NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 1112

(ClinicalTrials.gov NCT #: 01730937)

Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy Followed by Sorafenib in Hepatocellular Carcinoma

Amendment 12: September 23, 2022

RTOG 1112

Informed Consent Template for Cancer Treatment Trials
(English Language)

RANDOMIZED PHASE III STUDY OF SORAFENIB VERSUS STEREOTACTIC BODY RADIATION THERAPY FOLLOWED BY SORAFENIB IN HEPATOCELLULAR CARCINOMA (27Oct2017)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have primary liver cancer, referred to as hepatocellular carcinoma, that is unsuitable for surgical resection or standard regional therapies (including transarterial hepatic chemo-embolization or TACE).

Why is this study being done? (28-JUN-2019)

The standard treatment for hepatocellular carcinoma that is unsuitable for surgery or regional therapy is sorafenib, an oral drug that has been shown to increase the survival of patients compared to no active treatment.

Stereotactic body radiation therapy (SBRT), referring to the use of focused high dose radiation generally delivered in 5 or fewer treatment sessions, has also been used to treat hepatocellular carcinoma and has led to tumor shrinkage in many patients.

The purpose of this study is to compare the effects of sorafenib alone (the present standard of care treatment) with SBRT followed by sorafenib (the experimental treatment) on you and your liver cancer to find out which is better. In this study, you will get either SBRT followed by sorafenib or the sorafenib alone.

How many people will take part in the study? (25-MAR-2020)

About 292 people will take part in this study.

What will happen if I take part in this research study? (27Oct2017)

Before you begin the study

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

- History/physical exam, including examination for confusion and assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Assessment by radiation oncologist
- Assessment by medical oncologist and/or hepatologist (liver specialist)
- Liver/Multiphase liver computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan
- Chest CT and abdominal/pelvis CT or MRI
- Radiation planning liver CT scan (for all patients randomized to SBRT and optional for non-SBRT patients for pre-randomization assessment)
- Blood tests
- Liver cancer staging and classification scores

You will need to have the following exams, tests or procedures before study treatment begins. These exams, tests or procedures are part of regular cancer care. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Documentation of liver disease
- Blood tests, including pregnancy test if you are a woman of childbearing potential

Other exams, tests or procedures that may be done before study treatment begins include the following. <u>These evaluations are highly recommended</u> as part of good clinical care of patients on this trial <u>but are not required</u>. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Blood tests
- Endoscopic assessment (insertion of a flexible tube down your mouth so the lining of the stomach can be visualized) and appropriate treatment of varices (enlarged veins) if required.
- Assessment of portal vein thrombosis enhancement
- Documentation of all prior treatments for liver cancer, and documentation of any causes of liver disease and any other factors associated with liver disease (for example, presence of HIV)
- Begin treatment (if not treated) of viral Hepatitis B under the supervision of a hepatologist

- *If judged necessary by doctor and randomized to SBRT*: consultation with interventional radiology or surgery
- *If judged medically appropriate by doctor:* discontinuation of certain medicines you may be taking.

During the study (25-MAR-2020**)**
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Physical exams, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Blood tests

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in group 1 (often called "Arm 1"), you will take 400 mg of sorafenib by mouth twice a day. Depending upon how well your body tolerates the drug, the sorafenib dose may or may not be reduced. The total length of time that you take the sorafenib will be at your doctor's discretion, but will last for no more than 5 years.

If you are in group 2 (often called "Arm 2"), you will receive stereotactic body radiation therapy (SBRT) for 1-2 weeks, followed by sorafenib. You will take sorafenib by mouth at half dose (200 mg twice a day) for 28 days, beginning one day after completion of SBRT. After a period of time determined by your doctor (but no less than 28 days), sorafenib may be increased to full dose (400 mg twice a day) at your doctor's discretion, according to how well your body tolerates the drug. The total length of time that you take the sorafenib will be at your doctor's discretion, but will last for no more than 5 years.

You will be asked to maintain a medication diary to allow your doctors to keep track of the exact number and dose of sorafenib pills that you take. Daily doses of sorafenib will be logged. The Pill Diary is to be returned at each clinic visit. You should take the sorafenib tablets 1 hour before or 2 hours after meals. You should not take St. Johns wort. Over-the-counter drug lists should be reviewed by your healthcare team for potential drug-interaction.

During SBRT, you will need the following tests and procedures. They are part of standard cancer care.
Weekly (following at least one SBRT fraction):

- Physical exam, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Blood tests
- Assessment of any side effects that you may be experiencing as a result of the treatment
- Assessment by radiation oncologist, medical oncologist and/or hepatologist

Prior to starting sorafenib (after the last fraction of SBRT):

- Physical exam, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Assessment by radiation oncologist, medical oncologist and/or hepatologist
- Assessment of any side effects that you may be experiencing as a result of the treatment

During treatment with sorafenib, you will need the following tests and procedures. They are part of standard cancer care.

Every month or as recommended by your doctor:

- Physical exam, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Assessment of any side effects that you may be experiencing as a result of the treatment
- Blood tests
- Assessment by radiation oncologist, medical oncologist and/or hepatologist

All patients (including patients who have stopped taking sorafenib) will need these tests and procedures during the follow-up period.

Every 3 months from the time of study entry for 2 years:

- Physical exam, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)
- Assessment by radiation oncologist medical oncologist and/or hepatologist
- Blood tests
- Multiphase liver CT scan/ MRI scan

Beginning at year 2, every 6 months:

- Physical exam, including an assessment of your ability to carry out activities of daily living (which will include questions such as whether you are able to feed, bathe, and dress yourself)

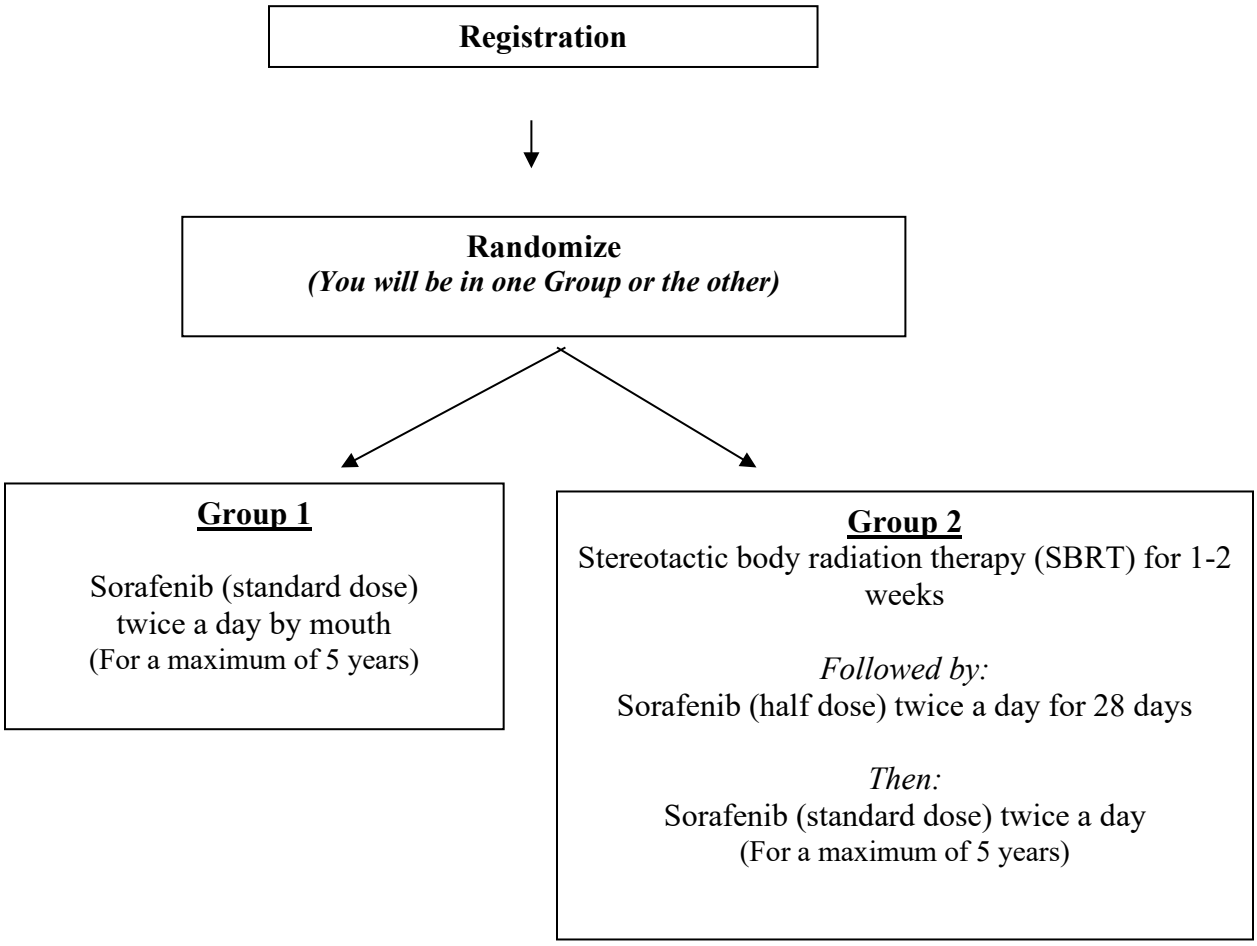
- Assessment by radiation oncologist, medical oncologist and/or hepatologist
- Blood tests
- Multiphase liver CT scan/ MRI scan

Yearly from study entry

- CT chest

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study?

If you are in group 1, you will be asked to take standard dose sorafenib (400 mg orally twice a day). The total length of time that you take the sorafenib will be at your doctor's discretion, but will last for no more than 5 years.

If you are in group 2, you will receive SBRT for 1-2 weeks, followed by sorafenib twice a day at half the standard dose (200 mg orally twice a day) for 28 days, starting 1 to 5 days following completion of SBRT. After 28 days of half dose sorafenib, sorafenib can resume to the standard dose (400 mg orally twice a day) at your doctor's discretion. The total length of time that you take the sorafenib will be at your doctor's discretion, but will last for no more than 5 years.

After you are finished taking the sorafenib alone (group 1) or after receiving SBRT followed by sorafenib alone (group 2), the study doctor will ask you to visit the office for follow-up exams and laboratory tests for at least 5 years.

Can I stop being in the study?

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

It is important to tell the study doctor if you are thinking about stopping so any risks from the sorafenib alone or radiation therapy (SBRT) followed by sorafenib can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study? (14-SEP-2020)

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

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

Risks and side effects related to the sorafenib include those which are:

Risk Profile for Sorafenib (BAY 43-9006: Nexavar) (CAEPR Version 2.10, June 24, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving sorafenib (BAY 43-9006; Nexavar), more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Pain • Diarrhea, nausea • Tiredness • Bruising, bleeding • Weight loss, loss of appetite • Infection, especially when white blood cell count is low • Hair loss, rash • Redness, pain or peeling of palms and soles

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving sorafenib (BAY 43-9006; Nexavar), from 4 to 20 may have:
• Chest pain • Fluid in the belly • Constipation, vomiting • Bleeding from multiple sites including nose • Internal bleeding which may cause black tarry stool, blood in vomit, coughing up blood • Sores in the mouth which may cause difficulty swallowing • Swelling of arms, legs • Fever • A new cancer resulting from treatment of earlier cancer • Dizziness, headache • Difficulty sleeping • Kidney damage which may require dialysis • Cough, shortness of breath • Changes in voice • Dry skin • Itching • High blood pressure which may cause headaches, dizziness, blurred vision

RARE, AND SERIOUS In 100 people receiving sorafenib (BAY 43-9006; Nexavar), 3 or fewer may have:
• Heart failure, heart attack which may cause shortness of breath, swelling of ankles, and tiredness • A tear or hole in the bowels that may require surgery • Liver damage which may cause yellowing of eyes and skin, swelling • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Non-healing surgical site • Change in the heart rhythm • Bleeding in the brain which may cause confusion • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Severe skin rash with blisters and peeling which can involve mouth and other parts of the body • Blood clot which may cause swelling, pain, shortness of breath

Risks and side effects related to the *radiation therapy* include those which are:

COMMON, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, more than 20 may have:
• Tiredness • Swelling, redness, and/or sores in the area of radiation

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving radiation therapy, from 4 to 20 may have:
• Nausea, vomiting • Pain • Internal bleeding • Diarrhea, passing gas, blockage of the stomach • Broken bone • Bruising, bleeding

RARE, AND SERIOUS In 100 people receiving radiation therapy, 3 or fewer may have:
• Liver damage which may cause yellowing of eyes and skin, swelling

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study and for at least 6 months following the last dose of

SBRT and for at least 28 days following the last dose of sorafenib. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. **For more information about risks and side effects, ask your study doctor.**

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope stereotactic body radiation therapy (SBRT) followed by daily sorafenib will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about SBRT plus sorafenib as a treatment for cancer. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Sorafenib alone
- Radiation alone
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (27Oct2017)

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- NRG Oncology
- Other organizations in the National Clinical Trials Network (NCTN): Alliance for Clinical Trials in Oncology (ALLIANCE), ECOG-ACRIN Cancer Research Group (ECOG-ACRIN), SWOG, and Imaging and Radiation Oncology Core (IROC)
- 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 National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), an organization sponsored by the NCI to provide greater access to cancer trials

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.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

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

Taking part in this study is your choice. You may choose either to take part or not to take part in this study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you

will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

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

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Quality of Life Study

We want to know your view of how your life has been affected by cancer and its treatment. This "Quality of life" study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help

patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete two questionnaires at the following times: prior to protocol treatment and at 3, 6, and 12 months after you begin treatment. It takes about 20 minutes total to fill out the questionnaires.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the questionnaires. You may change your mind about completing the questionnaires at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the Quality of Life Questionnaires.

YES NO

Consent Form for Use of Tissue for Research

About Using Tissue and Blood for Research (27Oct2017)

Some patients require a biopsy to confirm if they have cancer. You may have already had a biopsy (or surgery) or you may be recommended to have a biopsy, as per routine care. If you have a biopsy, the results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases.

In addition, if you agree to participate in this part of the study, you will have blood drawn before you begin study treatment and at 1 month and 3 months after you begin treatment. You also may have blood drawn at a later time point determined by your doctor (if your cancer progresses). We would like to keep about 2 to 4 tablespoons of blood at each of these times for future research. If you agree, this blood will be kept to be used in research to learn more about cancer and other diseases.

Your tissue and/or blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue and/or blood is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue and/or blood will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and your blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and/or blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and/or blood. Then any tissue and/or blood that remain(s) will no longer be used for research.

In the future, people who do research may need to know more about your health. While the study doctor/ institution may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue and blood are used for genetic research (about diseases that are passed on in families). Even if your tissue and/or blood are used for this kind of research, the results will not be put in your health records.

Your tissue and/or blood will be used only for research and will not be sold. The research done with your tissue and/or blood may help to develop new treatments for cancer and other diseases in the future.

Benefits

The benefits of research using tissue and blood include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks (11/21/2013)

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included. The samples are given a code to protect your

privacy before they are used. Any related information given to researchers will also be coded. Researchers will receive the code instead of any information that might directly identify you.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives.

Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, life insurance companies may charge a higher rate based on this information.

Many states have laws to protect against genetic discrimination *[list appropriate state information if your state or locality has such laws]*. Additionally, a federal law called the Genetic Information Non-Discrimination Act, or GINA, is in effect. This law prohibits health insurer or employer discrimination. The law does not include other types of misuse by life insurance, disability, or long term care insurance. To learn more about the GINA Law, please ask *[Note to local investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at [IRB's phone number].

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

2. My specimens may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease), as follows:
   - Tissue ☐Yes ☐ No
   - Blood ☐Yes ☐ No

3. Someone may contact me in the future to ask me to take part in more research.
☐Yes ☐ No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

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

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

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

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.
Participant _____

Date _____