Protocol Title:

A Phase II Trial of Integrating Stereotactic Body Radiation Therapy with Selective Targeted Therapy in Stage IV Oncogene-driven Non-Small Cell Lung Cancer

DF/HCC Principal Research Doctor / Institution:
Henning Willers, MD/ Massachusetts General Hospital

A. INTRODUCTION

You are invited to take part in a clinical trial, a type of research study, because you have Stage IV non-small cell lung cancer (NSCLC) that has a mutated or displaced epidermal growth factor receptor (EGFR), anaplastic lymphoma receptor tyrosine kinase (ALK) or ROS proto-oncogene 1 (ROS1) gene (oncogene-driven NSCLC) and have been receiving treatment with a targeted biological agents such as erlotinib, crizotinib, or other drugs. This research study is studying a type of radiation therapy called Stereotactic Body Radiation Therapy (SBRT) as a possible treatment for this diagnosis and tumor stage.

The names of the study interventions involved in this study are:

- Stereotactic Body Radiation Therapy (SBRT)

For purposes of this research, you will be referred to as a “participant”.

It is expected that about 30 people will take part in this research study.

The MGH Federal Share of Program Income, which supports proton therapy research at MGH, is providing funding for this study.

This research consent form explains why this research study is being done, what is involved in participating in the research study, the possible risks and benefits of participation, alternatives to participation, and your rights as a research participant. The decision to participate is yours. If you decide to participate, please sign and date at the end of this form. We will give you a copy so that you can refer to it while you are involved in this research study. If you choose not to participate in this research study, the research doctors will discuss other treatment options with you and/or refer you back to your primary doctor.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions now and at any time in the future.

B. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational intervention to learn whether the intervention works in treating a specific disease. The investigational intervention in this study is SBRT with proton or photon radiation (explained below). "Investigational" means that the intervention is being studied. SBRT and proton radiation therapy are FDA approved radiation delivery systems. However, using it as a treatment for stage IV NSCLC is still investigational.

SBRT is a specialized, technologically advanced type of external beam radiation therapy that pinpoints high doses of radiation directly on the cancer. Because of high precision, these treatments spare healthy tissue and are associated with generally very little side effects. SBRT is very different from conventional therapy where radiation is delivered in small doses given daily over the course of several weeks. For SBRT, the total dose of radiation is typically administered in 4-5 daily sessions. SBRT can be delivered with standard, so called photon radiation, or proton beam. Generally, neither of these two types of radiation is superior over the other. There are technical differences between these two, and depending on your tumor location, size, shape, and other factors, your doctor will decide which type of radiation to use for which treatment.

Oncogene-driven cancers are a unique subset of NSCLC that respond well to a type of targeted therapy called tyrosine kinase inhibitors (TKI). Typically, people with oncogene-driven NSCLC respond better to TKI therapy than regular NSCLC. You have been offered to participate in this study because your cancer has been treated with a TKI such as erlotinib or crizotinib and has either responded or stabilized. We know from prior experiences that in virtually all patients the cancer eventually develops resistance to the TKI leading to a resumption of growth and spread in the body.

In this research study, we are looking to see if SBRT with protons (or, if indicated, photon radiation) on areas in your body that contain residual cancer after TKI treatment will be more effective at preventing your cancer from returning or from spreading to other parts of the body.

C. WHAT OTHER OPTIONS ARE THERE?

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following

- Receive standard treatment including continuation of your TKI alone.
- Take part in another research study.

- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

D. WHAT IS INVOLVED IN THE RESEARCH STUDY?

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **Confirmation of diagnosis** by reviewing test results for EGFR, ALK or ROS1 gene alterations
- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Physical exam** including weight and vital signs (breathing rate, pulse, temperature, blood pressure)
- **An assessment of your tumor** by one or more of the following standard assessment tools: CT (Computerized Tomography) scan of the chest with or without abdomen
- **MRI** (Magnetic Resonance Imaging) of the brain or Head CT for participants with known brain tumors or to investigate participants with symptoms that suggest cancer in the brain
- **MRI** of the spine if you have a history of cancer in the spine
- **Routine Blood tests** to check your overall health (about 2 teaspoons of blood)

If these tests show that you are eligible to participate in the research study, you will begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

After the screening procedures confirm you are eligible to participate in the research study:

If you are eligible to participate in this study, you will receive a stereotactic treatment course (SBRT with protons or photons) to the area of your tumor. Because tumors in the lung and liver move with each breath you take, which affects the precision of SBRT, it may be necessary to place fiducials next to the tumor. Fiducials are typically small gold seeds that are implanted through a CT-guided approach. During treatment fiducials can be imaged and their position can be used to enhance the precision of radiation delivery. This is a standard-of-care approach.

