Early Therapeutic Monitoring of Response to Therapy with Serial Ultrasound in Metastatic RCC

Are you participating in any **other** research studies?

Yes _____ No _____ (please answer by **initialing**)

If **yes**, please name the research studies (title or description, write 'unknown' if you don't remember). If **no**, write 'n/a':

_____

SUMMARY OF KEY INFORMATION

This research study aims to determine whether ultrasound can detect response to treatment for metastatic renal cell carcinoma (RCC) with combined anti-tumor blood vessel and immuno-therapy earlier than current standard-of-care computed tomography (CT) scans. There are no benefits offered for participating in the study. The information gained from the study may help future cancer patients by shortening the time it takes to determine whether the treatment is working or not.

Participation in this study is voluntary and you can withdraw from the study at any time point. If you do not wish to have ultrasound exams for research, you can choose to not participate, in which case you do not need to sign this consent form. Your decision to participate or to withdraw has no influence on your medical care.

Active participation in the study lasts for 6-10 weeks. If you decide to participate, you will have 3 ultrasound exams at your regular clinic visits: one within 4 weeks before starting treatment and one each after 3 and 6 weeks of treatment. Each exam will be performed with 2 different ultrasound scanners, one FDA-approved diagnostic scanner and one scanner only used for research. Up to 5 tumors will be examined with each scanner at each time point. There are no known risks from ultrasound as a diagnostic tool.

PURPOSE OF RESEARCH

You are invited to participate in a research study that investigates the utility of ultrasound imaging for determining whether your treatment is working.

Your doctor is planning to start treating you for your kidney cancer with a combination of an anti-tumor blood vessel drug (e.g. axitinib, cabozantinib, or lenvatinib, taken as a pill) and an immune-activating drug (e.g. pembrolizumab, nivolumab, or avelumab, given as infusion into a vein of your arm). You will receive this combination treatment for about 12 weeks before having a standard-of-care computed tomography (CT), positron emission tomography/CT (PET/CT), or magnetic resonance imaging (MRI) exam. Only then it will become clear whether the treatment is working in your case, and whether you should continue this treatment. Sometimes an additional scan after another 4 weeks is required to know definitively whether the treatment is effective.

Previous research has found that when the treatment works, the blood flow in kidney cancer tumors changes early on during therapy as the blood vessels in the tumor start deteriorating. Our primary objective in this research study is to determine whether ultrasound imaging of the blood flow in your tumor(s) can detect such changes in blood flow and thereby serve to know earlier than current standard-of-care scans whether the treatment is working. This research is very important because it could potentially improve kidney cancer treatment by reducing the amount of time that patients have to spend on therapy when the treatment turns out not to work.

This study is only conducted at Stanford Healthcare and we are looking for 20 kidney cancer patients who are planned to start treatment with a combination of anti-tumor blood vessel drug and immune-activating drug. You were selected as a possible participant

in this study because your doctor thinks you could be a good candidate.
If you decide to participate in this study, you will have 3 ultrasound exams for research in addition to your standard-of-care CT, PET/CT, or MRI scans. These ultrasound exams will be performed within 4 weeks before starting treatment and approximately 3 and 6 weeks after starting treatment. Each exam will be performed with 2 different ultrasound scanners, one FDA-approved diagnostic scanner that is used according to label and one scanner that is not FDA-approved for clinical ultrasound exams, but only used for research.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision whether or not to participate will not have any negative effect on you or your medical care. That means that you will receive the same treatment for your cancer and the same CT/MRI scans regardless whether you participate in this study or not. You can also decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

If you sign the consent, but decide to terminate your participation in this study later, please let Dr. Fan or research study staff know or call 650-498-6000.

DURATION OF STUDY INVOLVEMENT

This study is expected to take 3 years.
Your active participation is expected to last for about 6-10 weeks to complete the 3 ultrasound exams, or until you decide that you do not want to participate in the study any longer. After the active participation period, we will follow up on the course of your medical care in your medical records at any time point until the end of the study or, if this information is not available in your Stanford medical

record, we may contact you or your medical providers outside of Stanford for follow-up (e.g. to ask what were the outcomes of your treatment).

PROCEDURES

If you choose to participate in this study, Dr. Fan's and Dr. Dahl's research staff will contact you to coordinate the 3 ultrasound exams with you. The schedule of these exams is as follows:

You will have the first research ultrasound exam within 28 days before you start treatment during one of your regular clinic visits. Once you started treatment, you will come back to Stanford after 3 and 6 weeks (+/- 8 days) for your second and third ultrasound exam. Each exam will take 15-30 minutes.

If you don't have an appointment at the Stanford Cancer Center at any of these time points (e.g. because you have a telehealth visit with your doctor and receive treatment at Stanford Healthcare in San Jose or Redwood City), you would have to come to the Stanford Cancer Center for the research ultrasound exam within the allowed time window.

Each exam will be done with 2 ultrasound scanners, which differ in the type of ultrasound exam they can perform. One of the devices is an ultrasound scanner that is FDA-approved for clinical ultrasound exams, but in this study we will only use it for research. The other ultrasound scanner is only used for research and has been approved by Stanford for this study, as it is safe and has been used in previous research studies without any negative effects on adult patients or newborns.

Each exam will be performed by a licensed professional from Stanford radiology and research staff from the study team may be present during the exam to assist. First a gel will be applied onto your skin while you are lying on your back or on your stomach. Then the

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Expiration Date: August 3, 2022

measurements will be recorded with each of the 2 devices by slightly pressing a sensor onto the skin in different angles. The ultrasound waves are neither painful nor will you hear any sound.

If you have several tumors that are larger than 0.4 inches (1 cm) in diameter, the research team may perform measurements on several or all of them at the first exam to select up to 5 lesions that are best for repeat measurements.

Finally, you will have a scan (CT, PET/CT or MRI) after about 12 weeks from start of drug therapy as per standard of care.

Any of the ultrasound data used in this research may result in new products, tests, or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the Investigators, Stanford University and/or others. However, study participants do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests, or discoveries.

FUTURE USE OF IMAGING DATA AND PRIVATE INFORMATION

Research using ultrasound imaging and private health information like your response to treatment is an important way to try to understand the biology of cancer and how tumors respond to treatment. You have been given this information because the investigators want to include the ultrasound images and measurements from your disease and private health information in a research project and because they want to save the image data for future research. There are several things you should know before allowing your image data to be studied:

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Approval Date: August 3, 2021
Expiration Date: August 3, 2022

1. A code consisting of a sequence of numbers will be used for each participant, so your private information including name, phone numbers, and medical record numbers cannot be identified from the imaging data. Only the investigators and designated research coordinators will be able to link the code to your identity. The coded ultrasound imaging data will be stored electronically on an encrypted and password-protected computer.

2. To interpret the biological information gained from the imaging data, we will record your demographic and medical information for research, for example: age, sex, race, clinical history, pathology of the tumor(s), other conditions, results of laboratory tests and imaging studies, duration and outcomes of treatments, survival data. All data will be stored in the investigators' secured electronic databases and study site archives until the end of the study.

3. Identifiers might be removed from identifiable private information and/or imaging data and, after such removal, the information and/or imaging could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

4. The results of the study of your data 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 Directors and study staff.
- Tell the Protocol Directors or research study staff about any discomfort, concerns, or tenderness around the area which the sensor is placed.
- Ask questions as you think of them.

- Tell the Protocol Director or research staff if you change your mind about staying in the 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 decide to withdraw your consent to participate in this study, you should notify Dr. Fan at 650-498-6000.
The Protocol Directors 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 Directors and study staff.
- The Protocol Director decides that continuing participation could be harmful to you.
- 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.

Currently there are no known risks of the type of ultrasound exams that are used for this study, since they are not different from a clinical ultrasound exam, and because we adhere to American Institute of Ultrasound in Medicine safety guidelines for ultrasound.

There may be momentary discomfort or pain from slightly pressing the sensor onto a particularly sensitive tumor site. If you experience any discomfort during the exam, please tell the person performing the procedure so that he/she can reduce the pressure or choose a different angle for the sensor that causes you less discomfort. Moreover, the study may delay your scheduled activities by up to 30 minutes on the days of your ultrasound exams.

While every effort has been made to identify risks associated with this study, there may be unforeseeable risks.

POTENTIAL BENEFITS

Information from this study may help doctors learn more about kidney cancer and how to detect response to treatment earlier than with the methods currently used in clinic. This information may benefit other patients with kidney cancer or a similar condition in the future. We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

The alternative is not to participate in the study.

PARTICIPANT'S RIGHTS

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

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Approval Date: August 3, 2021
Expiration Date: August 3, 2022

you decide not to participate, please tell the Protocol Director, Dr. Fan, or her clinical or research staff.

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.

ClinicalTrials.gov

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.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risks that even de-identified information might be re-identified.

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.

CERTIFICATE OF CONFIDENTIALITY

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or specimens that

IRB Use Only
Approval Date: August 3, 2021
Expiration Date: August 3, 2022

may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use.

Information, documents, or specimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by The National Institutes of Health (NIH) which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent,

IRB Use Only
Approval Date: August 3, 2021
Expiration Date: August 3, 2022

which is your demographic and medical information needed for research, for example: age, sex, race, clinical history, pathology of the cancer, other conditions, results of laboratory tests and imaging studies, duration and outcomes of treatments.

Participant ID:

STUDY

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 study is to determine whether ultrasound imaging can detect response to therapy in kidney cancer patients earlier than standard CT, PET/CT, or MRI imaging. To interpret the biological information obtained in this research study, we will correlate it with your health information and the results may be presented at scientific conferences or published in scientific journals.

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. Alice Fan, Stanford Cancer Center, 875 Blake Wilbur Dr, Palo Alto, CA 94304, or contact her by phone at 650-498-6000.

What personal information will be obtained, 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, name, medical record number, age, sex, race, clinical history, pathology of the cancer, other conditions, results of laboratory tests and imaging studies, dates, duration, and outcomes of treatments, survival data, and other information related to your treatment for cancer.

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 Directors (Dr. Fan and Dr. Dahl)
- The Stanford University Administrative Panel on Human Subjects in Medical Research, and any other unit of Stanford University as necessary
- Co-investigators, study coordinators, and 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
- The National Institutes of Health (NIH).

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 August 1, 2120.

_____	_____
Signature of Adult Participant	Date
_____	
Print Name of Adult Participant	
_____	_____
Signature of Legally Authorized Representative (LAR) (e.g., parent, guardian or conservator)	Date
_____	_____
Print Name of LAR	LAR's Authority to Act for Participant (e.g., parent, guardian or conservator)

FINANCIAL CONSIDERATIONS

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

Costs
There is no cost to you for participating in this study, other than basic expenses like transportation and the personal time it will take to come to all of the study visits.

Sponsor
The following institutions and companies are providing financial support and/or material for this study:

- Stanford University
- The National Institutes of Health (NIH).

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.**

IRB Use Only
Approval Date: August 3, 2021
Expiration Date: August 3, 2022

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. Fan, at 650-724-1231. You should also contact her 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, 1705 El Camino Real, 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.

Signing your name means you agree to be in this study and that you will receive 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)
(e.g., parent, guardian or conservator) Date

_____
Print Name of LAR

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

_____ _____
Signature of Person Obtaining Consent Date

_____

Participant ID:

STUDY

IRB Use Only
Approval Date: August 3, 2021
Expiration Date: August 3, 2022

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

_____
Print name of Witness

(e.g., staff, translator/interpreter, family member)

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.

Participant ID:

STUDY