UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A Phase 1/1b, Open-Label, Dose-Escalation Study of RMC-5552 Monotherapy in Adult Subjects with Recurrent Glioblastoma

Principal Investigator:	Nicholas Butowski, MD University of California, San Francisco [redacted]
Study nurses:	[redacted]

This is a clinical research study. The Principal Investigator, who is the person in charge of this study, or one of the members of the study team from the UCSF Department of Neuro-Oncology will explain the study to you.

Research studies include only people who choose to take part. It is your choice whether or not you want to take part in this study. Please take your time to make a decision about participating. You can discuss your decision with your family, friends, and health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you have recurrent glioblastoma that can't be surgically treated.

STUDY SUMMARY

Introduction: We are asking you to consider taking part in a research study being done at UCSF.

The first part of this consent form gives you a summary of this study. We will give you more details about the study later in this form. The study team will also explain the study to you and answer any questions you have.

Purpose of the study:

The purpose of this study is to test the safety, tolerability, and effectiveness of an investigational drug called RMC-5552 in patients with recurrent glioblastoma.

This study has two phases, Phase 1a and 1b.Cohort A will be enrolled in Phase 1a. Cohorts B and C will be enrolled in Phase 1b.

> In Phase 1a - Cohort A, we want to test the safety of RMC-5552 at different dose levels. We want to find out what good and/or bad effects it has on patients with recurrent glioblastoma.
>
> In Phase 1b – Cohort B, we want to find out what good and/or bad effects RMC-5552 has on patients with recurrent glioblastoma who are scheduled to have surgery to remove their tumor. We also want to find out if RMC-5552 is able to reach brain tumors.
>
> In Phase 1b – Cohort C, we want to find out what good and/or bad effects RMC-5552 has on patients with recurrent glioblastoma, at the highest and safest dose level found in Phase 1a of the study.

This consent form is for participation in Cohort A or C only. Your study doctor will let you know which cohort you will participate in.

RMC-5552 is a type of medicine called an mTOR inhibitor. These types of drugs prevent the formation of a specific group of proteins called mTOR. This protein controls cancer cell growth, and the study doctors believe stopping mTOR from forming will help to kill cancer cells.

RMC-5552 is an investigational drug—this means the drug has not been approved for use by the U.S. Food and Drug Administration (the FDA).

RMC-5552 will be manufactured and provided by Revolution Medicines at no cost to you. The National Institute of Health (NIH) and the Gateway for Cancer Research are providing financial support for this research study.

Study Procedures: If you choose to be in this study, you will be given the study drug (RMC-5552) once a week for as long as your cancer responds to the treatment. In addition, the main study procedures include brain MRIs, blood draws for safety and research tests, and physical exams with neurological exams.

You will be in this study for about 1 year and visit the research site approximately 55 times. This is dependent on how long you are on treatment. If you are found to be having some benefit from this treatment, it may be longer. If you are found not to have any benefit, or if your symptoms start to worsen and your doctor decides it is not in your best interest, you will have less visits on this treatment.

Possible Risks: There are risks to taking part in a research study. Some of the most likely risks of participation in this study include:

- Stomatitis/mucositis (swelling and redness in the lining of your mouth)
- Decreased appetite
- Fatigue (tiredness)
- Anemia (decrease in red blood cells)
- Dehydration (loss of fluid in your body)

There are also rare but serious risks of participation, like:

- Serious infusion-related reactions (such as a sudden drop in blood pressure)

We'll tell you about the other risks later in this consent form.

Possible Benefits: You may or may not benefit from participating in the study.

Your Other Options: You do not have to participate in this study. Your other choices may include:

- Getting treatment or care for your cancer without being in a study (for example, bevacizumab, nitrosoureas, or radiation therapy).
- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before agreeing to participate in this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions you want to help you decide whether to join the study. If you join this study, we will give you a signed copy of this form to keep for future reference.

DETAILED STUDY INFORMATION

This part of the consent form gives you more detailed information about what the study involves. Some of the information from above may be repeated here.

Why is this study being done?

The purpose of this study is to test the safety, tolerability, and effectiveness of an investigational drug called RMC-5552 in patients with recurrent glioblastoma.

This study has two phases, Phase 1a and 1b. Cohort A will be enrolled in Phase 1a. Cohorts B and C will be enrolled in Phase 1b.

In Phase 1a - Cohort A, we want to test the safety of RMC-5552 at different dose levels. We want to find out what good and/or bad effects it has on patients with recurrent glioblastoma.In Phase 1b – Cohort B, we want to find out what good and/or bad effects RMC-5552 has on patients with recurrent glioblastoma who are scheduled to have surgery to remove their tumor. We also want to find out if RMC-5552 is able to reach brain tumors.

In Phase 1b – Cohort C, we want to find out what good and/or bad effects RMC-5552 has on patients with recurrent glioblastoma, at the highest and safest dose level found in Phase 1a of the study.You are being asked to participate in Cohort A or C only. Your study doctor will let you know which cohort you will participate in.

RMC-5552 is a type of medicine called an mTOR inhibitor. These types of drugs prevent the formation of a specific group of proteins called mTOR. This protein controls cancer cell growth, and the study doctors believe stopping mTOR from forming will help to kill cancer cells.

RMC-5552 is an investigational drug—this means the drug has not been approved for use by the U.S. Food and Drug Administration (the FDA).

RMC-5552 will be manufactured and provided by Revolution Medicines at no cost to you. The National Institute of Health (NIH) is providing financial support for this research study.

What is the usual care for my condition?

The usual care for your condition (recurrent glioblastoma that can't be surgically treated) is treatment with bevacizumab, nitrosoureas, radiation therapy, or enrollment in clinical trials. There are no widely available standard treatments for recurrent glioblastoma. Talk to your doctor about all your treatment options. You are being asked to take part of this clinical trial due to your condition, and your doctor feeling as if this is a good option for your treatment options at this time.

How many people will take part in this study?

About 42 people will take part in this study at UCSF.

Up to 18 people will participate in Phase 1a. Twelve people will participate in Phase 1b.

An additional 12 people will participate in a different part of the study, called "Part B." Part B is described on a different informed consent form.

What will happen if I take part in this research study?

Before you begin the main part of the study:

You will need to have the following tests and procedures to find out if you can be in the main part of the study. Some of these tests and procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Your medical and disease history will be reviewed from your medical records.
- You will have a physical examination including measurement of your height, weight, and vital signs (temperature, blood pressure, respirations, and heart rate) and a neurological exam (an assessment of reflexes, senses, and mental functions).
- You will be asked about your ability to perform daily tasks such as dressing yourself and getting out of bed.
- You will be asked about any medicines you are taking including over-the-counter medicines, vitamins, or herbal treatments. You may have to change or stop taking certain medications, based on which medications may interact with the study drug. Please see the list at the end of this consent form for more information, and ask your doctor if you have any questions.
- You will be asked if you are feeling any unwanted effects (for example, from previous treatments).
- Your blood will be collected by inserting a needle into a vein in your arm. The blood sample (about 2 tablespoons in total) will be used for the following:
    - If you are a woman of childbearing age, blood will be collected for a pregnancy test. You must have a negative pregnancy test to participate in this study. Less than half a teaspoon of blood will be collected.
    - Hepatitis B virus (HBV) and Hepatitis C virus (HCV) tests: You will have a local HBV and HCV serology tests performed during screening. If your serology test shows that you had been previously infected with the Hepatitis B or C virus, you will be required to have Hepatitis B or C DNA testing done. You will receive the test results in person and will be counseled about the meaning of these results before and after the test. Positive test results will be reported to the public health department as required by state law. See the Risks and Confidentiality sections of this form for more details on this testing.
    - Routine safety tests such as blood cell counts and blood chemistry, to evaluate levels of certain substances in your blood that are related to your symptoms. You will be asked to fast (not eat for 8 hours before the test) for the blood glucose, triglyceride, and cholesterol tests.
    - Your blood will be collected for hemoglobin A1C tests. This test measures your average blood sugar levels
    - Coagulation tests to measure your blood's ability to clot, and how long it takes to clot.