Each treatment course may be delivered daily or spread out over 2 weeks (no weekends or holidays), depending on the dose prescribed by your physician and other considerations. Each treatment will require that you lie on a table for 30-60 minutes. You may not receive TKI treatment on the days of radiation therapy. You will receive radiation therapy as an outpatient at Massachusetts General Hospital.

If you have more than one active site of cancer, you will be treated with another stereotactic treatment course in a following week. The amount of time between each stereotactic treatment course will be a minimum of one week, and a maximum of two months. During these intervals, you will resume standard treatment with TKI therapy with your primary doctor. The total duration of SBRT courses (from the first day of any SBRT course to the last day of any SBRT course) will not exceed 4 months.

You will receive SBRT until all active disease sites have been treated, and then you will resume TKI therapy without interruptions.

Additional Research Procedures:

- **Research Biopsy,** participants will be offered an optional tumor biopsy at the time of standard-of-care fiducials placement for guiding SBRT treatments. Please refer to Section O for more information.

Research Study Plan:

	Pre-Study	During each SBRT course (4-10 fractions)	Follow up
Confirmation of diagnosis	X		
TKI therapy	X		X
Evaluation by radiation oncologist	X	X[A]	X[B]
Physical exam (including weight and performance status)	X		X[B]
Medical History	X		
Routine Blood Tests	X		X[D]
Assess for side effects	X	X[A]	X[B]
CT chest +/-abdomen	X		X[D]
Brain MRI or Head CT	X		X[C]
Spine MRI	X		X[C]

A: You will be seen at least once during your SBRT course.
B: Following completion of all stereotactic treatments, you will continue to have follow-up appointments as per your regular care. You will have visits with your medical oncologist or radiation oncologist or both. For the purpose of this study, you may be seen if needed at 6 weeks after the last SBRT appointment, and then every 3 months (+/- 4 weeks) for the first 2 years, every 6 months (+/- 4 weeks) in year 3, and then as needed up to year 5. You may be seen more frequently by your medical oncologist if needed for your care.
C: If indicated per standard of care. D:CT scans will be conducted every 3 months (+/- 4 weeks) per standard of care. CT scans outside this schedule, will be allowed if needed per standard of care. Laboratory studies will be conducted during follow up visits at the discretion of the treating physician.
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E. HOW LONG WILL I BE IN THIS RESEARCH STUDY?

You will be in this research study for a maximum of 4 months, depending on the number of SBRT courses you receive. You will be followed for up to 5 years at the schedule described above.

The research doctor may decide to take you off the research study for many reasons including if:

- It is considered to be in your best interest

- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- A decision is made to close the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

If you are removed from the research study, the research doctor will explain to you why you were removed.

In addition, you can stop participating in the research study at any time; however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study. If you decide to stop participating in this research study, we encourage you to talk to the research doctor and your primary doctor first.

F. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a treatment that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. Typically few patients experience side effects during or after SBRT. If you experience side effects, they may subside soon after completion of the SBRT course. Most side effects are mild and transient; but others can be long lasting or/and more severe. Life-threatening or fatal complications are extremely rare.

Since the effect of SB .RT with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. We do not know much about interactions of SBRT with TKI therapy and it is possible, that SBRT may worsen the side effects of TKI treatment, and TKI may enhance the side effects of SBRT.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with SBRT:

Lung

Common (More than a 10% chance that this will happen)

- Fatigue
- Skin redness/irritation

Uncommon (Less than a 10% chance that this will happen)

- Nausea/decreased appetite
- Cough
- Difficulty/painful swallowing
- Skin breakdown Lung inflammation which may cause difficulty breathing and low oxygen levels in the blood which may cause shortness of breath, confusion or drowsiness (hypoxia). Lung inflammation, as explained above, is rarely severe or life-threatening
- Coughing up blood
- Rib fracture
- Chest wall pain
- Inflammation of lining of heart which may manifest as chest pain that varies with each breath. Pain often increases when lying down and decreases upon sitting up. Fever, cough, and palpitations are common as well. This may be serious and require medical intervention (pericarditis)

