PATIENT CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

A PHASE I/II STUDY OF FRACTIONATED STEREOTACTIC RADIOSURGERY TO TREAT LARGE BRAIN METASTASES

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Are you participating in any other research studies? _____ Yes _____No

INTRODUCTION TO RESEARCH STUDIES

A research study is designed to answer specific questions, sometimes about a drug's or device's safety and effectiveness. Being in a research study is different from being a patient. When you are a patient, you and your doctor have a great deal of freedom in making decisions about your health care. When you are a research participant, the Protocol Director and the research staff will follow the rules of the research study (protocol) as closely as possible, without compromising your health.

PURPOSE OF RESEARCH

You are invited to participate in a research study of multi-fraction stereotactic radiosurgery to treat brain metastases. We hope to determine the maximum tolerated dose of 3 session (i.e., treatment) stereotactic radiosurgery to treat brain metastases greater than 4.2 cm^3 in size. By increasing radiation dose, we will determine if there is a better outcome without greater toxicity. You were selected as a possible participant in this study because of your diagnosis of a brain metastasis that is greater than 4.2 cm^3 in size (approximately 0.8 inches in diameter).

Your participation in this study is entirely voluntary.

Your decision whether or not to participate will not prejudice you or your medical care. If you decide to participate, you are free to withdraw your consent, and to discontinue participation at any time without prejudice to you or effect on your medical care. If you decide to terminate your participation in this study, you should notify Dr. Scott Soltys at [redacted]

This research study is looking for patients with brain metastases of greater than 4.2 cm^3 in size. This study is being conducted at Stanford University where we expect to enroll 63 research study participants.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 3 years. Your active study involvement will be complete 12 months after radiosurgery.

PROCEDURES

SCREENING:

If you choose to participate, Dr. Scott Soltys and his research study staff will:
Perform a full screening, including:

- Review of medical records (including medical history, physical examination, and any available imaging studies, such as an MRI). You may be asked to sign a release form in order to receive these records.
- A complete evaluation, including physical exam and blood tests, will be performed by Dr. Soltys and his research staff less than 4 weeks prior to the radiosurgical treatment.

TREATMENT:

Your radiation oncologist or neurosurgeon will explain the standard procedures, risks, and benefits involved with this treatment whether you participate in this study or not. There are 2 groups in this study. You will be in one of these 2groups depending on the size of your tumor and whether or not the tumor can be resected with surgery:

Group 1: Patients with 4.2 - 14.1 cm^3 size tumors (0.8 - 1.2 inches) that can be surgically resected will undergo surgery first. Once you have healed from your surgery, you will receive stereotactic radiosurgery targeting the cavity left by surgery to decrease the risk of tumor coming back.

Group 2: Patients with 14.2 – 33.5 cm^3 size tumors (1.2 - 1.6 inches) that can be surgically resected will undergo surgery first. Once you have healed from your surgery, you will receive stereotactic radiosurgery targeting the cavity left by surgery to decrease the risk of tumor coming back.

All patients will be treated using the standard of care radiosurgery brain metastasis treatment:

- As part of the treatment planning process, a computerized tomography (CT) scan of your brain will be obtained at Stanford. A magnetic resonance imaging (MRI) scan of you brain may also be obtained at Stanford.
- On the days of your treatment, you will be brought to the treatment center. You will be asked to lie on your back on the treatment table with your head rested on a custom headrest. A facemask will be custom made to fit you so as to maintain the same head position during treatment.
- You may be asked to take Decadron to decrease the risk of side effects, such as nausea.

There will be 3 separate radiosurgery treatment sessions over 3 total days. Each session will take about 1 hour.

The first group of participants will receive the standard dose of radiation in three sessions (also called "fractions"). For later participants, the dose of radiation during each fraction will be based on dose escalation rules developed by the Protocol Director.

The dose will be gradually increased with each six participants to determine the highest dose that can be tolerated without toxicity.

Following your treatment, you will be followed by your doctors at 1, 3, 6, 9, and 12 months with follow up MRI scans at 3, 6, 9, and 12 months. At your follow-up time points, you will be asked to complete quality of life questionnaires.

MRI (Magnetic Resonance Imaging)

MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body interior. The scanning procedure is very much like an X-ray or CT scan. You will be asked to lie on a long narrow couch for a certain amount of time 30-60 minutes while the machine gathers data. During this time you will not be exposed to x-rays, but rather a strong magnetic field and radiofrequency magnetic fields, which you will not feel. You will, however, hear repetitive tapping noises that arise from the Magnetic Resonance scanner. We will provide earplugs or headphones that you will be required to wear. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the "claustrophobic" feeling.

Risks:

Magnetic fields do not cause harmful effects at the levels used in the MRI machine. However, the MR scanner uses a very strong magnet that will attract some metals and affect some electronic devices. If you have a cardiac pacemaker or any other biomedical device in or on your body, it is very important that you tell the operator/investigator immediately. As metallic objects may experience a strong attraction to the magnet, it is also very important that you notify the operator of any metal objects (especially surgical clips), devices, or implants that are in or on your body before entering the magnet room. All such objects must be removed (if possible) before entering the magnet room. In some cases, having those devices means you should not have an MRI scan performed. In addition, watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items. If you have any history of head or eye injury involving metal fragments, if you have ever worked in a metal shop, or if you could be pregnant, you should notify the operator/investigator.

If you have had a previous reaction to Gadolinium-based contrast agents, a history of severe allergies, or a history of kidney disease, please notify the operator/investigator.

CT (COMPUTERIZED TOMOGRAPHY)

A CT scan is an X-ray technique that produces images of your body that visualize internal structures. You will be asked to lie on a long narrow couch for a certain amount of time 10-30 minutes while the machine gathers data. Like other X-ray imaging exams, CT scans involve a brief, targeted exposure to a small amount of ionizing radiation. No radiation remains in your body after the scan is over.

Risks:
High doses of high energy ionizing radiation can cause cancer. However, it is not known whether the small amount of low energy radiation you get from medical imaging is enough to cause cancer.

If you have had a previous reaction to CT contrast agents or a history of iodine or shellfish allergy, please notify the operator/investigator. Side effects of CT contrast include warm or flushed sensation during injection, metallic taste in the mouth, and itching with hives. More serious reactions, although much less likely, may include injury to the kidneys, breathing difficulty and swelling of the throat.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY THE OPERATOR AND YOU CAN DISCONTINUE THE EXAM AT ANY TIME.

Women of Childbearing Potential
If you are a woman who is able to become pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant, you may not participate in this study. You understand that if you are pregnant or if you become pregnant during this study, you or your child may be exposed to radiation, a known risk for cancer and birth defects in children.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the Protocol Director or research study staff to reschedule as soon as you know you will miss the appointment.
- Tell the Protocol Director or research study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the Protocol Director or research staff if you believe you might be pregnant.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the Protocol Director or research staff if you change your mind about staying in the study.

While participating in this research study, you should not take part in any other research project without approval from the Protocol Directors of each study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you wish to withdraw from the study, tell the Protocol Director or the research staff.

The Protocol Director may also withdraw you from the study, without your consent for one or more of the following reasons:

- Failure to follow the instructions of the Protocol Director and study staff.
- The Protocol Director decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the Protocol Director if you have any questions.

- You will have the responsibility of traveling to Stanford several times over the course of the study for treatment and follow-up visits.
- Our treatment protocol may involve risks to the participant which are currently unforeseeable.
- Participants in this study may receive a higher dose of radiation than non-study patients receiving SRS for this type of metastases. There is a risk that this could result in toxicities that outweigh the benefit of the treatment. You will be monitored closely to detect toxicities and lessen their effects.
- Radiation risks from imaging studies: A CT scan will be used to plan your radiosurgery treatment. The radiation exposure from this test is considered small and is not likely to adversely affect you or your disease.
- Side effects of CT contrast include warm or flushed sensation during injection, metallic taste in the mouth, and itching with hives. More serious reactions, although much less likely, may include injury to the kidneys, breathing difficulty and swelling of the throat.

- An MRI scan will be used to plan your radiosurgery treatment. There is no radiation exposure from this study. At the time of the MRI scan, IV contrast will be given. Potential risks of IV contrast include pain from having the IV placed, bruising, clot formation, and allergic reaction to contrast.

POTENTIAL BENEFITS

By treating your brain metastasis over 3 fractions, we may be able decrease the risk of tumor coming back. Second, this treatment may decrease the risk of late side effects. Third, the information gathered from this study will help guide the treatment of future patients.

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY.

ALTERNATIVES

Alternate treatment options are as follows:

- For those patients that can have surgery, surgery alone without radiation is an option. However, after surgery alone, the risk of tumor coming back at the site of surgery is over 50%. Therefore, radiation is recommended after surgery.
- Whole brain radiation therapy (WBRT). With WBRT, the patient's entire brain (both tumor and normal brain) is treated with radiation. Treatments are conventionally given in 10 – 20 daily treatments over two to four weeks. Compared to stereotactic radiosurgery alone, WBRT decreases the risk of having brain metastases appearing elsewhere in the brain. However, there is no survival benefit to having WBRT compared to radiosurgery, and WBRT alone is not effective in treating brain etastases larger than 4.2 cm^3 in size and is associated late side effects, including memory problems and dementia.
- Single fraction stereotactic radiosurgery (SRS) targets just the tumor with relative sparing of the normal brain. Similar to fractionated radiosurgery, it is associated with a higher risk of brain metastases appearing elsewhere in the brain compared to WBRT. It is not very effective in treating brain metastases larger than 4.2 cm^3.
- Multi-session SRS using 2 to 5 treatment sessions, much like the treatments being studied in this research.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction.

If you decide not to participate, tell the Protocol Director. You will still receive care for your disease and will not lose any benefits to which you would otherwise be entitled.

You will be told of any important new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study.

CONFIDENTIALITY

Your identity will be kept as confidential as possible as required by law. Except as required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. Your research records may be disclosed outside of Stanford, but in this case, you will be identified only by a unique code number. Information about the code will be kept in a secure location and access limited to research study personnel.
The results of this research study may be presented at scientific or medical meetings or published in scientific journals. However, your identity will not be disclosed**.**

Patient information may be provided to Federal and other regulatory agencies as required. The Food and Drug Administration (FDA), for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of multi-fraction radiosurgery; the results will be provided to the sponsor, the Food and Drug Administration and other federal and regulatory agencies as required.

Authorization to Use Your Health Information for Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?
The goal of this study is to determine the maximum tolerated dose for stereotactic radiosurgery delivered over several fractions to treat brain metastases of size greater than 4.2 cm^3. Records of participation in this research project will be maintained and kept confidential as required by law. The study doctor and the study staff will know your name, and the personal information in the research records will not be coded. You will be identified by a unique code number for all others who may review your information. Your health information may be used in scientific publications, but your identity will not be disclosed.

Do I have to sign this authorization form?
You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study. Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?
If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (e.g., necessary to maintain integrity of research). If you wish to revoke your authorization for the research use or disclosure of your health information in this study, you must write to: Dr. Scott Soltys at Stanford Cancer Center, Department of Radiation Oncology 875 Blake Wilbur Drive Stanford, CA 94305-5847.

What Personal Information Will Be Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to, your name, medical record number, date of birth, treatment history, and follow-up information.

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director Dr. Scott Soltys
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research Staff

Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- The Office for Human Research Protections in the U.S. Department of Health and Human Services
- Your personal physician, if you request in writing and a release form is signed
- Authorized representatives of the U.S. Food and Drug Administration

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will expire on December 31, 2060.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (e.g., if included in your official medical record).

_____ _____
Signature of Adult Participant Date

FINANCIAL CONSIDERATIONS

Payment
You will not be paid to participate in this research study.

Costs
If you participate in this study, there may be additional costs to you. These include the personal time it will take to come to all of the study visits.

The study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care. If you would like to review the list of such covered services, supplies, procedures and care, please tell us now or at any time during the study.

Participation in this study is not a substitute for health insurance. You and/or your health insurance must pay for those services, supplies, procedures, and care (including MRI and CT scans and radiosurgery treatments) that you require during this study for routine medical care. **You will be responsible for any co-payments and/or deductibles as required by your insurance.**

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, you may be responsible for these costs. If you are unable to pay for such costs, the Protocol Director will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital.

Additionally, Stanford is not responsible for research and medical care by other institutions or personnel participating in this study. You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Stanford Institutional Review Board (IRB) to speak to someone independent of the research team at [redacted] or toll free at [redacted]. You can also write to the Stanford IRB, Stanford University

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of

treatment, you should ask the Protocol Director, Dr. Soltys [redacted]). You should also contact him at any time if you feel you have been hurt by being a part of this study.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ☐Yes ☐No

Signing your name means you agree to be in this study and that you were given a copy of this signed and dated consent form.

_____ _____
Signature of Adult Participant Date

Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short form foreign language consent.

_____ _____
Signature Date
(e.g., staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

- Translated short form must be signed and dated by both the participant (or their LAR) AND the witness.
- The English consent form ("summary form"):
  - Must be signed by the witness AND the Person Obtaining Consent (POC).
  - The non-English speaking participant/LAR does not sign the English consent.
  - The non-English speaking participant/LAR should not sign the HIPAA participant line
  - If the participant or the LAR is non-English speaking, the Person Obtaining Consent (POC) must ensure that 1) the LAR's Description of Authority is completed and 2) that any questions or options presented by the consent form are documented and initialed by the POC on the Summary Form, per the participant's wishes, as they are understood during the consent process.