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 using a method of treating lung cancer with focused radiation called Stereotactic Ablative Radiotherapy (SABR). The purpose of this investigation is to evaluate local tumor control with individually optimized lung tumor SABR.

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. Maximilian Diehn at (650) 721-1550.

This research study is looking for 260 patients with lung cancer. Stanford University expects to enroll 250 research study participants. In a collaborative effort, some patients will be accrued at Hokkaido University in Japan. We expect no more than 10 patients to be enrolled at this site.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 48 months. Should you choose to transfer your care to another physician in the future, we ask that further follow-up information be sent to us by your physician.

PROCEDURES

Introduction to the Research Study

The standard treatment for localized tumors of the lung often consist of either surgery or radiation therapy (radiation therapy is a form of cancer treatment, using high energy x-rays). For tumors located in the lung, SABR has been shown to be highly effective in controlling tumors. Currently, lung tumors treated with SABR are given the same dose, irrespective of

tumor size. In this study we will prescribe stereotactic ablative radiotherapy in a "personalized" fashion, with tumors of different sizes and in different locations receiving different doses and number of treatments. Stereotactic ablative radiotherapy will be performed using radiation delivery machines that use multiple beams of radiation to concentrate large doses of radiation within a tumor in a very precise manner. The purpose of this study is to evaluate the efficacy of the individualized dosing approach as well as potential improvements in side effects that might result from it.

Description of Procedure

If you decide to participate in this trial you will receive the following treatment. First, you must be evaluated by a radiation oncologist to determine if you are a candidate for the study. If you satisfy the study criteria, you will receive SABR, with the dose and number of treatments determined by the size and location of your tumor(s). In addition, we will perform imaging of your tumor before and after treatment, using CT and/or PET/CT scans which involve visualizing the utilization of glucose (sugar) by your tumor. This will help us determine if the treatments have been effective.

Prior to radiotherapy, 3 to 5 small markers (or coils) may be implanted in and around your tumor in order to help visualize your tumor on the treatment machine. This may have already been done prior to your signing this consent form. These markers can be placed percutaneously (through the skin) or via bronchoscopy. The markers are implanted in and/or around your tumor.

If you give permission, we may also obtain specimens of your tumor for correlative studies.

Several days after having the markers placed, you will go through a planning session, called a simulation, when a custom cushion or foam mold will be made to help immobilize your back and chest during your radiation treatments. This will be followed by a very accurate PET/CT scan (a computerized x-ray) through the area of your cancer. During the scan, you may be asked to hold your breath at various levels to find a position that gives the best separation between the tumor and other organs. You may be shown a video display that helps you to repeat the breath hold reliably. In addition, you may be given an oxygen enriched gas to breathe in order to make the breath hold more comfortable. The same breath hold procedure may be used during the actual treatments as well.

Approximately one to three weeks after the placement of the markers, you will be treated with the linear accelerators (radiation delivery machines). Each radiation treatment will last 30-60 minutes and is not associated with any discomfort. During treatment you will be expected simply to lie reasonably still, after which you can leave the hospital and participate in your normal activities.

Follow-up after SABR treatment will be comparable to that which you would normally undergo after any other therapy for lung tumors.

- You will have a doctor visit with lab work 3 months following your radiation treatment.
- You will have a follow-up CT scan (and usually a PET/CT scan) 3 months after the radiation treatment, or sooner if determined to be necessary by your doctor.
- After the 3-month follow-up, you will have CT scans (and PET/CT scans as needed) every 3 months for the first year (so follow-up will be at months 6, 9, and 12). After year 1, you will be followed for progression and survival outcome.
- Blood tests and clinic visits will be done at the same intervals.
- We will also ask you to fill out a quality of life survey before radiotherapy and at visits following radiotherapy. This questionnaire should take about 10 minutes to complete.
- Additional tests may be warranted depending on the clinical situation.

To summarize, your schedule for treatment and follow-up is:

Treatment:

Marker placement (some patients) → Treatment simulation scan → SABR

Follow-up:

- 3, 6, 9, and 12 months after SABR: Doctor visit, scans, labs including study labs, and quality of life survey (optional).
- More frequent visits, assessments, or scans may be determined to be necessary by your doctor.

A Note to 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 ionizing radiation. If you are pregnant or currently breast feeding, you may not participate in this study. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you or your child may be exposed to an unknown risk.

To confirm to the extent medically possible that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.

You must agree to avoid sexual intercourse or use a birth control method judged to be effective by the investigator and which will not interfere with the proposed investigation. You must accept the risk that pregnancy could still result despite the responsible use of reliable method of birth control. You agree to notify the investigator as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

A Note to Sexually Active Men

If you are a man participating in this study and your partner is able to become pregnant, you and your partner must use adequate contraception while you are participating in the study and for up to 4 weeks following the study. Your doctor will discuss with you what methods of birth control are considered adequate. You should inform your study doctor if your partner becomes pregnant.

A Note About Blood Sampling for Research

A companion study at Stanford is looking at protein markers in the blood that can identify whether a person has lung cancer. The results of this study may make it possible for future patients to be diagnosed without having PET or CT scans. If you participate in this companion study, 30 ml of blood will be drawn from your vein at your setup appointment, at your last treatment, and at your 3-month follow-up appointment. You will not need to make any extra visits to Stanford to participate in this companion study.

Your blood will be stored under your name and medical record. Your name or other identifiers will not be included with any data shared with other investigators. Samples will be analyzed at Stanford University.

Please go to page 15 to indicate whether your blood samples may be saved for future research.

A Note About Tissue Sampling for Research

Research using tissues is an important way to try to understand human disease. You have been given this information because the investigators want to study your tissues as a part of this research project and because they want to save the samples for future research. There are several things you should know before allowing your tissues to be studied.

Your tissues will be stored under your name and medical record. Your name or other identifiers will not be included with any data shared with other investigators. Samples may be sent to laboratories outside of Stanford for analyses.

You have the right to refuse to allow your tissues to be studied now or saved for future study. You may withdraw from this study at any time. The investigators might retain the identified samples, e.g., as part of your routine clinical care, but not for additional research.

Please go to page 15 to indicate whether your tissue samples may be saved for future research.

A Note About Tissue Sampling for Genetic Testing

As part of the analysis on your samples, the investigators may do genetic testing. Genetic research is research that studies genes, including gene characteristics and gene versions that are transmitted by parents to children. Genetic research may include looking at information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual and family medical histories, reactions to medications and responses to treatment. Genetic research raises certain questions about informing you of any results. Possible risks of knowing results include: anxiety; other psychological distress; and the possibility of insurance and job discrimination. A possible risk of not knowing includes being unaware of the need for treatment. These risks can change depending on the results of the research and whether there is a treatment or cure for a particular disease.

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.

The results of the study of your samples will be used for research purposes only and you will not be told the results of the tests.

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 or gotten your partner pregnant.
- 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.

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.

Cancer treatments often have side effects. The treatment used in this study may cause side effects. In addition, there is always the risk of very uncommon or previously unknown side effects occurring. There may also be unforeseeable risks that occur.

Treatment-related side effects are expected to be the standard side effects patients can experience when treated with radiation therapy in the thorax. Complications due to radiation therapy of tumors in and around the lungs may include: 1) fatigue and tiredness for no apparent reason, which is a temporary effect, and usually resolves within a month of completion of treatment; 2) skin changes, similar to that of a mild sunburn; 3) esophagitis (heartburn-like symptoms); 4) pneumonitis, which is inflammation of the lungs and may require steroids for treatment; 5) loss of appetite, nausea and/or vomiting; 6) long term side effects include esophageal stenosis, pulmonary fibrosis, bronchial obstruction, rib fracture, chest wall pain, spinal cord damage and damage to other organs and soft tissues. We estimate these complications to occur in less than 10% of the patients treated.

Your physician will be checking you closely to see if any of these side effects occur. Routine blood tests and imaging tests will be performed to monitor the effects of your treatment. Should side effects occur after treatment they are typically short lived. However, there is no guarantee that they will not be long lasting and/or irreversible. In the meantime, your doctor

may prescribe medication to keep these side effects under control. The use of medication to help control side effects could result in added costs.

Blood Draw:
Whenever possible, blood samples will be obtained at the same time as other routine laboratory studies so you will not be subjected to additional blood draws. Although trained phlebotomists will be obtaining the blood samples, there are minimal risks associated with this procedure including bleeding and infection. Taking blood (blood drawing) may cause some discomfort, bleeding, or bruising where the needle enters the body, and there is a small risk of infection. In rare cases, blood drawing may result in fainting. Please let your study doctor know if you have ever fainted during a blood draw. Left-over tissue may be retained for future research studies.

Completing quality of life questionnaires: You may get tired or bored when we are asking you questions or you are completing questionnaires. You do not have to answer any question you do not want to answer.

You may also develop more symptoms and be less comfortable as a result of this treatment.

You will be expected to continue follow-up at Stanford after undergoing SABR, and this may result in the inconvenience of traveling from your home to Stanford.

POTENTIAL BENEFITS

There may be no direct benefit to you from being in this study. However, a possible benefit is that you will receive only as much radiation as necessary to control your tumor. It is hoped that the results of individualized SABR will advance our knowledge and understanding of lung cancer.

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

ALTERNATIVES

Standard treatments will not be withheld and the alternative to this study is to not participate.

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 effectiveness of stereotactic ablative radiotherapy (SABR) for lung tumors; 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 purpose of this research study is to assess the effect of Stereotactic Ablative Radiotherapy (SABR) on lung cancer. Your health information may be included anonymously in future publications.

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. Maximilian Diehn
875 Blake Wilbur Drive, MC 5847
Stanford, CA 94305

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 medical records, blood samples, questionnaire responses, PET/CT scans, physical examinations, X-rays and MRI's.

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. Maximilian Diehn
- The Stanford University Administrative Panel on Human Subjects in Medical Research and any other unit of Stanford University as necessary
- Research team, co-investigators and research lab personnel

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
- Data Safety Monitoring Committee (DSMC)
- Regulatory authorities in the United States, e.g., the Food and Drug Administration (FDA).
- Samples may be analyzed in laboratories outside of Stanford

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 end on December 31, 2100 or when the research project ends, whichever is earlier.

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

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of Legally Authorized Representative (LAR)

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

PRIVACY CONSIDERATIONS FOR PATIENTS OUTSIDE THE U.S.

As described elsewhere in this informed consent form, during the study, data (including medical images) pertaining to your participation in the study will be generated and recorded and your health and related data (including medical images) may be retrieved from your medical record, and biological samples will be collected from you. We refer to such data (which may include biological samples to which your data may be attached) as "Your Study Data." Your Study Data may be processed or used for the following purposes, which we refer to, collectively, as "Data Processing":

- to carry out the study;
- to confirm the accuracy of the study;
- to monitor that the study complies with applicable laws as well as best practices developed by the research community;
- to seek approval from regulatory authorities to market any products under review in the study;
- to comply with legal and regulatory requirements, including requirements that data from this study, without information that could directly identify you, be made available to other researchers not affiliated with the study sponsor or with the study team. It is possible, for example, that as part of efforts to make research data more widely available to researchers, regulatory authorities in some countries may require that Your Study Data, without information that could directly identify you, be made publicly available on the internet or in other ways.

The following entities and organizations may engage in Data Processing that uses Your Study Data:

- the study team, including other people who, and organizations that, assist the study team;
- representatives from the study sponsor and its authorized service providers/representatives;
- the ethics committee or institutional review board that approved this study; and
- domestic and foreign regulatory agencies and government officials who have a duty to monitor or oversee studies like this one.

Some of the entities listed above that receive Your Study Data for Data Processing may be located in the United States and in other countries where the laws do not protect your privacy to the same extent as the laws in your country of residence. In such cases, Data Processing that involves Your Study Data may be subject to the less restrictive data protection laws of these foreign countries rather than the laws of your own country. However, all reasonable steps will be taken to protect your privacy.

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 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.

You and your insurance company will be responsible for the entire cost of this treatment and subsequent evaluation. This includes the cost of blood draws, scans, medical appointments, and the SABR procedure. Insurance companies usually cover radiation therapy because it is a generally accepted method for the treatment for lung cancer. However, because this type of therapy is relatively new, your insurance company may not be aware of this treatment. In such cases, treatment may result in significantly higher out-of-pocket cost.

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.

You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

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. Maximilian Diehn at (650) 721-1550. You should also contact him at any time if you feel you have been hurt by being a part of this study.

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 (650) 723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 3000 El Camino Real, Five Palo Alto Square, 4th Floor, Palo Alto, CA 94306.

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.

Are you participating in any other research studies? ☐Yes ☐No

YOUR INITIALS INDICATE WHETHER WE MAY USE YOUR BLOOD AND/OR TISSUE SAMPLES FOR FUTURE RESEARCH.

_____ I consent to my blood samples being saved for future research.

_____ I consent to my tissue samples being saved for future research.

_____ I do not consent to my samples being saved for future research.

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

_____
Print Name of Adult Participant

_____ _____
Signature of Legally Authorized Representative (LAR) Date
(e.g., parent, guardian or conservator)

_____
Print Name of Legally Authorized Representative (LAR)

_____
LAR's Authority to Act for Participant
(e.g., parent, guardian or conservator)

Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

_____
Print Name of Person Obtaining Consent

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

_____
Print Name of witness

- Translated short form must be signed and dated by both the participant (or their LAR) and the witness.
- The English consent form (referred to as the "Summary Form" in the regulations):
  - 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.