Rare (Less than a 1% that this will happen)

- An abnormal connection between two different organs. This side effect may lead to life-threatening complications including serious infections, bleeding or dysfunction of the organs.
- Nerve damage due to pressure on the nerves (possible loss of function in area controlled by the nerves)
- Loss of feeling or movement due to spinal cord damage
- Heart failure, heart attack or damage to blood vessels in your heart

Gastrointestinal

Common (More than a 10% chance that this will happen)

- Abdominal discomfort
- Fatigue
- Skin irritation/redness
- Nausea, vomiting, loss of appetite

Uncommon (Less than a 10% that this will happen)

-Painful/impaired swallowing
-Loose stools
-Abnormally high levels of enzymes produced by the liver meaning that your liver is not functioning properly and can cause fatigue, and jaundice (yellowing of the skin and eyes). Although this is usually mild and reversible, this can be serious or life threatening.

Rare but serious (Less than a 1% that this will happen)

- Damage to the kidneys, which is when both of your kidneys fail and your body holds which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. You may experience fatigue, nausea, and loss of appetite. When this happens, you need treatment to replace the work of your kidney (ex. Dialysis).
- Bowel scarring, obstruction and/or perforation requiring surgery
- Vessel damage and clots

A chronic condition where the liver functions poorly leading to fatigue, weakness, fluid retention in the abdomen and other complications.

Spine

The side effects or risks of spine SBRT are variable and dependent on the vertebral level being treated. This includes:

Common (More than a 10% chance that this will happen)

- Pain flare
- Fatigue

- Skin irritation/redness

Uncommon (Less than a 10% chance that this will happen)

- Sore throat
- Painful swallowing
- Nausea and vomiting
- Loose stools
- Transient nerve injury
- Difficulty swallowing
- Vertebral fracture

Rare but serious (Less than a <1%that this will happen)

- Loss of feeling or movement due to spinal cord damage.
- Damage to the kidneys, which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. You may experience fatigue, nausea, and loss of appetite. When this happens, you need treatment to replace the work of your failed kidneys (ex. Dialysis).

- Bands of scar tissue in the bowels that form between abdominal tissues and organs causing them to stick together which may cause abdominal discomfort that this cramp-like and requires surgery for removal (abdominal adhesions)

Risks Associated with fiducials placement, with or without optional tumor biopsy,are:

Common (More than a 10% chance that this will happen)

- Mild lung collapse (pneumothorax) not requiring treatment
- Localized minor bleeding within the biopsied organ not requiring treatment
- Self-limited mild blood coughing (hemoptysis)
- Localized mild pain at biopsy site

Uncommon (Less than a 10% chance that this will happen)

- Lung collapse (pneumothorax) which may be painful and causing shortness of breath requiring hospital admission or/and placement of a drainage tube (chest tube), this risk only applies to a lung biopsy.

Rare but serious (About a 1% chance or less that this will happen)

- Major organ bleeding requiring transfusion or other intervention
- Entry of air into vessels and causing serious harm to organs such as brain or heart (air embolism)

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the CT or MRI scans. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.
Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Radiation Risks Associated with Scans and X-Rays:
While you are in this research study, CT scans, PET/CT scans, Bone Scans, x-rays, and/or other scans utilizing radioactivity may be used to evaluate your disease. The frequency of these exams is the same as what you would receive as standard care. In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment of your cancer.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Reproductive Risks:
The treatment used in this research study may affect a fetus. While participating in this research study, you should not become pregnant or father a baby and should not nurse a baby. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child. We can provide counseling about preventing pregnancy for either male or female study participants.

Non-Physical Risks:
Because of the side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

G. WHAT ARE THE BENEFITS OF THE RESEARCH STUDY?

This study may or may not help you, but researchers should learn if the addition of SBRT to your treatment can prevent the spread of cancer in your body over the next year. The reason why we think this is a possible benefit of SBRT is that radiation has a very high likelihood of eradicating residual and potentially TKI-resistant cancer, thereby preventing it from regrowing and spreading. Therefore, you may be able to stay on you current TKI treatment for longer and do not have to switch to other treatments. We do not know if this would prolong your life but it may be possible. If you agree to undergo an optional tumor biopsy for research purposes, researchers will learn about the ways how your tumor may develop resistance to the TKI you are taking. It is possible that this biopsy may detect alterations in your tumor that could be targeted with drug treatments when your tumor regrows. This study may also help researchers learn things that may help people in the future.

H. CAN I STOP BEING IN THE RESEARCH STUDY AND WHAT ARE MY RIGHTS?

You have the right to choose not to sign this form. If you decide not to sign this form, you cannot participate in this research study.

You can stop being in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the treatment. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

I. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid to take part in this research study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

J. WHAT ARE THE COSTS?

Taking part in this research study might lead to added costs to you or your insurance company.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care, including radiation therapy. You will not be charged for the cost of additional scans that are done for research purposes. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services is:

- Massachusetts General Hospital: (617) 726-2191

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov or 1-800-4-CANCER (1-800-422-6237

K. WHAT HAPPENS IF I AM INJURED OR SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments will be billed to your insurance company. You will be responsible for deductibles and co-payments. There are no plans to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

L. WHAT ABOUT CONFIDENTIALITY?

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a DF/HCC research database.

The results of this research study may be published. You will not be identified in publications without your permission.

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.

M. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Massachusetts General Hospital

- Henning Willers, MD: (617) 726-5184

24-hour contact: MGH: Henning Willers, MD at (617) 726-5184 or page at 781-221-2366 beeper 30046

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at DFCI (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

N. PRIVACY OF PROTECTED HEALTH INFORMATION

Federal law requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug for the purpose of this or other research relating the study drug and its use in cancer; and
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, and its agent(s)
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

O. OPTIONAL RESEARCH STUDIES:

Please Note: You do not have to agree to this test and your refusal to do so will not affect your participation in the main study.

Research Biopsy: You are being asked to participate in the optional tumor biopsy at the time of standard-of-care fiducials placement for guiding stereotactic radiation treatments. A needle biopsy of the tumor will be performed in the same session and is not thought to provide more than minimal additional risk to participants. With this biopsy component, we hope to obtain information on your tumor's response to tyrosine kinase inhibitors (TKI).

Please note that this biopsy is not necessary for your medical care and is for research purposes only.

If you agree to have tumor samples used for future testing, these samples will be labeled with a unique study ID and stored securely. However, in spite of all the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters and other relatives. Consequently, it may be possible that researchers looking at your genetic information could guess your identity based on other genetic information that they might know about your relatives. Similarly, it may be possible that genetic information from you could be used to help identify your relatives.
In order to allow the greatest amount of research to be performed on the tissue that you donate, researchers for this study may share results of sequencing your genes (which shows how your DNA is organized) with other scientists. In particular, the National Institutes of Health (NIH) and other organizations have developed special data (information) repositories that analyze data and collect the results of certain types of genetic studies. These central banks will store your genetic information and samples, and provide them to qualified researchers to do more research. Some of this information may be made available over the internet and will be freely available to anyone who is interested (an open access database). Other, more detailed information may only be accessed by scientists at other research centers who have received special permission to review your de-identified data (a controlled access database). Neither type of database will contain information that is traditionally used to identify you, such as your name, address, medical record number, telephone number or social security number. However, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a relative) in another database and be able to identify you (or a relative). Because the DNA sequence of each individual is unique (with the

exception of identical twins), there is a very remote possibility that if a complete sequence determination of your DNA were publicly disclosed, it could be used by a researcher to determine your identity. It is also possible that there could be violations to the security of the computer systems used to share the codes linking your genetic and medical information to you. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her relatives.

In order to appropriately analyze your tumor samples, it may be necessary to send part of the samples to outside institutions for specialized testing. This would include sequencing of tumor DNA at the Broad Institute, Cambridge, Massachusetts, and detection of damages to tumor DNA at the National Institute of Standards and Technology, Gaithersburg, Maryland. No identifiable health information will be attached to your samples. The same privacy risk considerations as above will apply.

There may be other privacy risks that we have not foreseen. While we believe the risks to you and your family are very low; we are unable to tell you exactly what all the risks are.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health, and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328

I agree to participate in the Research Biopsy during fiducials placement.

Please initial and date one of the following options:

Yes:_____ No:_____

DATE:_____

P. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

Adult Participants

To be completed by person obtaining consent:

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative, or, where the participant is a minor, the participant's parent or legal guardian.

For Adult Participants

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

As someone who understands both English and the language spoken by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is illiterate

The consent form was read to the participant who was given the opportunity to ask questions.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate