENT FOR CANCER RESEARCH

Project Title: CASE 1216, "Phase I/II Study of CB-839 and Capecitabine in Patients with Advanced Solid Tumors and Fluoropyrimidine Resistant PIK3CA Mutant Colorectal Cancer"

Sponsor: Case Comprehensive Cancer Center

University Hospitals' Principal Investigator: David Bajor, MD

Phase 1 consent

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at University Hospitals (UH).

What is the usual approach to my cancer?
You are being asked to take part in a clinical research study sponsored by the Case Comprehensive Cancer Center that tests CB-839, an investigational drug, in combination with capecitabine, a standard medication used for colon and rectal cancer.

You are being asked to take part in this study because you have a solid tumor cancer and have no remaining effective treatments for your disease. The usual approach to your cancer would be to provide you with comfort or palliative care rather than treatment.

If you have colon or rectal cancer, you are being asked to take part in this study because the first standard drugs you received (capecitabine or its sister drug 5-fluorouracil or 5-FU and either oxaliplatin or irinotecan) are no longer effective treatment for your disease. The usual next approach to your cancer would be for you to receive another standard treatment for colon or rectal cancer. This may include either oxaliplatin or irinotecan if you haven't had them before, regorafenib or TAS-102. These are all standard medications used to treat colon and rectal cancer. By taking part in this study, you may be choosing to receive the study treatment instead of standard treatment, which may work better.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, for example, with comfort/palliative care

Why is this study being done?
This study has two portions. The main goal of the Phase I portion of this research study is to see what doses of CB-839 and capecitabine can safely be given to subjects without having too many side effects. Other purposes of this research study will be to determine what side effects are seen with this combination of medicines. The Phase II portion of the study will test how many subjects show shrinkage in their tumor with this combination of medicines and what changes occur inside the cancer cells and blood cells after treatment. You are being asked to participate in the Phase I portion of this research study.

CB-839 is an investigational (experimental) anti-cancer agent that has not been approved by the Food and Drug Administration (FDA) for use in patients with cancer. CB-839 blocks one of the pathways that cancer cells use to metabolize nutrients. Blocking this process may block the cancers energy supply and keep it from growing.

Capecitabine is an anti-cancer agent that is commonly used for patients with colon cancer, rectal cancer, and breast cancer and is approved by the Food and Drug Administration for treatment of these types of cancer. If you have had colon cancer, rectal cancer, or breast cancer, most likely you have had this medicine or a similar type of medicine as part of your treatment. It is possible that when CB-839 is given with capecitabine, it will help the capecitabine work better, even if it had stopped working in the past, although this has not been proven.

What are the study groups?
The research study you are being asked to take part in is a Phase I study. Phase I studies test drugs or drug combinations that have not been studied in humans or have only been tested in a few human studies. The purpose of this phase I study is to determine the highest dose of CB-839 and capecitabine that can be given together safely to subjects with advanced solid tumor cancers. This dose is called the maximum tolerated dose (MTD). To determine the MTD, different subjects will receive different amounts of both CB-839 and capecitabine.

Because this study is designed to determine the largest dose of CB-839 and capecitabine that can be given safely, you may not receive the same dose of the drug as other subjects enrolled in the study. At the beginning of the study, 3-6 subjects will be treated with a low dose of CB-839 and capecitabine.

If no serious side effects are reported, the next set of 3-6 subjects enrolled in the study will receive a higher dose of CB-839 and capecitabine. Again, if no serious side effects occur, another set of subjects in the study will be enrolled at the next higher dose level. This will continue as long as CB-839 and capecitabine are tolerated by subjects or until the maximum doses of each individual drug are reached.

The dose level of the study drug you receive will depend on when you enter the study, and whether subjects enrolled before you had any serious side effects at their dose levels. Neither you nor your doctor will be able to choose which dose of CB-839 and capecitabine you receive. If serious side effects are seen indicating that the dose used is not tolerated, the dose of the study drug may be lowered.

A total of 9-24 subjects (men and women who are 18 years and older) will be enrolled in the Phase I portion of this trial.

How long will I be in this study?
You will receive study drugs until any of the following happen:

- your doctor has determined that your cancer has progressed,
- the study treatment becomes intolerable,
- the completion or termination of the study,
- severe side effects occur,
- you or your physician wishes to discontinue treatment, or
- the study Sponsor finds it necessary to limit or end this study.