- You will be asked to provide a urine sample for urinalysis. The urinalysis will look at the appearance, acidity level, and the chemistry of your urine.
- Your heart function will be evaluated by:
    - An electrocardiogram (ECG). An ECG records the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. This takes about 15-30 minutes.
    - An echocardiogram (ECHO) or a multigated acquisition scan (MUGA).
        - ECHO: This examination uses sound waves to make pictures of your heart, which helps determine how well your heart squeezes blood. You will be asked to lie on your left side while a technician places a probe with gel on your chest to create images of your heart to determine the function and size. The procedure is done in the cardiology department and will take approximately 45-60 minutes.
        - MUGA: This is a test that makes a motion picture that shows how well your heart pumps blood. The scan is performed by taking a small sample of your blood that is then "labeled" with a radioactive substance. The labeled blood sample is then re-injected into a vein in your arm and allowed to circulate in your body. Once the labeled blood has circulated around your body, a series of images (similar to a movie) are taken of your heart. You will be asked to lie flat on a table and remain still for about 10-20 minutes while the pictures of your heart are being taken. This test is done in the Nuclear Medicine Department and takes about 90 minutes.

- You will have a breathing test performed where you breathe in and out of a machine to measure your breathing capacity (using one of two procedures; spirometry or plethysmography)
- You will have a chest x-ray to look at your lungs. This will take approximately 15-30 minutes to complete.
- You will have a brain MRI. An MRI scan takes an image of your head or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is a contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed, which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the Radiology Department and takes approximately an hour and a half to complete.

During the main part of the study:

<u>If you enroll on Phase 1a of the study:</u>

If the tests and procedures show that you can be in the main part of the study, and you choose to take part, then you may receive different doses of RMC-5552, depending on the dose level you are assigned to. Treatment may continue until your disease gets worse, or if you experience bad side effects. You will be told what your dose level is found to be after you complete your screening procedures.

One cycle of treatment lasts for 21 days. RMC-5552 is infused intravenously (through a vein in your arm) over 1-2 hours, once a week (Days 1, 8, and 15 of each cycle).

If you enroll on Phase 1b of the study:

If the tests and procedures show that you can be in the main part of the study, and you choose to take part, then you will receive the maximum dose level of RMC-5552 that was determined to be safe. This dose level will be decided in Phase 1a.

One cycle of treatment lasts for 21 days. RMC-5552 is infused intravenously (through a vein in your arm) over 1-2 hours, once a week (Days 1, 8, and 15 of each cycle).

The following tests and procedures will be done during the main part of the study:

Cycle 1 Day 1

- You will have a complete physical exam (including neurological exam).
- Your vital signs will be collected.
- You will be asked about any medicines you are taking.
- You will be asked about your ability to perform daily tasks.
- You will be asked if you're having any unwanted effects (side effects).
- You will be asked to use a corticosteroid mouthwash (dexamethasone plus tacrolimus and dexamethasone alcohol-free solution) at least 15 minutes before your RMC-5552 infusion. You will be instructed to swish the mouthwash for 2 minutes and continue to use it up to 4 times a day. You will not be able to eat or drink for at least 1 hour after each mouthwash rinse. The study team will give you a diary to keep track of your mouthwash use. You will be instructed to bring the diary to every clinic appointment.
- Your blood will be collected (about half a tablespoon in total). The sample will be used for routine safety tests.
- You will receive RMC-5552 as an infusion, through a vein in your arm. The infusion will take about 1-2 hours.
- Your blood will be collected for research tests.
    - **For Phase 1a:** About 1 tablespoon of blood will be collected for research tests. Blood will be taken 9 different times, once before your infusion, once after the start of your infusion, once at the end of your infusion, and 6 times after your infusion. You will be asked to stay in the clinic about 6 hours after the end of the infusion in order for the study team to take these research samples. Your vital signs will be monitored during this time.

- **For Phase 1b:** About 1 teaspoon of blood will be collected for research tests. Blood will be taken 2 times, once before your infusion, and once at the end of your infusion. Your vital signs will be monitored during this time.

Cycle 1 Day 2

- You will be contacted by a member of the study staff to check on your health status. This may be done by a phone call, review of your medical records, or other method.
- You will be asked about any medicines you are taking.
- You will be asked if you're having any unwanted effects (side effects).

Cycle 1 Day 8

- Your vital signs will be collected.
- You will be asked about any medicines you are taking.
- You will be asked about your ability to perform daily tasks.
- Your blood will be collected (about half a tablespoon in total). The sample will be used for routine safety tests.
- You will be asked to use a corticosteroid mouthwash (dexamethasone alcohol-free solution). The study team will check your mouthwash diary.
- You will receive RMC-5552 as an infusion.

Cycle 1 Day 15

- Your vital signs will be collected.
- You will be asked about any medicines you are taking.
- You will be asked about your ability to perform daily tasks.
- Your blood will be collected (about half a tablespoon in total). The sample will be used for routine safety tests.
- You will be asked to use a corticosteroid mouthwash (dexamethasone plus tacrolimus and dexamethasone alcohol-free solution). The study team will check your mouthwash diary.
- Your blood will be collected for research tests.
    - **For Phase 1a:** About 1 tablespoon of blood will be collected for research tests. Blood will be taken 9 different times, once before your infusion, once after the start of your infusion, once at the end of your infusion, and 6 times after your infusion. You will be asked to stay in the clinic about 6 hours after the end of the infusion in order for the study team to take these research samples. Your vital signs will be monitored during this time.
    - **For Phase 1b:** About 1 teaspoon of blood will be collected for research tests. Blood will be taken 2 times, once before your infusion, and once at the end of your infusion. Your vital signs will be monitored during this time.

- You will receive RMC-5552 as an infusion.

Cycle 2+ Day 1

- You will have a complete physical exam (including neurological exam).
- Your vital signs will be collected.
- You will be asked about any medicines you are taking.
- You will be asked about your ability to perform daily tasks.
- You will be asked if you're having any unwanted effects (side effects).
- Your blood will be collected (about half a tablespoon in total). The sample will be used for routine safety tests.
- If you are a woman of childbearing age, blood will be collected for a pregnancy test. Less than half a teaspoon of blood will be collected.
- You will be asked to use a corticosteroid mouthwash (dexamethasone plus tacrolimus and dexamethasone alcohol-free solution). The study team will check your mouthwash diary.
- You will receive RMC-5552 as an infusion.
- Starting Cycle 3 Day 1:
    - Your blood will be collected to measure your fasting blood glucose and your lipid panel (triglycerides and cholesterol). You will be asked to fast (not eat for 8 hours before the test) for these tests. About 1 teaspoon of blood will be collected. This test will be repeated every 2 cycles (Cycle 5 Day 1, Cycle 7 Day 1, etc).
    - You will have an MRI of your brain on Cycle 3 Day 1 and Cycle 5 Day 1. Then you will have an MRI every 2-3 cycles (your study doctor will let you know how often).
- Starting Cycle 5 Day 1:
    - Your blood will be collected for hemoglobin A1C tests. This test measures your average blood sugar levels. Less than 1 teaspoon of blood will be collected. This test will be repeated every 4 cycles (Cycle 9 Day 1, Cycle 12 Day 1, etc).

Cycle 2+ Day 8 and Day 15

- Your vital signs will be collected.
- You will be asked about any medicines you are taking.
- You will be asked about your ability to perform daily tasks.
- Your blood will be collected (about half a tablespoon in total). The sample will be used for routine safety tests.
- You will be asked to use a corticosteroid mouthwash (dexamethasone plus tacrolimus and dexamethasone alcohol-free solution). The study team will check your mouthwash diary.
- You will receive RMC-5552 as an infusion.

When you are finished receiving RMC-5552:

You will have an End of Study visit. This visit will occur about 30 days after your last dose of RMC-5552. The following procedures will be done:

- You will have a complete physical exam (including neurological exam).
- Your vital signs will be collected.
- You will be asked about any medicines you are taking.
- You will be asked about your ability to perform daily tasks.
- You will be asked if you're having any unwanted effects (side effects).
- Your blood will be collected (about half a tablespoon in total). The sample will be used for routine safety tests.
- If you are a woman of childbearing age, blood will be collected for a pregnancy test. Less than half a teaspoon of blood will be collected.
- Your blood will be collected for coagulation tests (less than half a tablespoon will be taken).
- Your urine will be collected for a urinalysis.
- You will have an electrocardiogram.
- If it has been more than 2 cycles since your last Brain MRI, you will have a brain MRI.

After your last dose of study drug, the study team will contact you over the phone to ask about your cancer status. They will contact you every 3 months, until you pass away.

Study location:

Most study procedures will be done at the UCSF Parnassus Campus. Some procedures, such as your MRIs, may occur at other locations. Your study team will let you know as they schedule your appointments all of the locations where you will need to go.

How long will I be in the study?

You will be asked to take RMC-5552 until your disease gets worse, or until June 2026, when the investigational product will no longer be available for this study. After you are finished taking RMC-5552, the study doctor will ask you to visit the office for an end of study visit (about 30 days after your last dose). The study team will also contact you over the phone every 3 months until you pass away.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. They will tell you how to stop your participation safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the RMC-5552 can be evaluated by your doctor. Another reason to tell your doctor that

you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

If you withdraw from the study, any data or specimens we have already collected from you will remain part of the study records. After you withdraw, the researchers may still get information from your medical records if it is relevant to the study (e.g., laboratory results, treatment courses, health outcomes). You must tell the study team you do not want this information to be collected when you withdraw, otherwise it will be collected.

The study doctor may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the RMC-5552. In some cases, side effects can be serious, long-lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you experience while taking part in the study

Minimal clinical data is currently available for RMC-5552, the possible side effects are not fully known at this time.

Many drugs that are infused, such as RMC-5552, can be associated with infusion-related reactions. Symptoms of infusion-related reactions may include fever, rash, chills, and/or sweating. More serious infusion-related reactions may include significant drop in blood pressure. As with any drug, an allergic reaction can also occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or breathing difficulties.

You may have some or all of the side effects listed in this section. It is also possible that you might have other side effects that are not known at this time. As with any experimental drug, unknown and potentially serious or life-threatening side effects could occur with RMC-5552. Once the study drug is stopped, it is not known how long the side effects will last.

RMC-5552 may increase the number of immune system cells in your body to fight cancer. These cells may cause inflammation in the tumor, as well as in other tissues.

Therefore, if you have an autoimmune disease (an inflammation against a part of your own body), it may get worse.

The possible side effects listed below are based on results from animal studies with RMC-5552, from other drugs that are similar to RMC-5552, and because RMC-5552 is administered as an intravenous infusion.

General risks	• Lethargy, decreased energy, weakness, fatigue • Weight loss and/or loss of appetite • Fever • Decrease in body temperature (hypothermia) and/or feeling cold • Swelling of the feet, legs, hands, arms, or face • Infusion-related reaction (rash, fever, chills, sweating, decreased blood pressure) • Allergic reaction (swelling of the throat, difficulty breathing) • Increased risk of nosebleeds
Heart and blood vessels	• Decrease in blood pressure (hypotension) and/or increase in heart rate • Changes or abnormal heart rhythm
Lungs	• Lung inflammation, feeling short of breath, and/or cough
Stomach and intestines	• Nausea, vomiting, and diarrhea
Liver	• Abnormal blood tests that may indicate that your liver is not working properly or is damaged or inflamed
Blood cells and immune system	• Decrease in red blood cells (the cells in your blood that carry oxygen), also called anemia. This may make you feel more fatigued, lightheaded, or short of breath. • Decrease in white blood cells, which may increase your risk of infection and decrease your ability to fight an infection • Decrease in platelets (the cells that help your blood to clot). This may increase your risk of bleeding.
Skin	• Sores and inflammation in the mouth or on the lips • Itchiness of skin, skin rash, dry skin, and/or skin redness • Bleeding, bruising, itchiness, or other reactions at infusion sites

Kidneys	• Decrease in your kidneys' ability to filter toxins from your blood • Abnormal blood tests that may indicate that your kidneys are not working properly (blood urea nitrogen and creatinine)
Reproductive system	• Women: Menstrual cycle changes, early menopause, decreased fertility, and/or decreased ability to carry a baby in the future due to changes in the ovaries, uterus, and vagina • Men: Decreased fertility
Nervous system	• Headaches • Changes in taste
Other risks	• High blood sugar (hyperglycemia) • High cholesterol and fat in the blood (hyperlipidemia, hypercholesterolemia, hypertriglyceridemia) • Low amounts of phosphate in the blood (hypophosphatemia)

The risks below were identified from 14 patients who have received RMC-5552 (with cancers other than glioblastoma). As we discover more safety information regarding the drug, the risks section below will be updated and you will be identified of any new risks.

Risks related to RMC-5552

Likely (about 20%-40% of patients)

- Stomatitis/mucositis (swelling and redness in the lining of your mouth)
- Decreased appetite
- Fatigue (tiredness)
- Anemia (decrease in red blood cells)
- Dehydration (loss of fluid in your body)
- Nausea
- Vomiting
- Hyponatremia (low sodium in your blood)

Risks related to Study Procedures

- **Blood Drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.
- **Chest X-ray risks:** An x-ray involves the risks of radiation. See Radiation risks.
- **Dose escalation risks (for patients in Phase 1a only):** Since patients will be assigned to different doses of study drug some patients may receive a dose of the drug that is too small to be effective while others may receive a higher dose that may cause increased side effects. You can ask your study doctor what dose you will be given.

- **ECG risks:** The adhesive on the leads may cause skin irritation including redness, itching, swelling or rash. These symptoms are generally mild and clear up on their own.
- **Echocardiogram (ECHO) risks:** The cardiac echogram might cause you to be uncomfortable from the pressure of the probe on your chest or lying still for the examination.
- **Hepatitis testing risks:** Being tested for Hepatitis may cause anxiety regardless of the test results. A positive test indicates that you have been infected with the Hepatitis virus. If you test positive, we will refer you to a source of medical care and treatment. Receiving positive results may make you very upset. If other people learn about your positive test results, you may face discrimination. If your test is negative, there is still the possibility that you could be infected with the Hepatitis virus and test positive at some time in the future.
- **MRI scan risks:** Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from happening; loose metal objects, like pocketknives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

  Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear earplugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

  Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this study.

- **Contrast agent (gadolinium) risks:** A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

  Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

- **MUGA scan risks:** The MUGA scan involves exposure to radiation. Like all injections it may feel like a small sting and there may be possible bruising at the injection site. You may be uncomfortable lying flat.
- **Radiation risks:** No radiation risk beyond routine clinical care: This study involves radiation exposure as part of routine clinical care. You will not receive additional radiation as a result of participating in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.
- **Reproductive risks:** RMC-5552 may cause harm to a developing fetus (unborn child) or your fertility; these risks are not yet known.

  If you are a woman: If you decide to take part in this study and you are able to become pregnant, you must have a pregnancy test done during the screening period and at the safety/end-of-treatment visit. You cannot take part in this study if you are pregnant or breastfeeding, or plan to become pregnant during your study participation, because you or your child/fetus may be exposed to an unknown risk. It is not known if RMC-5552 is transferred into breast milk. Therefore, if you are breastfeeding and wish to be in this study, you will be required to discontinue nursing during study treatment and for an additional 3 months after stopping RMC-5552.

  If you are pregnant or think you could be pregnant, it is important for you to tell the study doctor or study staff immediately. If you become pregnant during the study, RMC-5552 will be stopped and you will be asked to return to the study clinic for a follow up visit. The study doctor or study staff will discuss with you the possible risks to your unborn child, as well as options available to you. Your health and your baby's health will be monitored throughout your pregnancy. Even if you are no longer in the study, your study doctor will contact you after your baby is born to find out about the baby's health. This information will be shared with Revolution Medicines, the company that manufactures RMC-5552.

  Furthermore, you must avoid becoming pregnant while you take part in this study. If you are able to become pregnant, you must be using highly effective methods of birth control during this study and for at least 3 months after the last dose of RMC-5552. Your study doctor will talk to you about the best method of birth control for you.

  Acceptable methods of birth control include the following:

  - True abstinence: When this is in line with your preferred and usual lifestyle. Periodic abstinence(e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Sterilization: Surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago.
  - Male Partner Sterilization
  - Use of a combination of any two of the following:

- Placement of an intratuterine device (IUD) or intratuterine system (IUS)
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- Appropriate hormonal contraceptives (including any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent including oral, subcutaneous, intrauterine, or intramuscular agents)

If you are a man: There may be risks to a fetus (unborn baby) that you father during or after the study. The study doctor will talk to you about the birth control options you and/or your partner must use during the study and for at least 3 months after the last dose of study drug. You must also agree not to donate sperm during the study and for at least 3 months after the last dose of study drug.

If you are in an **exclusive same-sex relationship** *and are not engaged in attempts to become pregnant or father a child, are not planning to donate eggs or sperm*, and are not breastfeeding, it is not necessary to use birth control. If you are a female, you will still have to have pregnancy tests according to the study protocol.

You must notify the study doctor if you suspect that your partner may be pregnant. The study doctor will ask for information about the pregnancy and the health of the baby after birth. This information will be shared with Revolution Medicines, the company that manufactures RMC-5552.

- **Unknown Risks:** The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

  For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

You may or may not benefit from participating in the study.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study (for example, bevacizumab, nitrosoureas, or radiation therapy).
- Taking part in another study.
- Getting no treatment.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It

does not treat the cancer directly but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about your choices before deciding if you will take part in this study.

How will my specimens and information be used?

Researchers will use your specimens and information to conduct this study. Once the study is done using your specimens and information, we may use the remaining specimens and information collected for future research studies or share them with other researchers so they can use them for other studies in the future. We will not share your name or any other personal information that would let the researchers know who you are. We cannot guarantee that this will prevent future researchers from determining who you are. We will not ask you for additional permission to share the de-identified information and specimens.

Researchers may use your specimens (for example, blood, tissue, saliva, etc.) to look at all of your DNA (this is called “whole-genome sequencing. DNA contains information that determines things like eye color, height, or disease risk that are passed on from parent to child.

Research results: There may be times when researchers using your information and/or specimens may learn new information. The researchers may or may not share these results with you, depending on a number of factors.

Commercial Use: Your specimens and/or information obtained from your specimens may be used for commercial use. If this happens, you will not share in any profits.

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and any information added to your medical record as a result of your participation. Study tests that are performed by research labs, and information gathered directly from you by the researchers will be part of your research records and may be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

California regulations require that new cases of Hepatitis B and C be reported to the county public health department.

The reports include details like participant name, social security number, and other identifying information. Information about these infections is used to track these diseases statewide and nationwide. Other than this required reporting, test results will be treated confidentially by the study staff and personally identifying information will not be reported to other departments or agencies. For a full list of reportable conditions, go to the following link:

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/ReportableDiseases.pdf

Authorized representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- Representatives of Revolution Medicines.
- Representatives of Gateway for Cancer Research
- Representatives of the National Institutes of Health
- Representatives of the University of California
- Representatives of the Food and Drug Administration (FDA)
- Representatives of the Office of Human Research Protections (OHRP)

Are there any costs to me for taking part in this study?

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

If you have questions about what costs you will be responsible for, please talk with the study investigator before deciding to enroll in the study. Depending on the type of study, some of your costs could be substantial.

Revolution Medicines will provide RMC-5552 at no cost to you.

Will I be paid for taking part in this study?

You will not be paid for taking part in this study.

Will I be reimbursed if I pay expenses related to my participation in this study?

You will not be reimbursed for expenses if you take part in this study

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

It is important that you tell your study doctor, Nicholas Butowski, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call the study team [redacted]

> **Treatment and Compensation for Injury:** If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board [redacted].

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

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this 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 regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

You may request a copy of the health information collected from you as part of this research after the study is completed. You may not have access to this information while the study is still being conducted.

Who can answer my questions about the study?

You can contact the research team with any questions, concerns, or complaints you have about this study [redacted]

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the office of the Institutional Review Board at 415-476-1814.

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. The National Clinical Trial (NCT) number for this study is NCT05557292.

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OPTIONAL RESEARCH PARTICIPATION

This section of the informed consent is about optional future contact of participants in the main study. You can still be in the main study even if you say "no" to allowing optional future contact.

Future Contact

We want to know if we may contact you in the future to see if you are interested in participating in other research studies.

If you agree and we contact you to tell you about a study, you have no obligation to actually participate in any study. You can decide when you are told about the study if you want to receive more information about the study. There would be a new consent process for that study.

If at any time you decide you no longer want to be contacted about future studies, please let us know [redacted]

Making Your Choice

Please read the sentence below and mark your choice by putting your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care or your participation in the main study.

1. **Someone may contact me in the future about taking part in more research.**

YES	***NO***

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CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
	Name of Participant (Printed)
Date	Signature of Person Obtaining Consent
	Name of Person Obtaining Consent (Printed)
Date	Witness Signature – Only required if the participant is a non-English speaker
	Witness's Name (Printed) – Only required if the participant is a non-English speaker

Prohibited Medications List

A partial list of drug classes that potentially prolong QTc interval and drugs that are strong CYP3A inhibitors and/or inducers is provided below.

Medications Known to Prolong QTc Interval		
Amiodarone	Anagrelide	Arsenic trioxide
Azithromycin	Chloroquine	Chlorpromazine
Cilostazol	Ciprofloxacin	Citalopram
Disopyramide	Dofetilide	Donepezil
Dronedarone	Droperidol	Erythromycin
Escitalopram	Flecainide	Fluconazole
Haloperidol	Ibutilide	Levofloxacin
Methadone	Moxifloxacin	Ondansetron
Oxaliplatin	Pentamidine	Pimozide
Procainamide	Propofol	Quinidine
Sevoflurane	Sotalol	Thioridazine
Vandetanib	—	—
Time-Dependent Strong CYP3A Inhibitors		
Boceprevir	Clarithromycin	Telaprevir
Ritonavir	Cobicistat	Conivaptan
Indinavir and ritonavir	Saquinavir and ritonavir	Tipranavir and ritonavir
Danoprevir and ritonavir	Lopinavir and ritonavir	Troleandomycin
Diltiazem	Nefazodone	Verapamil
Elvitegravir and ritonavir	Nelfinavir	Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
Strong CYP3A Inducers		
Carbamazepine	Mitotane	Rifampin
Enzalutamide	Phenytoin	St. John’s wort

Note that this list is not comprehensive.

The list of medications that are known to prolong QTc has been obtained from www.crediblemeds.org. Check www.crediblemeds.org for any updates.

For additional information and updates concerning strong CYP3A inhibitors and inducers and strong P-gp inhibitors, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. In addition, consult the prescribing information when determining whether a concomitant medication can be safety administered with study intervention. Contact the Investigator if questions arise regarding medications not listed.

Permitted Medications with Limitations

A partial list of drug classes that are non–time-dependent strong CYP3A inhibitors, strong P-gp inhibitors, and/or sensitive CYP2C8 or CYP3A4 substrates is provided below. These medications are permitted during study intervention with limitations.

Non–Time-Dependent Strong CYP3A Inhibitors		
Itraconazole	Ketoconazole	Posaconazole
Voriconazole	—	—
Strong P-gp Inhibitors		
Carvedilol	Cyclosporin	Itraconazole
Lapatinib	Propafenone	Ranolazine
Sirolimus	Tacrolimus	—
Sensitive CYP2C8 substrate		
Repaglinide	—	—
Sensitive CYP3A4 substrate		
Alfentanil	Avanafil	Budesonide
Buspirone	Darifenacin	Darunavir
Ebastine	Eletriptan	Eplerenone
Felodipine	Indinavir	Lomitapide
Lovastatin	Lurasidone	Maraviroc
Midazolam	Naloxegol	Nisoldipine
Quetiapine	Saquinavir	Simvastatin
Sildenafil	Tacrolimus	Ticagrelor
Tipranavir	Tolvaptan	Triazolam
Vardenafil	—	—

Note that this list is not comprehensive.

For additional information and updates concerning strong CYP3A inhibitors and strong P-gp inhibitors, refer to the following link: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

In addition, consult the prescribing information when determining whether a concomitant medication can be safety administered with study intervention. Contact the Investigator if questions arise regarding medications not listed.