ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE ABTC-1604

PHASE 0/I STUDY OF AMG 232 (KRT 232) CONCENTRATIONS IN BRAIN TISSUE IN PATIENTS WITH RECURRENT GLIOBLASTOMA AND OF AMG 232 (KRT 232) IN COMBINATION WITH RADIATION IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA AND UNMETHYLATED MGMT PROMOTERS

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[X] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[X] Other: Updated CTSU Language	

No recommended IRB level of review is provided by the Alliance as the CIRB is the IRB of record for this trial.
The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page

- The word "Name:" has been removed from the contact information for Dr. Eudocia Lee.
- Institutional affiliation and telephone numbers have been removed for all Co-Chairs to align with the Alliance Model Protocol Template.
- Drs. Priscilla Brastianos and Jan Sarkaria have replaced Dr. Eva Galanis as the Neuro-Oncology Committee Co-Chairs; all contact information has been updated.
- Sarah Reed has replaced Erin Twohy as the Primary Statistician; all contact information has been updated.
- The Secondary Statistician, Dr. Susan Geyer, has been removed.
- The email address for Alexandra LeVasseur, the Protocol Coordinator, has been updated.
- The list of Limited Access Institutions has been updated as follows:
    - UCLA and University of Pennsylvania have been removed as these institutions do not hold an Alliance membership.

- UCSF, Sharp Memorial Hospital, MGH, MSKCC, Columbia, and MDACC have been added.

Cover Page (Page 2)

- Dr. Nathalie Agar has replaced Michelle Rudek as the contact for the Pharmacology Laboratories and as the Participating Investigator for the Intratumoral Drug Level Studies, Blood Pharmacokinetic Studies, and MIC-1 serum studies; all contact information has been updated accordingly.
- The institution name and telephone number for Lori Capello have been removed as all inquiries should be directed to the Nursing Contact via email.
- Dr. Donna Vattanakul has replaced Myounghee Lee as the Pharmacy Contact; all contact information has been updated accordingly.

Section 4.5 (Cranial Irradiation)

- In Section 4.5.2, the phrase "or other standard cranial immobilization device" has been added to the 1st sentence of the 2nd paragraph for clarity.
- In Section 4.5.3, in the 2nd paragraph, the word "physician" has been added to the 2nd sentence, and the phrase "and series" has been added to the 3rd sentence for clarity.
- In Section 4.5.4, the * symbol has been added to the 2nd-4th rows of the 1st column along with a corresponding footnote below the table which reads: "As noted below, in patients receiving a simultaneous integrated boost, "5400" or "5100" will replace "4600" in each of these structure names."
- In Section 4.5.4 under the **Detailed Specifications** heading, the specifications for GTV_4600, CTV_4600, GTV_6000, and CTV_6000 have been completely revised for clarity and accuracy, and a new final paragraph has been added that begins, "Alternatively, consistent with prior protocols, for patients receiving IMRT…"
- In Section 4.5.7, a new final paragraph and three subsequent statements has been added below the table entitled **Delivery Compliance criteria**.
- In Section 4.5.12, all text has been completely revised with updated CTSU boilerplate language.

Section 6.1 (AMG 232 [KRT 232] [NSC 789723])

- Under Investigator Brochure Availability, the instructions to obtain IBs have been updated as the PMB has switched from using the PMB Online Agent Order Processing (OAOP) application to the PMB AURORA application.
- Under Useful Links and Contacts, the 4th bullet point has been completely updated to provide the link for the AURORA application.
- In Section 6.1.1, the section has been completely updated as agent requests are now being done through the PMB AURORA application.

Section 7.0 (Procedures for Patient Entry on Study)

This section has been completely revised with updated CTSU boilerplate language.

Section 9.5 (Correlative Studies)

- In Table 9.5 "Synopsis of Correlative Biomarker Studies," the shipping location for the Plasma Pharmacokinetics, MIC-1 levels, and Tumor Tissue Pharmacokinetics has been updated to

Nathalie Agar, PhD as Dr. Agar has taken over as the contact for the Pharmacology Laboratory studies.

- In Section 9.5.2.1, in the 3rd paragraph, "Dr. Nathalie Agar" has replaced "the APC laboratory" to reflect the change in pharmacology laboratory. In the same section under the **Shipping** heading, the contact name and information has been updated to Dr. Nathalie Agar (previously, "Analytical Pharmacology Core Laboratory").
- In Section 9.5.3, in the section entitled "**Shipping of Specimen(s)**," the name "Dr. Nathalie Agar" has replaced "the APC Laboratory" for accuracy, and in the section entitled "**Site(s) Performing Correlative Study**," the name and contact information for Dr. Nathalie Agar has replaced the information for the ABTC Pharmacokinetics Center.
- In Section 9.5.4, in the section entitled "**Shipping of Specimen(s)**," the name "Dr. Nathalie Agar" has replaced "the APC Laboratory" for accuracy, and in the section entitled "**Site(s) Performing Correlative Study**," the name and contact information for Dr. Nathalie Agar has replaced the information for the ABTC Pharmacokinetics Center.

Section 12.1 (Data Reporting)
This section has been completely revised with updated CTSU boilerplate language.

UPDATES TO THE CONSENT FORM:
No changes have been made to the informed consent document.

A replacement protocol and model consent forms have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

Consent Form – Part 1-Drug Concentration

Study Title for Study Participants: ABTC 1604 – Testing the ability of AMG 232 (KRT 232) to get into the tumor in patients with brain cancer.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: ABTC 1604 – Phase 0/I study of AMG 232 (KRT 232) concentrations in brain tissue in patients with recurrent glioblastoma and of AMG 232 (KRT 232) in combination with radiation in patients with newly diagnosed glioblastoma and unmethylated MGMT promoters

What is the usual approach to my brain cancer?

You are being asked to take part in this study because you have a type of brain cancer called glioblastoma which has grown or has recurred and requires surgery. You have already been treated with surgery, radiation, and chemotherapy. People who are not in a study are usually treated with more chemotherapy and additional surgery if appropriate. Bevacizumab is also an available and FDA-approved treatment for patients with recurrent glioblastoma who have not previously received it, although it does not cure and its effect on survival is unknown. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

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
- you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms.

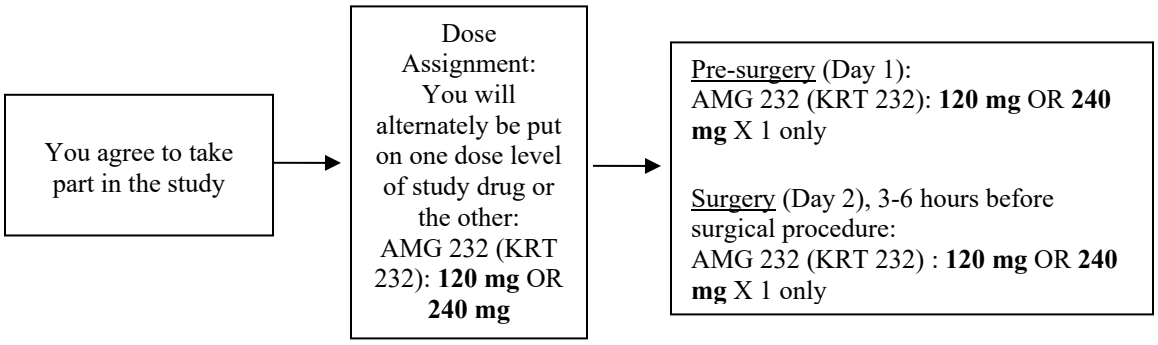
Why is this study being done?

This is Part 1 of the study. One reason that chemotherapy drugs might not work is that the drugs may not be able to get into the brain tumor and kill cancer cells. The purpose of Part 1 is to determine how much the study drug, called AMG 232 (KRT 232), reaches the brain tumor. Part 1 is only for people who require surgery for their brain tumor. AMG 232 (KRT 232) is not FDA-approved to treat brain cancer but it has slowed tumor growth in several types of tumors in animals.

There will be 20 people taking part in Part 1 of this study.

What are the study groups?

Part 1 study participants will be assigned to receive AMG 232 (KRT 232) at either 120 mg per day or 240 mg per day. The dose each patient is assigned will alternate between the two levels: the first person to enroll in the study will be assigned AMG 232 (KRT 232) at 120 mg per day and the next person will be assigned AMG 232 (KRT 232) at 240 mg per day, and so on.



All study participants will receive their assigned study drug, either AMG 232 (KRT 232) 120 mg or 240 mg, once a day for 2 days only. AMG 232 (KRT 232) is to be taken a day before the surgery day (Day 1) and on the day of the surgery (Day 2).

AMG 232 (KRT 232) tablet is to be taken by mouth on an empty stomach at least 2 hours after a meal and 2 hours before the next meal with a full glass (240 mL) of water. Take the tablet with water (no beverage). On the day of the surgery, AMG 232 (KRT 232) is to be taken 3-6 hours before the surgical procedure begins.

During your surgery a portion of your tumor will be taken to measure the concentration of the drug in the tumor and to determine certain characteristics of the tumor.

After recovery from surgery, within 45 days, if your tumor is found to have a characteristic called "*TP53* wild-type", you will receive AMG 232 (KRT 232) at 240 mg once daily for 7 consecutive days every 21 days, to look at side effects and determine how you respond to the study drug . Patients who do not have *TP53* wild-type tumors will be off study treatment.

You will keep a pill diary. You need to write down the amount of AMG 232 (KRT 232) tablet and the time it is taken in the pill diary. Take AMG 232 (KRT 232) tablet preferably at the same time each day. Missed dose for reasons other than side effects can be taken in the same day. Missed dose due to vomiting should not be re-taken and should wait until your next scheduled dose.

Every 21 days you will return to the clinic to see the study doctor again. The study doctor supplies the study drug during the clinic visits. Empty bottles, any remaining medication, and the medication diary should be returned to the study doctor at each visit.

How long will I be in this study?

If your tumor is found to have a characteristic called *TP53* wild-type, you will continue to receive the study drug and be in the study until your tumor grows, or you have side effects that cause your condition to worsen, or you desire to stop treatment. If you do not have *TP53* wild-type tumor, you will be off study treatment following surgery. For all patients, after you stop taking the study drug, your doctor will continue to watch you for side effects and follow your condition for at least 30 days.

You will be contacted every 2 months for two years after you stop the study drug to find out how you are doing. After 2 years, you will be contacted every 6 months.

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, if you choose to take part in the study, then you will need the following extra tests. They are not part of the usual approach for your type of cancer.

Before you begin the study:

- Collection of 2 extra blood samples for studies of drug levels and a protein level in your blood.
- Collection of stored pieces of cancer tissue, if available, from your initial surgery at the diagnosis of glioblastoma, to look at certain features of the tumor. The tissue will be requested from the facility where you had your initial surgery to remove the tumor.

During the study:

- Collection of 4 extra blood samples around the time of surgery for studies of drug levels in your blood and other characteristics.
- Collection of pieces of cancer tissue from your tumor during surgery to measure the amount of study drug in your tumor and to determine certain characteristics of your tumor. The tissue will be collected during your normal surgery to remove the tumor.
  If sufficient tissue is available a portion will be used so that scientists can try to "grow" the tumor cells in the laboratory to make new and better models to help them learn about cancer and to test new cancer drugs. Models are used to help understand the behavior of living tumor cells outside the human body. Animals such as mice provide a living system in which to grow human cancer cells.

These samples are required in order for you to take part in this study because the research on the samples is an important part of the study. The results of research studies performed with these samples will be published in scientific journals, but your name or other personally identifiable information will not be disclosed. The results of the research studies will not be reported to you, your family, or your doctor.

Neither you nor your health care plan/insurance carrier will be billed for the collection or processing of the research blood samples and tumor tissue that will be used for this study.

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 the AMG 232 (KRT-232) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

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.

There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you and your blood relatives could be found during a study.

The AMG 232 (KRT-232) 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.

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.
- [redacted]
- Some side effects may be mild. Other side effects may be very serious and may even result in death.