After you are finished with the study treatment, the study doctor will ask you to visit the office for a

treatment completion visit described below within 30 days after your last dose of study treatment.

What extra tests and procedures will I have if I take part in this study?
Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there may be some extra procedures that you will need to have if you take part in this study. Neither you nor your health care plan/insurance carrier will be billed for the collection of the research-only samples and procedures that will be collected/done for this study.

Pharmacokinetic (PK) studies measure the amount of CB-839 that you have in your blood at any point in time after starting CB-839 treatment. These PK tests will study how your body processes the drugs. This will only be checked one time during the study and this will be on the morning of the 15th day of treatment. This will be after CB-839 and capecitabine have been taken twice a day for 2 weeks. At this time point, about half a teaspoon of blood will be drawn for research purposes. These PK samples will be sent to a central laboratory for analysis.

During The Study
The study treatment is divided up into cycles. Each cycle is 21 days long. You will take CB-839 twice a day for each day of a cycle. You will take capecitabine twice a day but only for the first 14 days of each cycle.

On Cycle 1, Day 15, do not take your morning dose of CB-839 at home. You will take it in clinic instead, right after the PK blood sample is drawn.

Because both of the medicines in this study are taken by mouth, you will be responsible for keeping a diary of when you take your medicines. A diary will be given to you by the study team and the study team will show you how to fill it out. You will need to bring your study diary with you to every visit.

Neither of the study medications should be crushed and need to be swallowed whole. You should keep your medications out of reach of children and away from other people living in your home.

The CB-839 capsules should be taken twice a day with food. You should take your first dose of the day with breakfast and your second dose of the day with dinner.

The capecitabine tablets should also be taken twice a day but on a slightly different schedule. You should take your capecitabine tablets within 30 minutes after eating breakfast and within 30 minutes after eating dinner.

If you miss a dose it should not be made up. If you have any questions about how to take your medications you should contact your study doctor.

What possible risks can I expect from taking part in this study?
If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very

small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

The CB-839 and capecitabine used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.
Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about, including side effects of combining CB-839 and capecitabine. If important new side effects are found, the study doctor will discuss these with you.

Risks of CB-839:

Likely (occurs in more than 10% of people—more than 10 out of 100 people)
▪ feeling tired ▪ abnormal liver function tests which may indicate liver damage ▪ nausea ▪ temporary sensitivity to light or discomfort with light

Less likely (occurs in 5% to 10% of people—from 5 to 10 out of 100 people)
▪ vomiting ▪ decreased appetite

Findings from safety studies with the study drug in animals include reversible abnormalities in some tests of liver and gallbladder function.

Increases in liver enzymes, which could be a sign of liver damage, have been observed in participants treated with CB-839. Changes to date have been reversible and have not generally recurred on dose reduction.

If you do not understand any of these side effects, please ask the study doctor or study staff to explain these terms to you.

Risks of Capecitabine:

Likely (occurs in more than 20% of people – more than 20 out of 100 people)
▪ swelling of the body ▪ blisters on the skin ▪ redness, pain or peeling of palms and soles ▪ pain ▪ diarrhea, loss of appetite, nausea, vomiting ▪ sores in mouth which may cause difficulty swallowing ▪ anemia which may require blood transfusions ▪ infection, especially when white blood cell count is low ▪ bruising, bleeding ▪ feeling of “pins and needles” in arms and legs ▪ tiredness ▪ fever

Less likely (occurs in 3% to 20% of people – from 3 to 20 out of 100 people)
▪ blurred vision, dry or itchy eyes ▪ muscle spasms, body aches ▪ abnormal heartbeat ▪ restlessness, irritability ▪ swelling of face, fingers and lower legs ▪ constipation ▪ confusion ▪ difficulty with balancing

Rare, but serious (occurs in less than 3% of people – less than 3 out of 100 people)
▪ allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat ▪ difficulty speaking, walking or seeing ▪ internal bleeding which may cause blood in vomit or black tarry stools ▪ damage to the heart

The following should be **avoided**, if at all possible while you are on the study drug:

- There are many drugs that both CB-839 and capecitabine could potentially interact with, so you must discuss your medications with your study doctor. You must also inform your study doctor of any new medications you start while on this study. This includes over-the-counter medications, alternative therapies, or herbal medications.

