INFORMED CONSENT FORM-Sub-Study

Official title: INNATE: Immunotherapy during neoadjuvant therapy for rectal cancer, a phase II randomized multi-center trial with and without APX005M, an anti-CD40 agonist

NCT number: NCT04130854

IRB Approved Document date: 05-19-22

Title of Study: Optional Sub-study for MRI-based functional tumor imaging and analysis sub-protocol

Consent to be part of a Research Study
To be conducted at:
The University of Texas Southwestern Medical Center

Key Information about this Study

One of the challenges in treating rectal cancer is determining how well the cancer responded to radiation and/or chemotherapy. We try to determine how the tumor responded to radiation and/or chemotherapy prior to surgery by using CT and MRI scans, but this method is not always accurate. The goal of this study is to better image the cancer and possibly predict how the tumor is responding to radiation treatment.

Tumors have abnormal blood flow and some portions of the tumor do not have enough oxygen. Portions of the tumor that do not have good blood supply and do not have oxygen are more resistant to radiation treatment and chemotherapy. The imaging study attempts to use new MRI imaging to determine how well the tumor is supplied by blood and whether there are regions that do not have enough oxygen. These areas may change during radiation treatment, and this may be important for predicting how well the tumor responds to radiation treatment.

Your participation in this study will involve additional scans during the 5 radiation treatment visits. Our department has machines that combine radiation treatment with MRI imaging, called MRI-LINAC. This helps us to see the tumor better while you are receiving radiation treatment and allows us to perform imaging to assess the blood flow and oxygen status of the tumor. The images taken for this study will be obtained while you are waiting to receive radiation treatment on this machine. On the first and 5th treatment, you will receive a standard MRI contrast through an IV as part of the study. In addition, immediately prior to every radiation treatment, we will ask you to breathe supplemental oxygen through a mask while we obtain MRI images (lasting approximately 10 minutes). We may also collect 1 teaspoon of blood from your hand or arm after placing the IV, before the first treatment, to measure your kidney function.

Information about this form

You may be eligible to take part in a research study. This form gives you important information about the study.

Please take time to review this information carefully. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or a doctor) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

Please tell the researchers or study staff if you are taking part in another research study.

Your doctor is a research investigator in this study. They are interested in both your medical care and the conduct of this research study. At any time, you may discuss your care with another doctor who is not part of this research study. You do not have to take part in any research study offered by your doctor.

Voluntary Participation - You do not have to participate if you don't want to. You may also leave the study at any time. If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

General Information – "Who is conducting this research?"

Principal Investigator
The Principal Investigator (PI) is the researcher directing this study; the PI is responsible for protecting your rights,

safety and welfare as a participant in the research. The PIs for this study are Nina Sanford, MD, and Todd Aguilera, MD PhD, Department of Radiation Oncology at UT Southwestern Medical Center.

Funding
The University of Texas Southwestern Medical Center, Department of Radiation Oncology is funding this study.

Purpose – "Why is this study being done?"

You are asked to participate in this research study for MRI-based functional tumor imaging and analysis because you are participating in either Dr. Sanford's locally advanced rectal cancer trial (STU-2020-1394) or Dr. Aguilera's newly diagnosed locally advanced rectal cancer (STU-2019-1492).

The researchers hope to learn how to better image the cancer and possibly predict how the tumor is responding to radiation treatment.

Information about Study Participants – "Who is participating in this research?"

You are being asked to be a participant in this study because you are participating in either Dr. Sanford's locally advanced rectal cancer trial (STU-2020-1394) or Dr. Aguilera's newly diagnosed locally advanced rectal cancer (STU-2019-1492).

How many people are expected to take part in this study?
This study will enroll approximately 10 study participants.

Information about Study Procedures – "What will be done if you decide to be in the research?"

While you are taking part in this study, you will be asked to complete additional scans at 5 of your treatment visits.

The research procedures will be performed while you are on the table to receive radiation treatment and may add a few minutes to the length of the treatment visit.

Screening – The only screening for this trial is if you are participating on either Dr. Sanford's locally advanced rectal cancer trial (STU-2020-1394) or Dr. Aguilera's newly diagnosed locally advanced rectal cancer (STU-2019-1492).

Study Procedures - as a participant, you will undergo the following procedures for research purposes:
You will be receiving radiation treatment on an MRI-LINAC, an FDA-approved machine that combines MRI (imaging component) and linear accelerator (treatment component of the machine). This machine has already undergone extensive testing and is considered part of standard of care. Receiving radiation from this machine is not considered experimental treatment. Standard treatment on this machine requires you to lie still inside a large, doughnut-shaped machine, similar to an MRI scanner. We will image the pelvis area and then create a radiation plan based on your internal anatomy that day. After the planning is complete, the machine will deliver the radiation treatment. This is standard protocol for operating the machine. The MRI technologist can see and hear you during the procedure. You will also be given a squeeze ball to use for communication. You will be inside the MRI-LINAC for approximately 60 minutes. The imaging protocol will be performed while you are on the treatment table and your physicians are adjusting your radiation plan.

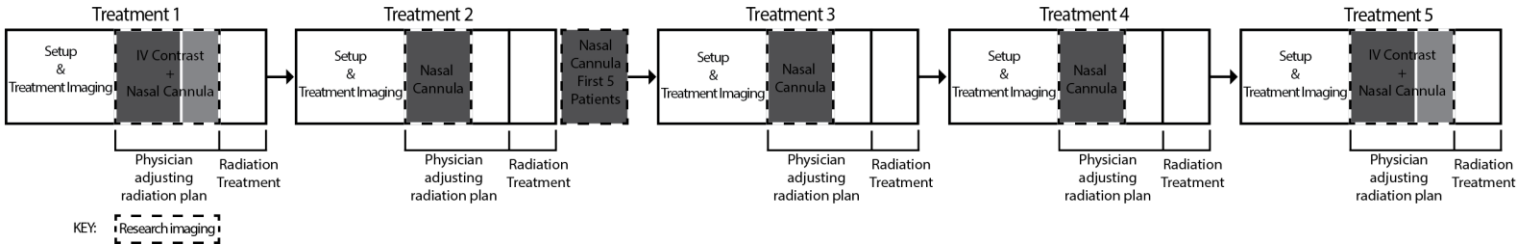
While your treatment team is planning the radiation delivery for that day, the following experimental imaging will be performed on the same machine, in the same position.

- Blood oxygen level-dependent (BOLD) imaging will be performed during the treatment contouring/planning window, while you are laying on the table, for every radiation treatment. This imaging will be repeated after the 2nd radiation treatment is delivered (if not possible after the 2nd treatment, it can be done at 3rd or 4th treatment). This imaging sequence requires oxygen administration via a mask or nasal cannula (a flexible tube placed under your nose).

- Dynamic contrast enhanced (DCE) imaging will be performed on the 1st treatment and 5th treatment of your standard of care treatments during the contouring/planning window, immediately after the BOLD imaging. This imaging sequence requires standard IV contrast. The contrast is used to highlight organs or tissues during imaging. For administration of the contrast, an intravenous catheter will be placed in your arm or hand prior to the 1st and 5th treatment.

As part of the protocol, you will receive imaging contrast (called Gadolinium) on the 1st and 5th radiation treatment per your physician's discretion and standard practices. The contrast is used to highlight organs or tissues during imaging. For administration of the contrast, an intravenous catheter will be placed in your arm or hand. You will also have a blood test to measure your kidney function. For this test, approximately one teaspoon of blood may be drawn from your arm or hand if this has not been recently performed or at your physician's discretion.

Protocol schema



Could your participation end early? There are several reasons why the researchers may need to end your participation in the study (early withdrawal). Some reasons are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- You do not follow instructions from the researchers.
- The study is stopped.

It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician.

Risks – "What are the risks of participation in the research?"

Risks from the research

The investigators have designed this study to learn how well the additional scans might better image the cancer and possibly predict how the tumor is responding to radiation.

Risks from the specific research procedures (drug(s), interventions, or procedures)

There are risks to taking part in this research study. One risk is that you may have side effects while on the study.

Side effects from this study will usually go away soon after you complete the study scans. In some cases, side effects can be long lasting or may never go away.

Everyone taking part in the study will be watched carefully for any side effects. However, the study doctors don't know all the side effects that may happen. Be sure to tell your study doctor immediately, about any side effect that you have while taking part in the study.

The following section will describe the risks related to each your participation in this research study. You should talk to your study doctor about any side effects or other problems that you have while taking part in the study.
Side effects can range from mild to serious. Serious side effects are those that may require hospitalization, or are life threatening. The frequency that people experience a certain side effect can range from many (common), few

(rare) or only one or two (very rare).

Risks and side effects related to the research protocol include:

- Common
  - The injection of Gadolinium may cause discomfort like headache, nausea, strange taste, or coldness at site of injection. These symptoms occur in less than 1 out of 20 of patients receiving Gadolinium and quickly go away.
  - Discomfort or bruising from IV blood draw.
  - Some discomfort and fatigue may also be experienced from lying still during imaging.
  - Oxygen mask and/or nasal canula may cause nasal dryness/discomfort during administration.
- Rare
  - People with severe kidney failure who receive Gadolinium (dye solution used to highlight organs or tissues during imaging) are at risk of developing a disorder called Nephrogenic Systemic Fibrosis (NSF). This disease can cause widespread tissue scarring or hardening (fibrosis). In rare cases NSF can lead to lung and heart problems and cause death. The risk of developing NSF is 1-5% for patients with severe kidney failure and receive gadolinium.
- Very rare
  - There is a small risk of a severe allergic reaction related to the Gadolinium dye that can cause breathing difficulties and/or low blood pressure. These symptoms are extremely rare (approximately 1 in 10,000 to 1 in 100,000 administrations).

For more information about risks and side effects, ask one of the researchers or study staff.

We will tell you about any significant new findings which develop during the course of this research which may relate to your willingness to continue taking part.

Are there Risks related to withdrawing from the study?
If you decide to withdraw from this study early, please discuss your decision with the principal investigator. There is no risk to you if you do not complete the final withdrawal procedures and you can choose not to participate in them.

Are there risks if you also participate in other research studies?
Being in more than one research study at the same time, or even at different times, may increase the risk to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers.

Reproductive Risks
Concerns for sexually active women: You should not become pregnant while taking part in this study because we do not know how the study drugs/procedures could affect a fetus, if a woman becomes pregnant during the study. It is important that you talk to your study doctor about avoiding pregnancy during this study. If you think you might have become pregnant while you are in this study, you must tell one of the study doctors right away so that management of the pregnancy and the possibility of stopping the study can be discussed.

If you are a woman who is pregnant or could be pregnant, you cannot take part in this study because we do not know how the procedures might affect a developing fetus. We will do a pregnancy test before you start treatment to make sure you are not pregnant.

Risks to babies who are being breastfed: Women who are breastfeeding cannot take part in this study because we do not know what effect the procedures might have on their breast milk.

What if a research-related injury occurs?

The researchers have taken steps to minimize the known or expected risks. However, you may still experience problems or side effects, even though the researchers are careful to avoid them. In the event of a research-related injury or if you experience an adverse reaction, please immediately contact your study doctor. See the section "Contact Information" for phone numbers and additional information. You may also need to tell your regular doctors.

If you are injured or made sick from taking part in this research study, medical care will be provided. This care may be billed to you or your insurance. Depending on the circumstances, this care may be provided at no cost to you. We have no plans to give you money if you are injured. The investigator can provide you with more information.

If you sign this form, you do not give up your right to seek additional compensation if you are harmed as a result of being in this study.

Benefits – "How could you or others benefit from your taking part in this study?"

You may not receive any personal benefits from being in this study. We hope the information learned from this study will benefit other people with similar conditions in the future.

Costs – Will taking part in this study cost anything?

Additional MRI images will be taken during your radiation treatment and IV contrast will be given on some of the days of radiation treatment. You and/or your health insurance company will not be billed extra for these images or for participating in this study. You or your health insurance company will be responsible for the cost of treatments and procedures (office visits, labs, standard imaging, etc.) that would be done whether or not you took part in this study.

Confidentiality – How will your records be kept confidential?

Information we learn about you in this study will be handled in a confidential manner, within the limits of the law. If we publish the results of the study in a scientific journal or book, we will not identify you. The Institutional Review Board and other groups that have the responsibility of monitoring research may want to see study records which identify you as a subject in this study.

How will my information be used?

With appropriate permissions, your collected information may also be shared with other researchers here, around the world, and with companies.

By agreeing to participate in this study, your information or tissue samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. The information that identifies you will first be removed from your information or tissue samples. If you do not want your information or tissue samples to be used for future research studies without your consent, you should not participate in this study.

Research policies require that private information about you be protected and this is especially true for your health information. However, the law sometimes allows or requires others to see your information. The information given below describes how your privacy and the confidentiality of your research records will be protected in this study. Medical information collected during this study and the results of any test or procedure that may affect your medical care may be included in your medical record. The information included in your medical record will be available to health care providers and authorized persons including your insurance company.

What is Protected Health Information (PHI)?

Protected Health Information is information about a person's health that includes information that would make it possible to figure out whose it is. According to the law, you have the right to decide who can see your protected health information. If you choose to take part in this study, you will be giving your permission to the investigators and the research study staff (individuals carrying out the study) to see and use your health information for this research study. In carrying out this research, the health information we will see and use about you will include: your medical history, information that we get from your medical record, information that is created or collected during your

participation in the study including medical and treatment history, information you give us during your participation in the study such as during office visits and the scans, demographic information like your age, marital status, the type of work you do and the years of education you have completed.

We will get this information by asking you, asking your doctor, being present at the time of scans, by looking at your chart at The University of Texas Southwestern Medical Center.

How will your PHI be shared?
Because this is a research study, we will be unable to keep your PHI completely confidential. We may share your health information with people and groups involved in overseeing this research study including:

- The Simmons Comprehensive Cancer Center Data Safety Monitoring Board: the committee that checks the study data on an ongoing basis, to determine if the study should be stopped for any reason.
- The members of the UTSW Radiation Oncology research team.
- The Institutional Review Board, Human Research Protection Program Office and the Compliance Office of the University of Texas Southwestern Medical Center, and other groups that oversee how research studies are carried out.
- The Research offices at the University of Texas Southwestern Medical Center
- The Food and Drug Administration (FDA) and other U.S. and international governmental regulatory agencies involved in overseeing drug or device research.
- Representatives of domestic and foreign governmental and regulatory agencies may be granted direct access to your health information for oversight, compliance activities, and determination of approval for new medicines, devices, or procedures.

If you decide to participate in this study, you will be giving your permission for the groups named above, to collect, use and share your health information. If you choose not to let these groups collect, use and share your health information as explained above, you will not be able to participate in the research study.

Parts of your PHI may be photocopied and sent to a central location or it may be transmitted electronically, such as by e-mail or fax. The groups receiving your health information may not be obligated to keep it private. They may pass information on to other groups or individuals not named here.

How will your PHI be protected?
In an effort to protect your privacy, the study staff will use code numbers instead of your name, to identify your health information. Initials and numbers will be used on any photocopies of your study records, and other study materials containing health information that are sent outside of the University of Texas Southwestern Medical Center for review or testing. If the results of this study are reported in medical journals or at meetings, you will not be identified.

Do you have to allow the use of your health information?
You do not have to allow (authorize) the researchers and other groups to see and share your health information. If you choose not to let the researchers and other groups use your health information, there will be no penalties but you will not be allowed to participate in the study.

After you enroll in this study, you may ask the researchers to stop using your health information at any time. However, you need to say this in writing and send your letter to:

Nina Sanford, MD or Todd Aguilera, MD, PhD
Department of Radiation Oncology
UT Southwestern Medical Center
2280 Inwood Rd
Dallas, TX 75390
Tel: 214/645-8525

If you tell the researchers to stop using your health information, your participation in the study will end and the study staff will stop collecting new health information from you and about you for this study. However, the study staff will continue to use the health information collected up to the time they receive your letter asking them to stop.

Can you ask to see the PHI that is collected about you for this study?
The federal rules say that you can see the health information that we collect about you and use in this study. Contact the study staff if you have a need to review your PHI collected for this study.

Because of the type of research, you can only access your PHI when the study is done. At that time, you have the right to see and copy the medical information we collect about you during the study, for as long as that information is kept by the study staff and other groups involved.

How long will your PHI be used?
By signing this form, you agree to let us use and disclose your health information for purposes of the study until the end of the study. This permission to use your personal health information expires when the research ends and all required study monitoring is over.

Contact Information – Who can you contact if you have questions, concerns, comments or complaints?
If you have questions now, feel free to ask us. If you have additional questions, concerns, comments or complaints later or you wish to report a problem which may be related to this study please contact:

Primary contact:
Dr. Nina Sanford, MD or Todd Aguilera, MD, PhD can be reached at 214-645-8525 during regular business hours and after hours and on weekends and holidays.

If primary is not available, contact
The Radiation Oncology Clinical Research Office at 214-645-7322.

The University of Texas Southwestern Medical Center Human Research Protection Program (HRPP) oversees research on human subjects. HRPP and Institutional Review Board (IRB) representatives will answer any questions about your rights as a research subject, and take any concerns, comments or complaints you may wish to offer. You can contact the HRPP by calling the office at 214-648-3060.

Title of Study: Optional Sub-study for MRI-based functional tumor imaging and analysis sub-protocol

Research Consent & Authorization Signature Section

If you agree to participate in this research and agree to the use of your protected health information in this research, sign this section. You will be given a copy of this form to keep. You do not waive any of your legal rights by signing this form.

SIGN THIS FORM ONLY IF THE FOLLOWING STATEMENTS ARE TRUE:

- You have read (or been read) the information provided above.
- Your questions have been answered to your satisfaction about the research and about the collection, use and sharing of your protected health information.
- You have freely decided to participate in this research or you are voluntarily giving your consent for another person to participate in this study because you believe this person would want to take part if able to make the decision and you believe it is in this person's best interest.
- You understand that a copy of this signed consent document, information about this study, and the results of any test or procedure that may affect your medical care, may be included in your medical record. Information in your medical record will be available to health care providers and authorized persons including your insurance company.
- You authorize the collection, use and sharing of your protected health information (another person's protected health information) as described in this form.

Adult Signature Section

Printed Name of Participant	Signature of Participant	Date	Time AM PM

Printed Name of Person Obtaining Consent	Signature of Person Obtaining Consent	Date	Time AM PM

Witness / Interpreter Signature Section

Interpreter/witness (Interpreter signature required per hospital policies when physically present.)

I attest that I have interpreted the information in this consent form and it was explained to, and apparently understood by the subject or the subject's legal authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative as indicated by their signature on the associated **short form**.

Printed Name of Interpreter	Signature of Interpreter	Date	Time AM PM

Witness Signature (required when interpreter is not physically present-e.g., Language Line is used):

By signing below:

I attest that the information in the consent form was accurately explained to, and apparently understood by the subject or the subject's legal authorized representative, and that informed consent was freely given by the subject or the subject's legally authorized representative as indicated by their signature on the associated **short form**.

Printed Name of witness	Signature of witness	Date	Time AM PM

Blind or Illiterate Signature Section *At the time of consent, also complete this section if consent is obtained from an individual who is unable to read and/or write but can otherwise communicate and/or comprehend English (e.g., blind, physically unable to write, etc.)*

Declaration of witness:

By signing below, I confirm I was present for the entire consent process. The method used for communication (e.g., verbal, written, etc.) with the subject was: _____ .

The specific means (e.g., verbal, written, etc.) by which the subject communicated agreement to participate was: _____.

Printed Name of Witness	Signature of Witness	Date	Time AM PM