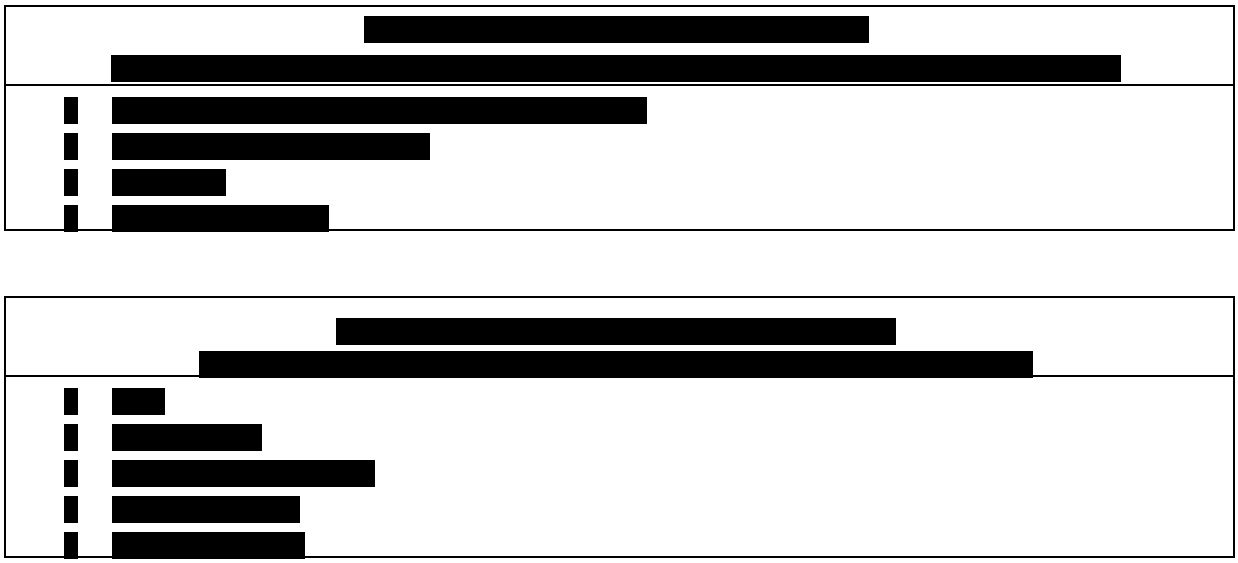
The study doctor will review the medications you are taking and discuss medications, over-the-counter products, or herbal medicines that you need to avoid while on study with AMG 232 (KRT 232). You will be provided with a patient medication handout and wallet card with information about possible drug interactions.

You can ask your study doctor questions about side effects at any time. Here are important points about how you and the study doctor can make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The table below shows the most common and the most serious side effects that researchers know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Table of Possible Side Effects for AMG 232 (KRT-232)



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

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study and through 5 weeks for women and 3 months for men after your last dose of study medication. The medication used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

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

This study is unlikely to help you. This study may help us learn things that may help people 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 rules

- If the study is stopped by the sponsor, 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.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number).*

What are the costs of taking part in this study?

The study drug AMG 232 (KRT 232) will be supplied at no charge while you take part in this study. The cost of getting the drug ready and giving it to you is also provided at no charge. It is possible that AMG 232 (KRT 232) may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and the drug company supporting this study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.

- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the study.

Participant's signature_____

Date of signature_____

Research Study Informed Consent Document - Part 2 - Dose Finding

Study Title for Study Participants: Finding the best dose of AMG 232 (KRT 232) combined with radiation therapy in patients with brain cancer.

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
ABTC 1604 – Phase 0/I study of AMG 232 (KRT 232) concentrations in brain tissue in patients with recurrent glioblastoma and of AMG 232 (KRT 232) in combination with radiation in patients with newly diagnosed glioblastoma and unmethylated MGMT promoters (NCT03107780)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have newly diagnosed brain cancer.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

Why is this study being done?

This study is being done to answer the following question: What is the best dose of AMG 232 (KRT) combined with radiation therapy for patients with brain cancer? We are doing this study because we want to find out if this approach is better or worse than the usual approach for your newly diagnosed glioblastoma.

What is the usual approach to my brain cancer?

The usual approach for patients who are not in a study is treatment with surgery, radiation, and chemotherapy. You have already been treated with surgery. Your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

What are my choices if I decide not to 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 research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will get 6 weeks of radiation on Mondays-Fridays, which is usual for your brain cancer. During those 6 weeks of radiation, you will be asked to take the study drug by mouth according to your assigned dose level and schedule. Your assigned schedule will determine if you will take the drug 2, 3, 4, or 5 times a week during your radiation. You will be provided a medication diary to help you keep track of your assigned study drug schedule, and so you can record when you take your study drug. You will have radiation and take the study drug for up to 6 weeks, then you will have a rest period of 4 weeks for a total of 10 weeks.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

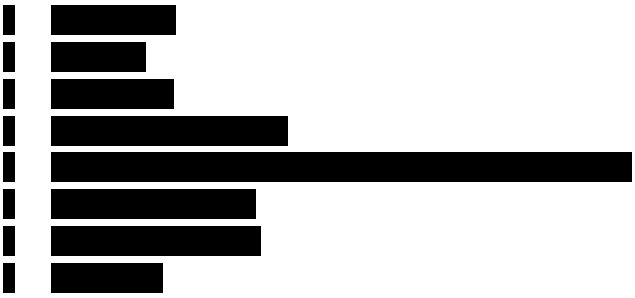
Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the study drug may not be as good as the usual approach to your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study drug. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:



There may be some risks that the study doctors do not yet know about.

Benefits

There is some evidence in people with brain cancer that adding AMG 232 (KRT 232) to the usual approach can stabilize cancer for longer than the usual approach alone. However, we do not know if this will happen in people with your type of cancer. It is unlikely that adding AMG 232 (KRT 232) to the usual approach will help you live longer than the usual approach alone. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your 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.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI) , Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (Alliance). The study sponsor is the organization who oversees the study.

What is the purpose of this study?

This is Part 2 of the study. Part 2 is a phase I study. A phase I study tests the safety, side effects, best dose, and timing of a new treatment. The purpose of Part 2 is to find the maximum tolerated dose and schedule of a study drug called AMG 232 (KRT 232) when given with standard radiation therapy (RT). AMG 232 (KRT 232) is an anticancer drug that may have activity against brain tumors and increase overall survival. This drug has been tested in people, including people with brain cancer. Part 2 tests different doses of AMG 232 (KRT 232) to see which dose is safer in people with brain cancer who are receiving standard radiation therapy.

There are some people who have a feature of their tumor called "p53 wild-type". This study only includes people with this tumor feature. Before you begin the study, some tissue from your original surgery for brain cancer will be requested to determine if your tumor shows evidence of p53 wild-type. If your tumor tissue does not have this feature, you will not be able to participate in the study.

There are some people who are less sensitive to TMZ. They have a type of tumor with a feature called "unmethylated MGMT promoter". This study only includes people with this type of tumor. If you participate in this study you will not receive TMZ during your radiation therapy; you will receive radiation therapy with the study drug AMG 232 (KRT 232). The combination of AMG 232 (KRT 232) and radiation therapy is experimental and not FDA approved for treatment of patients with MGMT promoter unmethylated newly diagnosed glioblastoma. After the study is over (after 10 weeks) you will go on to receive the standard TMZ treatment that usually follows radiation therapy.

There will be between 18 and 66 people taking part in Part 2 of this study.

What are the study groups?

Different people taking part in this study will get AMG 232 (KRT 232) starting at one of 2 different doses and dosing schedules, combined with standard RT.

Treatment schedule: You will either be in Schedule 1 or Schedule 2. If you are in schedule 1, you will get AMG 232 (KRT 232) at 120 mg per day by mouth, starting at 3 times per week, during the 6 weeks of standard RT. If you are in schedule 2, you will get AMG 232 (KRT 232) at 240 mg per day by mouth, starting at 2 times per week, during the 6 weeks of standard RT. Different doses and schedules of the study drug AMG 232 (KRT 232) will be given to groups of several study participants (3-6 people per group). The first group of study participants on each of the 2 schedules will take the dose the least number of times per week during standard radiation therapy. If the drug does not cause serious side effects, it will be given to a group of several other study participants on increasing numbers of days each week during radiation therapy. The schedules will continue to increase for every group of study participants until side effects occur that require the dosing schedule to be decreased. When the maximum tolerated dosing schedule of AMG 232 (KRT 232) given with radiation is found for each of the schedules, it will be given to an additional group of study participants on each schedule for additional safety evaluation (Expansion Cohorts). Then no more groups of study participants will be enrolled.

AMG 232 (KRT 232) is to be taken by mouth with a glass of water with or without food.

You should take AMG 232 (KRT 232) at approximately the same time each day. AMG 232 (KRT 232) should be taken 1-2 hours before each weekday session of radiation therapy.

If you miss a dose of AMG 232 (KRT 232) for reasons other than side effects, the missed dose can be taken later in the same day. If you miss a scheduled dose due to vomiting, you should not re-take the dose and should wait until your next scheduled dose.

During radiation therapy (6 weeks) you will return to the clinic to see the study doctor after about 3 weeks of treatment. The study doctor supplies the study drug during clinic visits. Empty bottles, any remaining medication, and the medication diary should be returned to the study doctor at these visits.

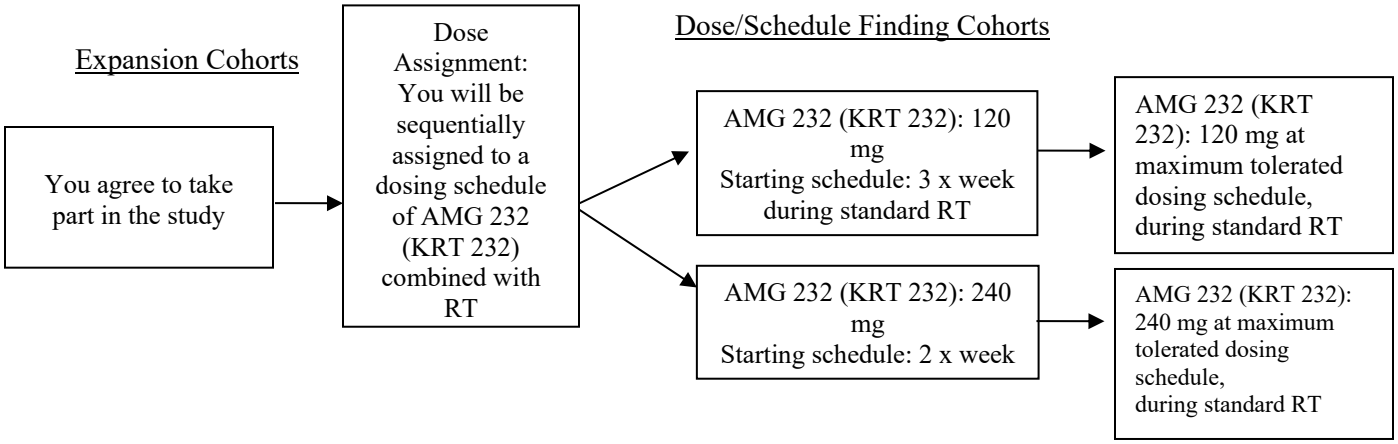
When you are finished with radiation therapy there will be a rest period of 4 weeks with no treatment, after which you will return to the clinic to see the study doctor. Then you will be finished with the study treatment, unless you are in the final group of study participants enrolled for additional safety evaluation at the maximum tolerated dose/schedule. If you are in one of the groups who go off study treatment after the rest period, you will likely then go on to treatment with cycles of temozolomide as standard therapy. Your study doctor will let you know.

If you are in the final group of study participants enrolled for additional safety evaluation, after the 4 week rest period you will continue to receive AMG 232 (KRT 232) at 240 mg once daily for 7 consecutive days every 21 days, to look at side effects and determine how you respond to the study drug.

You also will keep a medication diary. This helps you keep track of when you take your pills. The study doctor will show you how to use this diary. Each time you visit the clinic, you must bring the medication diary, any remaining pills, and the pill bottle.

Every 21 days you will return to the clinic to see the study doctor again. The study doctor supplies the study drug during the clinic visits. Empty bottles, any remaining medication, and the medication diary should be returned to the study doctor at each visit.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

Before you begin the study:

- Collection of stored pieces of cancer tissue from your initial surgery at the diagnosis of glioblastoma, to determine whether your tumor has a feature called "p53 wild-type" Unmethylated MGMT. The tissue will be requested from the facility where you had your initial surgery to remove the tumor. The results of this tissue analysis will determine whether you are eligible to participate in the study.
- Collection of 1 extra blood sample for studies of a protein level in your blood.

During the study:

- Collection of 16 extra blood samples during the first 5 weeks of treatment for studies of the effects of the study drug.

  If you are receiving AMG 232 (KRT 232) on <u>Schedule 1 or Schedule 2 up to 4 times/week</u>, these samples will be collected at the following times:

  - Week 1, Day 2: prior to your first dose (2 samples), and then 1 hour, 3 hours, 5 hours, and 8 hours post-dose (on week 1 day 2, you will need to wait in your clinic for 8 hours to complete all blood draws)

- Week 1, Day 3: 24 hours after dose was taken on Day 2 (2 samples) (prior to the next dose, if applicable)

- Week 3, Day 2: prior to your dose (2 samples)
- Week 3, Day 3: 24 hours after dose was taken on Day 2 (2 samples) (prior to the next dose, if applicable)

- Week 5, Day 2: prior to your dose (2 samples)
- Week 5, Day 3: 24 hours after dose was taken on Day 2 (2 samples) (prior to the next dose, if applicable)

If you are receiving AMG 232 (KRT 232) on Schedule 1 or Schedule 2 at 5 times/week, these samples will be collected at the following times:

- Week 1, Day 1: prior to your first dose (2 samples), and then 1 hour, 3 hours, 5 hours, and 8 hours post-dose (on week 1 day 1, you will need to wait in your clinic for 8 hours to complete all blood draws)
- Week 1, Day 2: 24 hours after dose was taken on Day 1 (2 samples) (prior to the next dose)

- Week 3, Day 1: prior to your dose (2 samples)
- Week 3, Day 2: 24 hours after dose was taken on Day 1 (2 samples) (prior to the next dose)

- Week 5, Day 1: prior to your dose (2 samples)
- Week 5, Day 2: 24 hours after dose was taken on Day 1 (2 samples) (prior to the next dose)

- Collection of stored pieces of cancer tissue, if available, from your initial surgery at the diagnosis of glioblastoma, to look at certain features of the tumor. The tissue will be requested from the facility where you had your initial surgery to remove the tumor.

These samples are required in order for you to take part in this study because the research on the samples is an important part of the study. Any leftover blood and tissue will be stored in a biobank for possible future studies. You will be asked at the end of this document to give your permission for these samples to be kept for unknown future use. There is a small risk that when these samples are used for the planned studies, they could be used up and not available.

Neither you nor your health care plan/insurance carrier will be billed for the collection or processing of the tissue samples that will be used for this study.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the AMG 232 (KRT-232) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The AMG 232 (KRT-232) used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 3 months for men and 5 weeks for women after you have completed the study.

Side Effect Risks

The AMG 232 (KRT-232) 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.

Here are important points about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, or some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and may even result in death.

Specific enzymes in the liver (named CYP2C8, CYP3A4 or UGT1A1) that help rid the body of certain medications may not work as well because of AMG 232 (KRT 232). Your study team will ask you to avoid certain medications because of this interaction. This includes some medicines used to reduce stomach acid.

You can ask your study doctor questions about side effects at any time.

Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.

- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

The table below shows the most common and most serious side effects doctors know about.Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Table of Possible Side Effects for AMG 232 (KRT-232) Version 2.4, December 8, 2023

COMMON, SOME MAY BE SERIOUS In 100 people receiving AMG 232 (KRT 232), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Tiredness • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving AMG 232 (KRT 232), from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Belly pain • Constipation • Bruising, bleeding, weight loss • Dizziness, headache • Change in taste

Additional Drug Risks

The study drug could interact with other drugs. Your study doctor will give you a drug information handout and wallet card that lists these possible interactions. Share this information with your family members, caregivers, other health care providers, and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Possible Side Effects of Standard Radiation Therapy

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, 20 to 100 may have:
• Reddening, tanning, or peeling of the skin • Mild pain • Hair loss • Tiredness • Diarrhea, nausea • Anemia, which may require transfusion • Infection, especially when white blood cell count is low

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, 4 to 20 may have:
• Thickening and numbness of the skin • Sores or ulcers on the skin or near the cancer location • Permanent hair loss • Bleeding from the skin • Sores in mouth which may cause difficulty swallowing

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Damage to internal organs • Abnormal opening in internal organs which may cause pain and bleeding

There is a risk that you will be unable to complete radiation therapy (a standard part of treatment for newly diagnosed glioblastoma) due to side effects from the combined treatment of radiation and AMG 232 (KRT 232).

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.
- Write down in your medication diary when you take the study drug at home.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 3 months for men, and 5 weeks for women after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your brain cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You or your insurance provider will not have to pay for the AMG 232 (KRT 232) while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database.

However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, right now we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor (*insert name of study doctor[s]*) at (*insert telephone number, and email address if appropriate*).

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at (*insert telephone number*).

Samples for unknown future studies:

I agree that my leftover samples and related health information may be kept in a biobank for use in future health research.

YES NO

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion

Date of signature