Potential Risk or Discomfort from Procedures:

<u>Blood Draws</u>

The insertion of the needle to draw blood is painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause

bleeding, bruising, discomfort, infections, dizziness, or fainting.

Reproductive Risks

Women who are pregnant or breastfeeding cannot take part in this study because we do not know what effect CB-839 or capecitabine will have on an unborn child or whether the drugs are passed to a baby through mother's milk. To avoid risk to the fetus, it is important that you not be pregnant while participating in this study. If applicable, you must stop breastfeeding if you are being treated with the study drug. If you are a woman capable of having children, you will be given a pregnancy test before you begin the study, which must be negative in order for you to take part.

Women

If you are a woman capable of having children and choose to have sex, you must use two forms of acceptable contraception, including one barrier method (e.g. latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/cream/film/suppository), while you are in this study and for 3 months after your last dose of the study drug. One of the acceptable methods of contraception is the use of a condom along with a diaphragm with spermicidal agent (foam/gel/cream/film/suppository).

Additional methods are:

- IUD or IUS (intrauterine devices or intrauterine system, except IUD progesterone T) in addition to a barrier method with spermicide.
- Vasectomy by sole male partner.
- Use of approved oral, injected, or implanted hormonal methods of contraception in addition to a barrier method with spermicide. This must be approved by your study doctor before you begin taking the study drug.

Even if you use birth control during the study, there is still a chance you could become pregnant. If you become pregnant or you think you may be pregnant during the study, you must immediately stop taking the study drug and tell your study doctor. If you become pregnant during the study, the pregnancy will be followed to determine the outcome. If you become pregnant during the study, the study drug may involve unforeseeable risks to the unborn baby.

Men

Men who are able to father children must use adequate contraception. If you are a man you must:

- Prevent pregnancy in a female partner.
- Prevent exposure of a partner to semen by any means (not just intercourse).
- Prevent the possible exposure of a pregnant female to the study drug from your semen.
- You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, she should promptly notify her doctor.

You should not donate sperm for 3 months after your last dose of study drug. In addition, acceptable methods of birth control include using one of the following while you are in this study and for 3 months after your last dose of the study drug (due to the unknown effects of the study drug on the sperm):

- Abstinence (no sex)
- Condom plus spermicidal agent (foam/gel/cream/film/suppository)
- Vasectomy

What possible benefits can I expect from taking part in this study?
There is no guarantee that you will receive any benefits from this study, and taking part in this study may or may not cause your health to improve. Information from this study may help doctors learn more about CB-839 and capecitabine. This information may benefit other patients with cancer in the future.

Can I stop taking part in this study?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:
- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?
Your involvement in this research study is voluntary and you will not be paid for your participation.

The investigational study agent, CB-839, will be provided free of charge and capecitabine will be billed to your insurance while you are participating in this study. Depending on your insurance, there may be a cost involved for the capecitabine. Neither you nor your insurance provider will be responsible for the costs of any research-only PK tests. The blood work for research purposes will not be charged to you. It will be paid for by the research study.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Notice for Managed Care (Medicare Advantage Plan) Beneficiaries
Certain services that are required for your care as a participant in a clinical trial can be billed to, and paid by, your medical insurance. These services are referred to as "covered" clinical trial services. However, if you have a Medicare Advantage Plan as part of your medical insurance, this insurance cannot be billed for covered clinical trial services. Instead, traditional Medicare will be billed, and will pay for those services.

This has an impact to you. When traditional Medicare pays for such services, you will be responsible for paying the coinsurance amounts applicable to these services, in addition to any other deductibles or co-insurance you may have on your other health coverage. Please speak with a financial counselor to understand what the specific financial impact will be for you associated with participating in this clinical trial.

What happens if I am injured or hurt because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury." There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the University Hospitals Cleveland Medical Center's Research Subject Rights phone line at [redacted]

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to David Bajor, MD, and the research study staff at University Hospitals for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the University Hospitals Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Calithera Biosciences (the company who makes CB-839), its study monitors and representatives;
- Calithera Biosciences' collaborators and licensees (people and companies who partner with Calithera);
- The Food and Drug Administration;

- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;
- The Office for Human Research Protections (OHRP);
- Other staff from the Principal Investigator's medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

David Bajor, MD
Case Comprehensive Cancer Center
University Hospitals Cleveland Medical Center
11100 Euclid Ave.
Cleveland, OH 44106

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic and/or University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

If you decide to withdraw from the study and do not request that your samples be destroyed, they will continue to be analyzed as planned.

Questions about the Research
If you have any questions, you can ask the Principal Investigator and/or research staff at [redacted].

Emergency or after-hours contact information
If you are a University Hospitals patient, and you need to contact study staff outside normal business hours, you may contact [redacted] and you will be transferred to the answering service, which can put you in contact with David Bajor, MD, or the oncologist (cancer doctor) on call.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects' issues, you may contact the University Hospitals Cleveland Medical Center's Research Subjects Rights Phone line at [redacted].

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, 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.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Signature of Participant	Date	Printed Name of Participant
Signature of Witness	Date	Printed Name of Witness

(To be used if the participant is illiterate, blind or cannot physically sign but is able to provide informed consent.)

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research

study.

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

Study Calendar

Study Days	Pre-Study	Cycle 1			Cycle 2 and beyond, Day 1	Cycle 3, Day 14-21	Every 9 weeks	30 Day Follow-Up
		Day 1	Day 8	Day 15				
Informed Consent	X							
Demographics	X							
Medical History	X							
Height	X							
Weight	X	X			X			X
Vitals	X	X			X			X
Physical Examination	X	X			X			X
Medication Assessment	X	X			X			
Performance Status	X	X			X			X
Symptom Assessment	X	X	X	X	X			X
Routine blood tests	X	X	X	X	X			X
Pregnancy test (if needed)	X							
Tumor scans (CT scans)	X					X	X	
Research PK blood test				X				
CB-839		X	X	X	X	X		
Capecitabine		X	X		X			

CONSENT FOR CANCER RESEARCH

Project Title: CASE 1216, "Phase I/II Study of CB-839 and Capecitabine in Patients with Advanced Solid Tumors and Fluoropyrimidine Resistant PIK3CA Mutant Colorectal Cancer"

Sponsor: Case Comprehensive Cancer Center

University Hospitals' Principal Investigator: David Bajor, MD

Cleveland Clinic Principal Investigator: Alok Khorana, MD

Phase 2 consent

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC) and University Hospitals (UH).

What is the usual approach to my colorectal cancer?
You are being asked to take part in a clinical research study sponsored by the Case Comprehensive Cancer Center that tests CB-839 an investigational drug, in combination with capecitabine, a standard medication used for colon and rectal cancer.

You are being asked to take part in this study because you have colon or rectal cancer and the standard drug capecitabine (or its sister drug 5-fluorouracil or 5-FU) in combination with either oxaliplatin or irinotecan but also sometimes as a single agent is no longer effective treatment for your disease. The usual next approach is to receive another standard treatment for colon or rectal cancer. This may include either oxaliplatin or irinotecan if you haven't had either of them before, regorafenib or TAS-102. These are all standard medications used to treat colon and rectal cancer. You also have an abnormal feature in your colon or rectal tumor (called a PIK3CA mutation) that may make you more likely to respond to the combination of medicines used in this study than patients who do not have this abnormality in their colon or rectal tumor. By taking part in this study, you may be choosing to receive the study treatment instead of standard treatment, which may work better.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach with described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, for example, comfort/palliative care

Why is this study being done?
This study has two portions. The main goal of the Phase I portion of the study was to find what doses of CB-839 and capecitabine could safely be given to subjects without having too many side effects. Other purposes were to determine what side effects were seen with this combination of medicines. The Phase I portion of the study is now closed.

You are being asked to take part in the Phase II portion of the study. The Phase II portion of the study will research how many subjects show shrinkage in their tumor with this combination of medicines and what changes occur inside the cancer cells and blood cells following treatment.

CB-839 is an investigational (experimental) anti-cancer agent that has not been approved by the Food and Drug Administration (FDA) for use in patients with cancer. CB-839 blocks one of the pathways that cancer cells use to metabolize nutrients. Blocking this process may block the cancers energy supply and keep it from growing.

Capecitabine is an anti-cancer agent that is commonly used for patients with colon cancer, rectal cancer, and breast cancer and is approved by the Food and Drug Administration for treatment of these types of cancer. Most likely, you have had this medicine or a similar type of medicine as part of your colon or rectal cancer treatment. It is possible that when CB-839 is given with capecitabine, it will help the capecitabine work better, even if it had stopped working in the past, although this has not been proven.

A total of 18 to 40 subjects (men and women who are 18 years and older) will be enrolled in the Phase II portion of this trial.

How long will I be in this study?
You will receive study drugs until any of the following happen:

- your doctor has determined that your cancer has progressed,
- the study treatment becomes intolerable,
- the completion or termination of the study,
- severe side effects occur,
- you or your physician wishes to discontinue treatment, or
- the study Sponsor finds it necessary to limit or end this study.

After you are finished with the study treatment, the study doctor will ask you to visit the office for a treatment completion visit described below within 30 days after your last dose of study treatment.

What extra tests and procedures will I have if I take part in this study?
If you agree to take part in the study, there are required research-only studies, which we would like to ask you to take part in. This portion of the study will research what changes occur inside the cancer cells and blood cells following treatment.

Pharmacokinetic (PK) studies measure the amount of CB-839 that you have in your blood at any point in time after starting CB-839 treatment. These PK tests will study how your body processes the drugs. This will only be checked one time during the study and this will be between the 10th and 15th day of Cycle 1. At this time point, about half a teaspoon of blood will be drawn for research purposes. These PK samples will be sent to a central laboratory for analysis.

Pharmacodynamic (PD) studies look at how CB-839 affects your body. At each time point, about 3 tablespoons of blood will be drawn for research purposes. This will be done before you start your CB-839 and capecitabine treatment. It will be done a second time between the 10th and 15th day of Cycle 1.

Research biopsies
Two tumor biopsies will be done to check the characteristics of your tumor. These biopsies are required

for you to take part in the study. Your tumor has cells that could be affected by the study drug. A tumor biopsy will be done on a tumor that is accessible. Genetic sequencing will be done on these biopsies in order to determine tumor genomic changes caused by treatment with CB-839 and capecitabine.

A total of three biopsy cores will be taken each time you have a biopsy procedure.

Before You Begin This Study:
At any time before taking part in the study, it will need to be determined if your cancer has an abnormal feature that would make you a possible patient to be treated as part of this trial. This abnormality is a mutation in one of your genes, the PIK3CA gene. This gene is thought to be abnormal in about 15-30% of patients with colon or rectal cancer. You should talk with your doctor about how the abnormality may be checked in your colon or rectal cancer.

Your first biopsy needs to be done before your first dose of CB-839 and capecitabine and may be done up to 2 weeks before you start treatment.

During The Study
If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will have the following extra research tests and procedures done (please also refer to the Study Calendar on the last page).

The study treatment is divided up into cycles. Each cycle is 21 days long. You will take CB-839 twice a day for each day of a cycle. You will take capecitabine twice a day but only for the first 14 days of each cycle.

A biopsy of your tumor will be done again after being on CB-839 and capecitabine treatment for 10-15 days.

On Cycle 1, Day 15, do not take your morning dose of CB-839 at home. You will take it in clinic instead, right after the PK blood sample is drawn.

Because both of the medicines in this study are taken by mouth, you will be responsible for keeping a diary of when you take your medicines. A diary will be given to you by the study team and the study team will show you how to fill it out. You will need to bring your study diary with you to every visit.

Neither of the study medications should be crushed and need to be swallowed whole. You should keep your medications out of reach of children and away from other people living in your home.

The CB-839 capsules or tablets should be taken twice a day with food. You should take your first dose of the day with breakfast and your second dose of the day with dinner.

The capecitabine tablets should also be taken twice a day but on a slightly different schedule. You should take your capecitabine tablets within 30 minutes after eating breakfast and within 30 minutes after eating dinner.

If you miss a dose it should not be made up. If you have any questions about how to take your medications you should contact your study doctor.

What possible risks can I expect from taking part in this study?
If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

The CB-839 and capecitabine used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.
Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about, including the side effects of combining the CB-839 and capecitabine. If important new side effects are found, the study doctor will discuss these with you.

Risks of CB-839:

More common (seen in 10% or more of patients):
▪ feeling tired ▪ abnormal liver function tests (an increase in specific laboratory tests, such as: alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, and alkaline phosphatase), which may indicate liver damage ▪ nausea ▪ temporary sensitivity to light or discomfort with light

Less common (seen in 5% to 10% of patients):
▪ vomiting ▪ decreased appetite ▪ decreased red blood cell count

Findings from safety studies with the study drug in animals include reversible abnormalities in some tests of liver and gallbladder function.

Increases in liver enzymes, which could be a sign of liver damage, have been observed in participants treated with CB-839. Changes to date have been reversible and have not generally recurred on dose reduction.

If you do not understand any of these side effects, please ask the study doctor or study staff to explain these terms to you.

Risks of Capecitabine:

Likely (occurs in more than 20% of people – more than 20 out of 100 people)
▪ swelling of the body ▪ blisters on the skin ▪ redness, pain or peeling of palms and soles ▪ pain ▪ diarrhea, loss of appetite, nausea, vomiting ▪ sores in mouth which may cause difficulty swallowing ▪ anemia which may require blood transfusions ▪ infection, especially when white blood cell count is low ▪ bruising, bleeding ▪ feeling of “pins and needles” in arms and legs ▪ tiredness ▪ fever
Less likely (occurs in 3% to 20% of people – from 3 to 20 out of 100 people)
▪ blurred vision, dry or itchy eyes ▪ muscle spasms, body aches ▪ abnormal heartbeat ▪ restlessness, irritability ▪ swelling of face, fingers and lower legs ▪ constipation ▪ confusion ▪ difficulty with balancing

Rare, but serious (occurs in less than 3% of people – less than 3 out of 100 people)
▪ allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat ▪ difficulty speaking, walking or seeing ▪ internal bleeding which may cause blood in vomit or black tarry stools ▪ damage to the heart

The following should be **avoided**, if at all possible while you are on the study drug:

- There are many drugs that both CB-839 and capecitabine could potentially interact with, so you must discuss your medications with your study doctor. You must also inform your study doctor of any new medications you start while on this study. This includes over-the-counter medications, alternative therapies, or herbal medications.

Potential Risk or Discomfort from Procedures

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

Research Biopsies

Risks associated with biopsies include pain, redness, swelling, low blood pressure, excessive bleeding, bruising, or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site. Two to 3% of patients require hospitalization after a tumor biopsy.

Reproductive Risks

Women who are pregnant or breastfeeding cannot take part in this study because we do not know what effect CB-839 or capecitabine will have on an unborn child or whether the drugs are passed to a baby through mother's milk. To avoid risk to the fetus, it is important that you not be pregnant while participating in this study. If applicable, you must stop breastfeeding if you are being treated with the study drug. If you are a woman capable of having children, you will be given a pregnancy test before you begin the study, which must be negative in order for you to take part.

Women

If you are a woman capable of having children and choose to have sex, you must use two forms of acceptable contraception, including one barrier method (e.g. latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/cream/film/suppository), while you are in this study and for 3 months after your last dose of the study drug. One of the acceptable methods of contraception is the use of a condom along with a diaphragm with spermicidal agent (foam/gel/cream/film/suppository).

Additional methods are:

- IUD or IUS (intrauterine devices or intrauterine system, except IUD progesterone T) in addition to a barrier method with spermicide.
- Vasectomy by sole male partner.
- Use of approved oral, injected, or implanted hormonal methods of contraception in addition to a barrier method with spermicide. This must be approved by your study doctor before you begin taking the study drug.

Even if you use birth control during the study, there is still a chance you could become pregnant. If you become pregnant or you think you may be pregnant during the study, you must immediately stop taking the study drug and tell your study doctor. If you become pregnant during the study, the pregnancy will be followed to determine the outcome. If you become pregnant during the study, the study drug may involve unforeseeable risks to the unborn baby.

Men

Men who are able to father children must use adequate contraception. If you are a man you must:

- Prevent pregnancy in a female partner.
- Prevent exposure of a partner to semen by any means (not just intercourse).
- Prevent the possible exposure of a pregnant female to the study drug from your semen.
- You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, she should promptly notify her doctor.

You should not donate sperm for 3 months after your last dose of study drug. In addition, acceptable methods of birth control include using one of the following while you are in this study and for 3 months after your last dose of the study drug (due to the unknown effects of the study drug on the sperm):

- Abstinence (no sex)
- Condom plus spermicidal agent (foam/gel/cream/film/suppository)
- Vasectomy

Genetic Information Nondiscrimination Act (GINA)

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, 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 we 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 we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

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.

What possible benefits can I expect from taking part in this study?

There is no guarantee that you will receive any benefits from this study, and taking part in this study may or may not cause your health to improve. Information from this study may help doctors learn more about CB-839 and capecitabine. This information may benefit other patients with cancer in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?
Your involvement in this research study is voluntary and you will not be paid for your participation.

The investigational study agent, CB-839 will be provided free of charge and capecitabine will be covered by your insurance while you are participating in this study. Depending on your insurance, there may be a cost involved for the capecitabine as this is a standard medicine used for colon and rectal cancers. Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures. The blood work for research purposes will not be charged to you. It will be paid for by the research study.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Notice for Managed Care (Medicare Advantage Plan) Beneficiaries
Certain services provided to you as a participant in a clinical trial are allowable to be billed to, and paid by, your medical insurance. These services are referred to as "covered" clinical trial services. If you have a Medicare Advantage Plan as part of your medical insurance, the Centers for Medicare & Medicaid Services (CMS) require that traditional Medicare will be billed for those covered clinical trial services. When this occurs, you will remain responsible for paying the coinsurance and deductibles according your Medicare Advantage Plan. Your Medicare Advantage Plan should cover any associated cost share related to Medicare. Please speak with a financial counselor to understand what the specific financial impact will be for you associated with participating in this clinical trial.

What happens if I am injured or hurt because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from University Hospitals, Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans

for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924 or University Hospitals Cleveland Medical Center's Research Subject Rights phone line at (216) 983-4979.

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to David Bajor, Alok Khorana, MD, and the research study staff at Cleveland Clinic and/or University Hospitals for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, University Hospitals Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Calithera Biosciences, (the company who makes CB-839), its study monitors and representatives;
- Calithera Biosciences' collaborators and licensees (people and companies who partner with Calithera);
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;
- The Office for Human Research Protections (OHRP);
- Other staff from the Principal Investigator's medical practice group; University Hospitals, including the Center for Clinical Research and the Law Department; Government representatives or Federal agencies, when required by law.

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and

disclosures at any time by writing to:

David Bajor, MD Case Comprehensive Cancer Center University Hospitals Cleveland Medical Center 11100 Euclid Ave. Cleveland, OH 44106	or	Alok Khorana, MD Case Comprehensive Cancer Center Cleveland Clinic 9500 Euclid Ave. Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic and/or University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic and/or University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) and/or University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

If you decide to withdraw from the study and do not request that your samples be destroyed, they will continue to be analyzed as planned.

Questions about the Research
If you have any questions, you can ask the Principal Investigator and/or research staff at (216) 844-6003.

<u>Emergency or after-hours contact information</u>
If you are a University Hospitals patient, and you need to contact study staff outside normal business hours, you may contact [redacted] and you will be transferred to the answering service, which can put you in contact with David Bajor, MD, or the oncologist (cancer doctor) on call.

If you are a Cleveland Clinic patient, you should contact the page operator at [redacted] or toll free at [redacted], and ask for the oncologist (cancer doctor) that is on call.

Where Can I Get More Information?

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB [redacted] or the University Hospitals Cleveland Medical Center's Research Subjects Rights Phone line at [redacted]

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, 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.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

_____	_____	_____
Signature of Participant	Date	Printed Name of Participant
_____	_____	_____
Signature of Witness	Date	Printed Name of Witness

(To be used if the participant is illiterate, blind or cannot physically sign but is able to provide informed consent.)

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

_____	_____
Signature of Person Obtaining Consent	Date

_____
Printed Name of Person Obtaining Consent

Study Calendar

Study Days	Pre-Study	Pre-treatment	Cycle 1			Cycle 2 and beyond, Day 1	Cycle 3, Day 14-21	Every 9 weeks	30 Day Follow-Up
			Day 1	Day 8	Day 15				
Informed Consent	X								
Demographics	X								
Medical History	X								
Height	X								
Weight	X		X			X			X
Vitals	X		X			X			X
Physical Examination	X		X			X			X
Current Medication Assessment	X		X			X			
Performance Status	X		X			X			X
Symptom Assessment	X		X	X	X	X			X
Blood tests	X		X	X	X	X			X
Pregnancy test (if needed)	X								
CT chest, abdomen and pelvis	X						X	X	
Tumor biopsy		X			X				
Research labs		X			X				
CB-839			X	X		X	X		
Capecitabine			X	X		X			