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PHASE 1 STUDY OF MUSCADINE GRAPE EXTRACT IN ADVANCED CANCER

Informed Consent Form to Participate in Research

Heidi Klepin, MD, MS & Rhonda Bitting, MD, Principal Investigators

INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to be in this study because you have cancer. 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 find the highest dose of muscadine grape extract that can be given to people with cancer without causing severe side effects. Muscadine grape extract is a natural product that has potential anti-cancer properties. It can be purchased commercially, but not at the concentration we are testing in this study. To participate in this study, we require that you take the pills provided. . Muscadine grape extract is an investigational drug. This means it has not been approved by the U.S. Food and Drug Administrations (FDA). Drugs and devices that do not have approval by the FDA cannot be sold or prescribed by your physician.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 30 people at the Comprehensive Cancer Center at Wake Forest University will be in this study. In order to identify the 30 participants needed, we may need to screen as many as 42 because some people will not qualify to be included in the study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, we will collect data from your medical record about your health and medicines, and ask you survey questions about how you are feeling. This will include questions about your symptoms, fatigue, general well-being and quality of life. The surveys may take approximately 10 minutes to complete. You will take muscadine grape extract pills twice daily at an assigned dose level which ranges from 1 pill twice daily to 5 pills twice daily. Your dose is assigned to you in a specific way so that we can examine closely the effects of the pills during the study. You will take the same number of pills per day for the duration of your participation in the study. You will be asked to report any side effects you feel and to keep a pill diary to record how many pills you have taken. If you currently take any supplements they should be stable for at least two weeks prior to starting the study, and you will be asked to not change your supplement usage during the study. You will have regular appointments for supportive care every 4 weeks with your oncology team to monitor changes in your symptoms and overall health. You will be asked about side effects at each in person visit and by phone 2 weeks after each visit. You will have blood drawn and give a urine sample to determine the amount of muscadine grape extract components in your blood and urine as well as measure

inflammation or growth factors that might be affected by the grape extract. To accomplish this, about 2 tablespoons of blood will be drawn at your baseline visit and then at 4 and 8 weeks if you remain on the muscadine pills. Your doctor will order scans to assess your cancer after 8 weeks of taking the pills as part of usual care. If you are tolerating the muscadine grape pills and your cancer is responding to treatment, you will be provided with pills to continue on treatment for as long as you continue to benefit.

We can send copies of your test results to your personal physician. Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

Do you request that we send important medical findings from your study tests/exams to your personal physician?

[ ] No [ ] Yes If yes, physician's name:_____ Your initials: _____

STORAGE OF BIOLOGICAL TISSUE

If you agree to participate in this study, we will bank any unused blood 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 Cancer Center at Wake Forest University Baptist Medical Center. The sample will be stored in the Hypertension Core Laboratory and it will be given only to researchers approved by Drs. Heidi Klepin and Rhonda Bitting. An Institutional Review Board (IRB) must also approve any future research study using your sample. In order to participate in this study, you must be willing to provide blood and agree to its storage for future research.

Your blood 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 an assigned number and only the research team 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.

HOW LONG WILL I BE IN THE STUDY?

You will participate in the study for about 8 weeks although we will continue to follow your status for the remainder of your life. You may continue on the study medication longer than 8 weeks if you are tolerating and benefiting from the muscadine grape extract. Follow-up appointments will continue every 4 weeks with your oncologist until you stop treatment. After 8 weeks no additional blood work or urine tests will be done as part of the study. You can stop participating at any time. 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.

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. Potential risks and side effects related to taking muscadine grape extract may include

- Excess gas
- Indigestion
- Diarrhea
- Nausea
- Abdominal cramping

Because muscadine grape extract use in the treatment of cancer is investigational, there may be other side effects that we cannot predict. Please tell the research team about all the medications, vitamins and supplements you are taking. This may help avoid or minimize additional side effects, interactions and other risks. It is unlikely but possible that you may experience an allergic reaction to the study drug. Allergic reactions may involve itching, rash, or in severe cases, difficulty breathing and changes in blood pressure or other symptoms. Alert the study team if you have any known allergies. Although unlikely, there may be a risk of death from taking muscadine grape extract.

In addition, there is a slight risk of a breach of confidentiality. We will do our best to protect your confidential 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 and any medical conditions 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. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

For blood draws, you may experience

- Discomfort
- Bruising and/or bleeding where the needle is inserted.
- Occasionally some people become dizzy lightheaded or feel faint.
- Infection may occur on rare occasions.
- Frequent donation of blood can result in low iron in your blood (iron deficient anemia).

If you experience side effects that you think might be related to the muscadine grape pills that are intolerable at any point during the study you can call the oncology clinic for assistance (phone number [redacted]).

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 potential must use a reliable method of birth control while participating in 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,

although 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 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

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 benefit 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 to slow the growth of your cancer.

Based on experience with muscadine grape extract in animals and other research studies, researchers believe the components of the muscadine grape may contain agents that benefit people with cancerous tumors. Because individuals respond differently to therapy, no one can know in advance if it will be helpful in your particular case.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive supportive treatment. You should talk to your doctor about all the choices you have. Your alternative is to not participate in this study.

What about My Health Information?

In this research study, any new information we collect from you and/or information we get from your medical records or other facilities about your health or behaviors is considered Protected Health Information (**PHI**). The information we will collect for this research study includes: demographics, medical history, medicines used, vital signs, analysis of your blood, CT images of your tumor(s), surveys about your quality of life, and questions about the effects the study pills may have on you.

If this research study involves the diagnosis or treatment of a medical condition, then PHI collected from you during this study will 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 PHI private. We will store records of your PHI in a cabinet in a locked office or on a password protected computer. Only the following people or organizations will be granted access to your PHI:

1) The study investigator and his/her staff, or others at Wake Forest University Health Sciences who oversee research
2) Other people or laboratories providing services for this research project on behalf of Wake Forest University Health Sciences and Wake Forest University Baptist Medical Center

If required by law or court order, we might also have to share your PHI with a judge, law enforcement officer, government agencies, or others. If your PHI is shared with any of these

groups it may no longer be protected by federal or state privacy rules.

Any PHI 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. 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 will not be able to obtain a copy of your PHI in the research records until all activities in the study are completely finished.

You can tell Dr. Heidi Klepin that you want to take away your permission to use and share your PHI at any time by sending a letter to this address:

Dr. Heidi D. Klepin
[redacted]

However, if you take away permission to use your PHI 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 PHI.

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 THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility. Neither you nor your insurance company will be billed for the muscadine grape extract pills.

WILL YOU BE PAID FOR PARTICIPATING?

You will not be paid or compensated for being in this study, however, parking validation will be provided for all study-related 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 the Chronic Disease Research Fund of Wake Forest University Health Sciences established by a private donor to conduct research on muscadine grape extract and cancer. The researchers do not hold a direct financial interest in the sponsor or the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE INJURY OR ILLNESS AS A RESULT OF BEING 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. Heidi Klepin at [redacted] or [redacted]

[redacted] after hours.

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, new information becomes available, you have an unexpected reaction or 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, Dr. Heidi Klepin at [redacted] or [redacted] after hours.

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].

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.

Participant Name (Printed):_____

Participant Signature: _____ Date: _____Time:_____ am / pm

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