IRB00054587

tGLI1 as a Therapeutic Target in Brain Tumors: A Window of OpportunityStudy in Breast Cancer Brain Metastases and Primary Gliomas

IRB Approval Date 19OCT2023

NCT03796273

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Informed Consent Form to Participate in Research
Roy Strowd, III, MD, Principal Investigator

SUMMARY

You are invited to participate in a research study. The purpose of this research is to find out the importance of a protein, tGLI1. It is thought to be important in developing certain types of brain tumors like brain metastases (cancer that spreads to the brain) and aggressive forms of brain cancer (cancer that started in the brain). We have recently discovered that a drug called ketoconazole may be able to block tGLI1. Ketoconazole has been safely used to treat fungal infections for many years. The goal of this research study is to figure out if ketoconazole may also help to treat brain tumors.

You are invited to be in this study because you have a brain tumor and your doctor thinks it is best to have surgery to remove it. Your participation in this research will involve 2 extra visits and last about 1 hour for each visit. As a part of the study, you may or may not receive ketoconazole to take for 4 days before your surgery. Before surgery and at the time of surgery, blood samples and a part of the brain tumor will be collected. We will study your brain tumor and the effects of ketoconazole.

Participation in this study will involve patients being split into two groups. One group will take ketoconazole by mouth once a day for 4 days before the surgery (treated group). The other group will not take the drug before surgery (untreated group). Before starting ketoconazole you will be asked questions about your medical history and medications. Blood work will be taken. You will have an EKG (a test of your heart) to make sure that ketoconazole is safe for you.

Research studies involve some risks. Risks of ketoconazole include: fatigue, nausea, vomiting, and decreased appetite. There is a possibility that you may benefit from participation in this study. Your physician may decide to continue ketoconazole after your surgery along with standard therapies. Ketoconazole is usually not a treatment option.

Your participation in this study is voluntary. You do not have to participate in this study if you do not want to. There may be other choices available to you. Some other choices may include having surgery without participation in the study, or other standard treatments as discussed with your doctors. You will not lose any services, benefits, or rights you would normally have if you choose not to participate.

The remainder of this form contains a more complete description of this study. Please read this description carefully. You can ask any questions if you need help deciding whether or not to join the study. The person in charge of this study is Dr. Roy Strowd. If you have questions,

suggestions, or concerns regarding this study, or you want to withdraw from the study, his contact information is: [redacted].

If you have any questions, suggestions or concerns about your rights as a volunteer in this study, contact the Institutional Review Board at [redacted] or the Research Subject Advocate at Wake Forest at [redacted].

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain knowledge that may help others in the future. You are being asked to take part in this study because you have either a breast cancer that has traveled to the brain (also called a brain metastases), or a cancer that started in the brain (primary brain tumor). Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to understand how brain tumors start and grow. There is a specific protein called tGLI1 that is often found in brain tumors. It has been linked to more aggressive tumors. Ketoconazole is an antifungal drug that has been shown in animals and cells to reduce tGLI1 and block its functions. This study is designed to see if blood markers and tissue markers associated with tGLI1 are decreased by ketoconazole. Ketoconazole is given to patients in this study for 4 days before a surgery. If ketoconazole changes tGLI1 markers, then it will provide us with more information about tGLI1 function. It may teach us how to treat or prevent these tumor types in the future.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Nineteen people at one research site will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

Prior to starting the study we will ask you questions and perform tests to make sure ketoconazole is likely safe for you. We will review your current medications. You will have a physical exam and your vital signs will be checked. An EKG will be performed, and blood work drawn. Blood work will check your liver and kidney functions. It will also check for hepatitis and check your blood cell counts. If you could be pregnant, a pregnancy test from your blood will be checked. You will also read, discuss and sign informed consent paperwork prior to starting.

You will be randomized into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will have equal chance of being placed in either group. Half of the patients will be in the ketoconazole treatment group. Half of the patients will be in the observation group.

On your first study visit, you will have a physical exam, vital signs will be tested, and blood work will be collected. Blood work will measure concentration of ketoconazole and blood markers of tGLI1. If you are in the treatment group, you will take 2 tablets, total of 400mg, of ketoconazole by mouth each day until the day you are scheduled for your surgery. On the day of

surgery, you will not take the ketoconazole – you will bring it with you, but you will wait to take it until 1 hour prior to your scheduled surgery. For example: If your surgery time is scheduled for 7:00 am you will take the medication at 6:00 am.

On the day of surgery, both groups will have vital signs checked and blood work. During your surgery, tissue that is left after the surgeon and pathologist have made their diagnosis will be collected for lab tests. These tests will include measuring the amount of ketoconazole in your CSF (cerebrospinal fluid), brain tissue, and blood. Markers of tGLI1 activity will also be measured. No additional tissue will be taken at the time of surgery for research purposes.

After surgery, if you are in the ketoconazole treatment group, your physician may decide to continue ketoconazole. Ketoconazole would be in addition to standard treatments. You will come in for one additional visit after surgery. This will be 30 days after surgery (+/- 14 days) for a follow up visit. At that visit, you will have a physical exam and vital signs checked. Your weight will be measured. Blood work will be drawn to check liver function. We will draw blood to check kidney function. We will draw blood to check blood cell counts. An EKG will be performed.

If you take part in this study, you will have the following tests and procedures:

You will be at home or in the hospital independent of being in the study. Your doctors will decide based on your situation if you should be at home or in the hospital.

If you are in either study group, you will have around 7 teaspoons of blood withdrawn from a vein on 3 occasions. The total amount of blood withdrawn during the study will be approximately 21 teaspoons (four ounces). These will be collected for study purposes.

If you are in either group, you will have two EKGs. One will be at the beginning. One will be at the follow up visit. This is for study purposes.

One half of the participants, 8, will be assigned to the treatment group and receive the study drug ketoconazole. Ketoconazole is an FDA approved drug used to treat fungal infections. The participants in the treatment group will take 2 tablets (400mg total) by mouth once a day for the three days prior to surgery. On the day of surgery, you will bring the last 2 tablets (400mg total), with you for your appointment. You will take the last dose of ketoconazole within one hour of your planned surgery time. You will be asked to keep a treatment diary. In the diary, you will record the date and time that you take ketoconazole. You will be asked to bring the diary with you on the day you have surgery. On the day of your surgery, when you take your last dose of ketoconazole, you will also record that date and time.

Things that would identify you (for example your name, address, date of birth) might be removed from the samples collected as part of the research. After the identifying information is removed, your private information or samples may be used for future research studies. It may be given to other researchers without getting another informed consent from you or your legal representative.

As part of this research study, you will be asked to provide a biological specimen (i.e. blood, urine, saliva, etc.) to be stored and kept for future research. The future research may include studying your genetic information. At some point in the future, we may be required to share genetic data with federal repositories. The National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that collect the results of genetic studies, especially when the research looks at all or large sections of individual's genetic code. This is often called whole genome sequencing. Genomic information relates to the structure and function of all of the genetic material in the body. These central banks will store your genetic information and give them to other qualified and approved researchers to do more studies. The data that we share with federal repositories will be coded in such a way that you would not be able to be identified. We will not share your name, birth date, or any other information that could directly identify you. The link to the code would be kept securely at the Wake Forest Baptist Health. Even so, there is a possibility that when your genomic information is combined with other information available to researchers, either now or in the future, they may be able to identify a group you belong to (like an ethnic group or a disease population) or, less likely, you personally. NIH prohibits people from trying to identify individuals whose genomic information is in an NIH-designated repository.

We do not think that there will be further risks to your privacy and confidentiality by sharing your genetic information with these banks. However, we cannot predict how genetic information will be used in the future. The genetic data could be used to study a wide variety of diseases.

Storage of Biological Tissue

If you agree to participate in this study, we will draw about 21 teaspoons total of blood. Any of remaining tissue after the completion of the outlined procedures above will be saved to use for future research. This sample will be kept and may be used in future research to learn more about other diseases. Your sample will be obtained in the Neuro-Oncology Department at Wake Forest University Baptist Medical Center. The sample will be stored in the laboratory of Hui-Wen Lo and it will be given only to researchers approved by Roy Strowd. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample.

Your blood/tissue sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc., will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be performed with your *blood/tissue* sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research performed with your *blood /tissue* will not be given to you or your doctor. The results will not be put in your medical record. The research using your *blood/tissue* sample will not affect your care.

Your *blood/tissue* sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of the research.

In the future, people who do research may need to know more about your health. While the study investigator may give reports about your health, he/she will NOT be given your name, address, phone number, or any other identifying information about who you are, unless you agree to be contacted in the future.

____YES you may contact for future research studies
____NO I do not want to be contacted regarding future research studies.

How Long Will I Be in the Study?

You will be in the study for about 40 days. Your doctor may decide to continue ketoconazole after surgery. If you continue ketoconazole, you will remain in the study as long as you take it.

You can stop participating at any time. If you decide to stop participating in the study we encourage you to talk to the study staff first. This is to learn about any potential health or safety risks.

What Are the Risks of the Study?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff. There are risks and side effects related to the surgery. Those risks would be the same with or without being in the study. Additional risk is associated with added collection of blood for study purposes. The risks of ketoconazole for people in the treatment group including:

- Damage to the liver
- Allergic reaction
- Muscle problems including cramping
- Irregular heartbeats

Most Common Risks

- Nausea
- Headache
- Diarrhea
- Stomach Pain
- Abnormal Liver Tests

These risks are not permanent. Permanent liver damage is rare.

