A Pilot Study to Assess lactate and bicarbonate detection within Malignant Brain Tumors using [1-^{13}C]-pyruvate DNP Magnetic Resonance Spectroscopy (MRS)

Informed Consent Form

NCT03565367

October 19, 2021

Arm 2 CNS Malignancy Participants INFORMED CONSENT FORM

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

PURPOSE OF RESEARCH

You are invited to participate in a research study to assess the safety of infusing ^{13}C-labeled hyperpolarized pyruvate (HP-pyruvate) prior to performing magnetic resonance spectroscopic imaging (MRSI). HP-pyruvate is "investigational", meaning that it is not approved by the US Food and Drug Administration (FDA) for use outside clinical research studies. Pyruvate is a naturally produced sugar intermediate in your body that is essential for making energy. Hyperpolarized MRSI is a new technology that enhances our ability to image the pyruvate by changing its magnetic properties, but otherwise the labeled pyruvate is identical to the sugar intermediate in your body. The hyperpolarized pyruvate is non-toxic and non-radioactive, and will be metabolized by your body is the same rapid manner as all naturally produced pyruvate.

In part because of their rapid growth rate, all cancer cells convert (metabolize) sugar into energy differently from normal cells. Investigators hope to learn whether an IV infusion of hyperpolarized pyruvate can be used to measure the metabolic state of malignant brain tumors. You were selected as a possible participant in this study because you have been diagnosed with Central Nervous System (CNS) malignancy.

Investigators believe finding drugs that reverse the abnormal cancer metabolism would be effective in slowing cancer growth with minimal side effects on normal cells. However, there is currently no good way to detect this abnormal cancer metabolism in patients. This research study hopes to test the use of hyperpolarized pyruvate as a way to detect abnormal cancer metabolism, which could help investigators study new ways to treat cancer.

If you decide to terminate your participation in this study, you should notify Dr. Lawrence Recht at (650) 498-6000.

This research study is looking for 5 healthy volunteers and 10 participants with a diagnosis of CNS malignancy, including metastases, who are eligible to undergo MRI. Stanford University expects to enroll 15 research study participants.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can 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.

DURATION OF STUDY INVOLVEMENT

This research study is expected to take approximately 3 days. Screening may take up to 14 days. During the first day of treatment, you will undergo the experimental procedure and afterwards, an EKG will be obtained. Once during the next 2-4 days, you will be contacted by the research study staff to collect information on any side effects of the procedure.

PROCEDURES

If you choose to participate, the Protocol Director Dr. Lawrence Recht and his research study staff will describe all procedures to be followed.

Screening

If you sign the informed consent form and agree to participate, the following screening procedures will be performed within 14 days prior to Day 1:

- Collect demographics
- Measure vital signs (heart rate, temperature, blood pressure), height and weight
- Blood drawn for laboratory safety tests, totaling 1-2 teaspoons
- Electrocardiogram (ECG): An ECG detects the heart's electrical activity through sticky pads attached to your body
- **If you are a female capable of bearing children**, you will be required to have a blood (less than 1 teaspoon) pregnancy test.

Treatment Period

On Day 1, imaging will be performed in the Richard M. Lucas Center at Stanford University. Production of HP-pyruvate will be coordinated with imaging schedule such that MRSI scan begins within 1 minute of HP-pyruvate administration.

Following injection of HP-pyruvate, patients will be imaged on a standard 3T MRI scanner. You will undergo the following procedures:

- Measure vital signs
- Magnetic Resonance Imaging (MRI) scan of brain, 45 min acquisition time using standard non-contrast clinical brain collection setup. MRI machines use a strong magnet and radiofrequency magnetic fields to make images of the body's 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 1 hour 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 MRI 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.

- Administration of HP-pyruvate through an intravenous (IV) tube placed in your arm
- Magnetic Resonance Spectroscopy Imaging (MRSI) scan of brain, 3 min acquisition
- MRI scan of brain, 10 min acquisition time using standard Gadolinium-enhanced contrast clinical brain collection. Gadolinium contrast agent may or may not be administered at the discretion of the Protocol Director.
- Within 10 minutes after the conclusion of image collection
  - Measure vital signs
  - Collect any adverse events and monitor injection site
- At least once more 20-45 min after the conclusion of image collection.
  - Measure vital signs
  - Collect any adverse events and monitor injection site
- Within 1 to 5 hours after HP-pyruvate administration:
  - Measure vital signs
  - ECG
  - Collect any adverse events and monitor injection site

Between Day 2 and Day 4, your study doctor or research staff will contact you by phone or in person at a clinic visit to see how you are feeling.

Future Use of Private Information

Research using private information is an important way to try to understand human disease. You are being given this information because the investigators want to save imaging data with private information for future research. All study files and images will be labeled with a subject identification (ID) number and possibly initials. Identifiers might be removed from identifiable private information and, after such removal, the information could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you.

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.

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. Lawrence Recht at (650) 498-6000.

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
- 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.

MRI / MRSI 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. You should also notify the operator/investigator if you have any tattoos on your body, including eyeliner and other

permanent makeup. Tattoos could become warm and irritated during the scan and remain so for several days. If you would prefer not to participate in the MR scan due to the presence of tattoos on your body, please inform a research team member.

There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, you may have the scan stopped at any time if this occurs. There is also a possibility of tinnitus (ringing in the ears) after the MRI.
If you have had a previous reaction to Gadolinium-based contrast agents or a history of severe allergies, please notify the operator/investigator. If you have kidney problems, please tell the operator.

It has been observed that deposits of Gadolinium-based contrast agent (GBCA) remain in the brains of some people who undergo four or more contrast enhanced MRI scans, long after the last administration. It is not yet known whether these Gadolinium deposits are harmful or can lead to adverse health effects. You should talk to the study doctor if you have any questions about the use of GBCAs with MRIs.

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

The scans performed in this study are for specific research purposes and are not optimized to find medical abnormalities. The investigators for this project may not be trained to perform medical diagnosis. The investigators and Stanford are not responsible for failure to find existing abnormalities with these MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a physician will be consulted as to whether the findings merit further investigation, in which case the investigator will contact you and your primary care physician and inform you of the finding. The decision as to whether to proceed with further examination or treatment lies solely with you and your physician. The investigators, the consulting physician, and Stanford are not responsible for any examination or treatment that you undertake based on these findings. Because the images collected in this study may not comprise a proper clinical MRI scan, these images will not be made available for diagnostic purposes.

HP-Pyruvate Risks:
In all clinical studies of HP-pyruvate performed to date, no dose-limiting side effects or toxicities deemed to be clinically significant were noted. However, it is possible some risks are currently unknown or unforeseeable. We will not exceed the maximum dosages used in prior studies.

In other clinical studies of HP-pyruvate, the following adverse events were noted:

- Bad or metallic taste in mouth
- Dizziness
- Diarrhea
- Flushing
- Headache
- Feeling hot
- Throat discomfort

All side effects noted in HP-pyruvate studies were mild, short-lasting reactions. The reported side effects are similar to those reported after IV injection of other contrast agents, such as those used for X-ray and MRI evaluations.

Study Procedure Risks:

Blood Draw: Blood sampling and needle punctures carry some risk. Possible side effects include, but are not limited to fainting, bleeding, bruising, discomfort, dizziness, infection and/or pain at the puncture site. Rare but permanent nerve damage can occur.

ECG Risk: An electrocardiogram (ECG) is a harmless and painless test with no serious risks. The ECG detects the heart's electrical activity and don't give off electrical charges, such as shocks. You may develop a mild rash where the electrodes (soft patches) were attached, which may go away without treatment.

POTENTIAL BENEFITS

Taking part in this study may or may not make your health better. This information could help future cancer patients.

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 this Study. Choosing to not participate in this Study will not affect the care you receive at Stanford Hospital.

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 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 US 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 risk 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.

The purpose of this research study is to obtain data or information on the safety and effectiveness of hyperpolarized [1-^{13}C]-pyruvate; 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?

This is a clinical research study to evaluate the safety and efficacy of hyperpolarized [1-^{13}C]-pyruvate, an investigational agent. Your health information will be used to verify the study conduct and data entry, assess the study drug effects, and prepare regulatory documents for submission to FDA. Your coded information may also be used in research related to the study drug, your cancer and related diseases, and/or diagnostics to inform treatment; or in scientific 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, including receiving any research-related treatment. 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:

Lawrence Recht, M.D.

875 Blake Wilbur Drive, Rm [redacted]
Stanford, California 94305-[redacted]

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,

- the history and diagnosis of your disease;
- specific information about the treatments you received, including previous treatment(s) you may have had;
- information about other medical conditions that may affect your treatment;
- medical data, including laboratory test results, tumor measurements, CT scans, MRIs, x-rays, and pathology results;
- information on side effects (adverse events) you may experience, and how these were treated;
- long-term information about your general health status and the status of your disease;
- data that may be related to tissue and/or blood samples that may be collected from you; and
- numbers or codes that will identify you, such as your social security number, medical record number, initials, and date of birth.

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. Lawrence Recht
- The IND Holder, Dr. Daniel Spielman
- 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
- The 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 end on December 31, 2050 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

FINANCIAL CONSIDERATIONS

Payment

You will receive a payment of $[redacted] to participate in this study.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You may need to provide your social security number to receive payment.

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.

Funding

Stanford University and NIH funding is providing financial support and/or material for this study.

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. Lawrence Recht at (650) 725-8630. 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, 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 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

_____
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.*