Numerous problems have been seen when ketoconazole is taken by people with liver disease. In very rare cases, a required liver transplant or even death has happened. The rate of any form of liver damage is approximately 1:12,000 patients. Reported symptoms with ketoconazole include: loss of appetite, weight loss, nausea or vomiting, tired feeling, stomach pain or tenderness, dark

urine or light-colored stools, yellowing of the skin or the whites of the eyes, fever and rash. Ketoconazole has also been linked to irregular heartbeat. This can be potentially life threatening. This risk is increased in patients who are also taking the following medications: dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, ergot alkaloids (including ergotamine, dihydroergotamine), and ranolazine. Potential symptoms include dizziness, lightheadedness, feeling faint, sensation of heart fluttering, irregular or skipped beats.

We will check your medications for things that should not be taken with ketoconazole. It can increase or decrease the amount of other medications in your system. It can increase the risk of side effects of medications when taken at the same time.

The most common side effects of ketoconazole include nausea (around 1 in 10 to 1 in 20 people), headache, diarrhea, stomach pain, and abnormal liver function tests.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your private information. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take. You should tell the staff about medical problems you have. This may help avoid side effects, interactions, and other risks.

Taking part in this research study may involve providing information that you consider confidential or private. Many efforts will be made to keep your records safe. Research records will be coded. Records will be kept in a secure location. Only authorized people will have access to research records.

There are some risks of having blood drawn. You may experience discomfort, bruising and/or bleeding where the needle is placed. Occasionally some people feel dizzy, lightheaded, or faint. Infection may occur on rare occasions. Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

Reproductive Risks and other Issues to Participating in Research

Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing age must use a reliable method of birth control during this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, but less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions.

Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test is required at least 14 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

Contraceptive Measures for Males

Your participation in this research study may damage your sperm, which could cause harm to a child that you may father while in this study. Such harm may be currently unforeseeable. If you

are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for one month afterwards (or one month after stopping ketoconazole should your physician decide to continue its use after surgery). Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should also promptly notify her doctor.

As part of this study, you will be tested for hepatitis, because of the risk of ketoconazole use in patients with hepatitis. You will be told of the results of the testing, and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with hepatitis, you will receive additional counseling about the significance of your care and possible risks to other people. We are required by law to report all positive results to the North Carolina State Board of Health. The test results will be released only as permitted by applicable law. If you do not want to be tested for hepatitis, you should not agree to participate in this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefits to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: consideration of continuing ketoconazole after surgery. This is up to your doctors. Ketoconazole may be added to standard treatments after surgery.
Based on experience with ketoconazole in animals, researchers believe it may be beneficial to people with brain tumors like yours. Because each person responds differently to treatment, no one can know in advance if it will be helpful in your case.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:

- Surgery alone without participation in this study
- Systemic therapies such as chemotherapies or immunotherapies in addition to surgery
- Radiation therapy in addition to or in combination with surgery and systemic therapies
- Non-surgical options as discussed with your primary team of treating physicians

WHAT ARE THE COSTS?

All study costs, including any study medications and procedures, will be paid for by the study. You will be responsible for costs of your regular medical care. These costs include surgery and standard tests and treatments that are no related to this study.

WILL YOUR RESEARCH RECORDS BE CONFIDENTIAL?

The results of this research study may be presented at scientific meetings or published in scientific journals. Your identity and personal health information will not be revealed except in specific situations. Those situations include: you have given permission, is required by law, or it is necessary to keep you or others safe. There is always some risk that even if your information is removed that it could later be identified.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

Your information may be given to Federal and regulatory agencies. The Food and Drug Administration (FDA) is an example. The FDA may read research records. They might learn your identity if this study falls within its authority.

WILL YOU BE PAID FOR PARTICIPATING?

You will receive no payment for taking part in this study. Parking will be validated for study visits.

The findings from this research may result in the future development of products that are of commercial value. There are no plans to provide you with financial compensation or for you to share in any profits if this should occur.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest Health Sciences. The researchers do not, however, hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at [redacted].

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by

law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Roy Strowd, [redacted].

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you and or your information we get from your medical record about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes**:** demographics, medical history, medications, height, weight, performance status, lab results including: blood count, liver function, kidney function, hepatitis diagnosis, EKG, post-treatment toxicity information.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information may be collected from you during this study may be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries. Should your screening bloodwork provide a new diagnosis of hepatitis, this requires we report this diagnosis to the North Carolina State Board of Health

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire and any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center.

You can tell Dr. Roy Strowd that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Roy Strowd, III, MD
Department of Neuro-Oncology
[redacted]

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form, you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this Web site at any time. Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the

study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best medical interest, your condition worsened, new information becomes available, you had an unexpected reaction, you failed to follow instructions, or because the entire study has been stopped.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Roy Strowd III, M.D. at [redacted] (after hours) or [redacted].

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB at [redacted] or the Research Subject Advocate at [redacted].

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent (Printed):_____

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm