Informed Consent/Authorization for Participation in Research

Title of Research Study: Pilot Trial of an Implantable Microdevice for In Vivo Drug Sensitivity Testing in Patients with Sarcomas

Study Number: 2019-0171

Study Chair: Joseph A. Ludwig

_____ _____
Participant's Name Medical Record Number

This consent and authorization form explains why this research study is being done and what your role will be if you choose to take part. You may choose not to take part in this study.

This research has been reviewed and approved by an Institutional Review Board (IRB - a committee that reviews research studies).

1. DESCRIPTION OF STUDY

The purpose of this clinical study is to evaluate the safety and feasibility of implantation, retrieval, and performance of microdevices in patients with sarcomas. We hypothesize that percutaneous device placement and subsequent removal of the devices at the time of surgical resection will be a safe and feasible method that enables high-throughput drug discovery in patients bearing orphan tumor types like sarcoma.

Microdevices are rice-sized materials that deliver 10 drugs, in very limited amounts, directly into the tumor. The study investigators will determine how well each microdevice-delivered drug affects the surrounding tumor cells and use this information to estimate how effective the drugs would have worked had they been delivered systemically. That information will be used to prioritize which drugs should be advanced to human clinical trials.

The drugs used in the microdevice are very unlikely to cause side effects, as they are typically provided as doses 1000-fold less than what is known to be safe.

The microdevice, drugs loaded within them, and the procedure associated with device insertion will be provided to patients in the study at no cost by MD Anderson. Drugs loaded into the microdevice include the following:

#	Drug (Active Pharmaceutical Ingredient)	Activity
1	Doxorubicin (Adriamycin)	Active
2	Temozolomide	Active
3	Irinotecan	Active
4	Pazopanib	Inactive
5	Gemcitabine	Inactive

This is an investigational study. All the study agents used in the microdevice are either FDA approved or have been proven safe in human clinical trials. The microdevice itself is investigational. Up to 20 people at MD Anderson will be enrolled on this research study.

2. STUDY PROCEDURES

The cylindrically shaped microdevice, which is 5mm in length and 750mm in diameter (i.e., comparable in size and shape to commonly used fiducial markers), will be placed in tumor tissue by established image-guided techniques that are identical to fiducial marker placement. The microdevices are biologically inert (inactive) and made of biocompatible materials commonly used in biomedical implants in common practice. They will remain in situ (in its original place) for up to two days, during which time multiple agents will be released into local, confined regions of the surrounding microenvironment, without overlap into adjacent drug regions. Each of the agents is released in the tumor at about one millionth of a systemic patient dose, thereby meeting the FDA's definition of a drug micro-dose, which has major regulatory implications, as will be discussed below. The device(s)—up to a maximum of three inserted per tumor—will be removed for analysis at the time of standard-of-care surgery.

Patients will undergo a percutaneous image-guided placement of the microdevice(s), each delivered using a biopsy needle and using standard IR and surgical techniques. Multiple devices may be placed in a tumor to increase the likelihood of obtaining at least one successful readout per patient, and to account for the effects of tumor heterogeneity. The goal will be to place all devices through a single skin entry by orienting the needle at different angles within the tumor; multiple entrances will be allowable but limited per the discretion of the interventional radiologist considering patient safety and comfort. At the completion of the procedure, an X-ray or CT scan will be performed to document precise location of each microdevice relative to the targeted tumor lesion. Patients will be monitored in the procedural recovery room after the device is placed. All patients will be provided with verbal and written instructions and a phone number to call with questions or concerns after discharge.

The patient will retain the device for up to three days, during which time they will leave the hospital, as is standard following uncomplicated biopsies. The patient will return for their surgical resection as planned. Preoperatively, the patient may undergo cross-sectional imaging to confirm and document the precise location of the device and to assess for any interval migration. Patients will undergo surgical resection per the

decision of their surgeon, according to standard of care. Each patient's surgical plan, as determined by their surgeon, will not deviate from what would have been performed for management of their sarcoma independent of their involvement in the study. Following resection, X-ray imaging of the specimen *ex vivo* will be performed to confirm the presence of the device(s) within the tissue.

If a device cannot be retrieved, we do not expect side effects from prolonged incubation. The microdevice consists of a polyaryletherketone (PEEK) polymer, which has demonstrated long-term safety and biocompatibility in multiple biomedical applications, such as trauma, orthopedic and spinal implants. A close comparable for the microdevice is the "Cassi Beacon" tissue marker, an FDA-approved fiducial marker used for long-term localization of breast tumors (*http://scionmedtech.com/products/breast-biopsy/cassi-beacon/*). The Cassi Beacon is structurally very similar to the microdevice (composed of PEEK), though it is more than 4 times larger by volume (cylindrical shape, 1.5mm in diameter and 5mm long). If devices cannot be retrieved 2 days following implantation, they will be removed from the patient along with the remainder of the tumor if a future surgical tumor resection is performed, which is maximally 6 months after implantation. In the rare circumstance where a patient did not have a device retrieved on Day 2 and has unresectable disease, the study surgeon will discuss alternative options for device removal with the patient. It is possible that additional neoadjuvant therapy may be given to facilitate curative resection which may extend the time the device is in place to more than 6 months. It is also possible that the device is intentionally and knowingly left in situ if the risks of surgery outweigh the benefit.

All surgical techniques for tumor resection and all postoperative care are established and will be determined by the operating surgeon and will not be altered for the purpose of this study.

Each patient will be followed up for 2 weeks after the device has been implanted and then surgically removed, unless study-related side effects occur, in which case the patient will be followed up until symptom resolution.

3. POSSIBLE RISKS

CT-guided Device Placement Radiation Exposure. Those patients who undergo CT-guided microdevice placement may receive a dose of additional radiation outside of their standard of care to briefly confirm localization following insertion of the devices. CT-associated radiation exposure incurs a slightly increased long-term risk of radiation-related malignancies, but these are typically associated with much higher radiation doses than what is used for performing imaging for this trial. Only appropriate personnel will operate the CT equipment. Efforts to limit radiation dose and the field of exposure will be taken whenever CT images are performed. All staff will follow appropriate safety precautions.

Infection. The microdevice and all instruments will be sterilized according to standard procedures. Drugs will be prepared in a sterile fashion. Each microdevice will remain

implanted for less than three days. Sites will be dressed in a sterile manner after procedures. All procedures will use standard sterile techniques. Fully loaded devices are pre-assembled into biopsy needles, which will be used for the device placement. These assemblies are packaged in sealed pouches and are sent to a contract sterilization facility for terminal gamma irradiation. Sterilization validation is performed independently by external providers. Pouches containing the devices in a sterile package will be supplied to the MDACC pharmacy for storage until use.

Bleeding. Microdevice placement is percutaneous (through the skin), and bleeding risk is known to be relatively low with biopsy needles of the size required for device placement. The risk of bleeding will be comparable to that already associated with standard of care CT-guided tumor biopsies and surgical resection of neoplastic lesions.

Pain. Potential for procedure-related pain is low and is comparable to a standard biopsy procedure. The amount of pain or discomfort is expected to be minimal and will be controlled with local anesthesia, as well as conscious sedation and parenteral analgesia in selected patients if needed. Given the small size of the microdevice, it is not expected to cause pain after placement.

Microdevice Migration. Devices will be placed into solid areas of tissue. Device will be indwelling for a short duration, leaving little time for migration. Devices will be imaged pre- and post-implantation in all cases to quantitate migration, if any. Pre-clinical studies and ongoing clinical studies in breast and lung cancer have not shown any significant migration under equivalent implantation and indwelling conditions. The device itself has an anchor at the base, further decreasing the likelihood of migration through tissue. There is a small chance of the device migrating to vessels and potential for embolism, but as per published reports, such events have been reported for time points of several months, so this is highly unlikely to occur during the 1-day implantation period.

Microdevice Fracture. The microdevice is extremely unlikely to fracture spontaneously when in tissue. In hundreds of devices implanted in animal models, fracture was not observed. One microdevice fracture was previously observed in an ongoing breast cancer clinical trial at Memorial Sloan Kettering. This was directly attributed to use of a vacuum-force powered retrieval tool, which will not be used in this study.

Difficulty with Microdevice Retrieval. In the unlikely event that a microdevice is not successfully removed at the time of surgery, adverse events due to extended device indwelling are unlikely. The device is constructed of long-term biocompatible materials, namely, PEEK (poly-ether-ether-ketone), an FDA-approved material used in multiple clinical applications including joint replacements. Implantable medical devices made of the same materials have been FDA-approved for long-term use in patients. The microdevice is also radio-opaque and can be visualized by X-ray, CT, ultrasound, and MRI (and is MRI compatible).

Drug Effects. The drugs that are pre-loaded into the microdevice will be released via passive diffusion, as has been extensively characterized in pre-clinical studies. *The*

drugs will only penetrate the local tumor tissues within 300-400 microns from the location of drug release, i.e., there is no systemic release of any of the drugs. The local tissue exposed to drug micro-doses will be surgically resected along with the device and no residual drug will remain. The amount of drug from a given reservoir is approximately 1 microgram, which is on the order of *one-millionth of a systemic dose*. The FDA defines micro-doses as <1% of the total systemic dose, so the drug release from a microdevice is less than a thousandth of what the FDA terms a micro-dose. Even in the unlikely event that the entire contents of drug in the device were to reach systemic circulation, they would be thousands of times less than a physiologically relevant dose, so the risk of drug toxicity is exceedingly low.

Confidentiality. Although every effort will be made to keep study data safe, there is a chance that your personal health information could be lost or stolen, which may result in a **loss of confidentiality**. All study data will be stored in password-protected computers and/or locked file cabinets and will continue to be stored securely after the study.

This study may involve unpredictable risks to the participants.

Pregnancy Related Risks

There are no foreseeable risk to risks to the embryo, fetus or nursing infant since the devices are localized to the tumor and no systemic chemotherapy exposure is anticipated from the intra-tumoral drug microdose.

4. POTENTIAL BENEFITS

The long-term benefits lay in the determination of safety and feasibility of this technique, as well as the potential for obtaining information that will lead to more effective chemotherapy regimens. There are no benefits for you in this study.

5. OTHER PROCEDURES OR TREATMENT OPTIONS

You may be treated with standard chemotherapy, surgery, or other investigative therapies as directed by your treating physician. The study doctor will discuss the possible risks and benefits of these treatments. You may be contacted by telephone or email to inquire about your clinical outcome.

6. COSTS AND COMPENSATION

If you suffer injury as a direct result of taking part in this study, MD Anderson health providers will provide medical care. However, this medical care will be billed to your insurance provider or you in the ordinary manner. You will not be reimbursed for expenses or compensated financially by MD Anderson for this injury. You may also contact the Chair of MD Anderson's IRB at 713-792-2933 with questions about study-related injuries. By signing this consent form, you are not giving up any of your legal rights.

Certain tests, procedures, and/or drugs that you may receive as part of this study may be without cost to you because they are for research purposes only. However, your insurance provider and/or you may be financially responsible for the cost of care and treatment of any complications resulting from the research tests, procedures, and/or drugs. Standard medical care that you receive under this research study will be billed to your insurance provider and/or you in the ordinary manner. Before taking part in this study, you may ask about which parts of the research-related care may be provided without charge, which costs your insurance provider may pay for, and which costs may be your responsibility. You may ask that a financial counselor be made available to you to talk about the costs of this study.

There are no plans to compensate you for any patents or discoveries that may result from your participation in this research. You will receive no compensation for taking part in this study.

ADDITIONAL INFORMATION

7. You may ask the study chair (Dr. Joseph A. Ludwig, at 713-792-3626) any questions you have about this study. You may also contact the Chair of MD Anderson's Institutional Review Board (IRB - a committee that reviews research studies) at 713-792- 2933 with any questions that have to do with this study or your rights as a study participant.
8. Your participation in this research study is strictly voluntary. You may choose not to take part in this study without any penalty or loss of benefits to which you are otherwise entitled. You may also withdraw from participation in this study at any time without any penalty or loss of benefits. If you decide you want to stop taking part in the study, it is recommended for your safety that you first talk to your doctor. It may be dangerous to suddenly stop study treatment, and the study doctor can discuss ways to safely withdraw. If you withdraw from this study, you can still choose to be treated at MD Anderson.

   If you stop being in the research, already collected data may not be removed from the study database. The study staff may ask if they can continue collecting the results of routine care from your medical record. If you agree, this data will be handled the same as research data.
9. This study or your participation in it may be changed or stopped at any time by the study chair, MD Anderson, the U.S. Food and Drug Administration (FDA), the Office for Human Research Protections (OHRP), or the IRB of MD Anderson. A possible reason for removal includes if the interventional radiologist, surgeon, or study PI determines it would be unsafe to implant a microdevice.
10. You will be informed of any new findings or information that might affect your willingness to continue taking part in the study and you may be asked to sign another informed consent and authorization form stating your continued willingness to participate in this study.

Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the researchers will not contact you to let you know what they have found. Patient-specific microdevice drug sensitivities may be shared with the patient but will not be used to guide clinical care since the device is investigational. Any unexpected microdevice-related toxicities observed during the trial will be shared with the patient if required by the MD Anderson IRB.

11. MD Anderson may benefit from your participation and/or what is learned in this study.

12. This study is sponsored and/or supported by: MD Anderson.

Authorization for Use and Disclosure of Protected Health Information (PHI):

A. During this study, MD Anderson will be collecting and using your PHI, including identifying information, information from your medical record, and study results. For legal, ethical, research, and safety-related reasons, your doctor and the research team may share your PHI with:

- Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP)
- The IRB and officials of MD Anderson
- MD Anderson, who is a sponsor or supporter of this study, and/or any future sponsors/supporters of the study.
- Study monitors and auditors who verify the accuracy of the information
- Individuals who put all the study information together in report form

Study sponsors and/or supporters receive limited amounts of PHI. They may also view additional PHI in study records during the monitoring process. MD Anderson's contracts require sponsors/supporters to protect this information and limit how they may use it.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

B. Signing this consent and authorization form is optional but you cannot take part in this study or receive study-related treatment if you do not agree and sign.

C. MD Anderson will keep your PHI confidential when possible (according to state and federal law). However, in some situations, the FDA could be required to reveal the names of participants.

Once disclosed outside of MD Anderson, federal privacy laws may no longer protect your PHI.

D. The permission to use your PHI will continue indefinitely unless you withdraw your authorization in writing. Instructions on how to do this can be found in the MD Anderson Notice of Privacy Practices (NPP) or you may contact the Chief Privacy Officer of MD Anderson at 713-745-6636. If you withdraw your authorization, the data collected about you up to that point can be used and included in data analysis, but no further information about you will be collected.

E. 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.

CONSENT/AUTHORIZATION
(Adult Participants Only)

I understand the information in this consent form. I have had a chance to read the consent form for this study, or have had it read to me. I have had a chance to think about it, ask questions, and talk about it with others as needed. I give the study chair permission to enroll me on this study. By signing this consent form, I am not giving up any of my legal rights. I will be given a signed copy of this consent document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

LEGALLY AUTHORIZED REPRESENTATIVE (LAR)

The following signature line should only be filled out when the participant does not have the capacity to legally consent to take part in the study and/or sign this document on his or her own behalf.

_____ _____
SIGNATURE OF LAR DATE

_____
PRINTED NAME and RELATIONSHIP TO PARTICIPANT

ADULT ASSENT

(Entire section must be completed if the participant is over 18 years old but incapable of providing informed consent.)

If written assent is not obtained on a participant, check reason why not:

____ 1.) The participant's intellectual age is less than seven.
____ 2.) Other:_____

I have been told what I will be asked to do in this study.

I have been told that I do not have to be in this study. If I decide not to be in this study, no one will be mad at me. I may quit at any time, but if I do, I may need to take a different treatment.

I have had a chance to talk about the study and ask the study doctor questions. All of my questions have been answered. I agree to be in this study and do what I am asked to do so long as I want to stay in this study. I agree that the study doctor can put me on this study. By signing this paper, I am not giving up any of my legal rights. I have been given a copy of this document.

_____ _____
SIGNATURE OF PARTICIPANT DATE

_____
PRINTED NAME OF PARTICIPANT

WITNESS TO CONSENT
I was present during the explanation of the research to be performed under this protocol.

_____ _____
SIGNATURE OF WITNESS TO THE VERBAL CONSENT PRESENTATION (OTHER THAN PHYSICIAN OR STUDY CHAIR) DATE
A witness signature is only required for non-English speakers utilizing the short form consent process (VTPS) and patients who are illiterate.

_____
PRINTED NAME OF WITNESS TO THE VERBAL CONSENT

PERSON OBTAINING CONSENT
I have discussed this research study with the participant and/or his or her authorized representative, using language that is understandable and appropriate. I believe that I have fully informed this participant of the nature of this study and its possible benefits and risks and that the participant understood this explanation.

_____ _____
PERSON OBTAINING CONSENT DATE

_____
PRINTED NAME OF PERSON OBTAINING CONSENT

PARENT/GUARDIAN PERMISSION

I have read and understand the description of this research. I have had a chance to discuss the study and ask questions. My questions have been answered. I give permission for my child or ward to take part in this study.

_____ _____
SIGNATURE OF PARENT/GUARDIAN DATE

_____
PRINTED NAME OF PARENT/GUARDIAN

_____ _____
SIGNATURE OF PARENT/GUARDIAN DATE
Signature of Other Parent (Optional, unless required by the IRB.)

_____
PRINTED NAME OF PARENT/GUARDIAN

____The IRB has determined that the signature of both parents is required.

If not obtaining both parental signatures, please indicate reason below:

____Other parent is deceased, unknown, incompetent, or not reasonably available.

____Parent/Guardian signing above has sole legal responsibility for the care and custody of the child.

_X__The IRB has determined that the signature of both parents is NOT required.

ASSENT OF MINOR

(Entire section must be completed if the participant's intellectual age is at least 7 and less than 18 years. Participants with an intellectual age of 7 - 12 are not required to sign.)

If written assent is not obtained on an age-appropriate participant, check reason why not:

____ 1.) The participant's intellectual age is less than seven.

____ 2.) The participant dissented, but the participant's parent(s)/guardian felt that the intervention(s) or procedure(s) involved in the research hold out the possibility of a direct benefit that is important to the health and/or well being of the participant and is available only in the context of this research study.

____ 3.) Other:_____

I have been told what I will be asked to do in this study.

I have been told that I do not have to be in this study. If I decide not to be in this study, no one will be mad at me. I may quit at any time, but if I do, I may need to take a different treatment.

I have had a chance to talk about the study and ask the study doctor questions. All of my questions have been answered. I agree to be in this study and do what I am asked to do so long as I want to stay in this study. I agree that the study doctor can put me on this study. By signing this paper, I am not giving up any of my legal rights. I have been given a copy of this document.

_____ _____
SIGNATURE OF MINOR (Age 13-17) DATE

_____
PRINTED NAME OF MINOR

TRANSLATOR

I have translated the above informed consent as written (without additions or subtractions) into_____and assisted the people
(Name of Language)
obtaining and providing consent by translating all questions and responses during the consent process for this participant.

_____ _____ _____
NAME OF TRANSLATOR SIGNATURE OF TRANSLATOR DATE

☐ Please check here if the translator was a member of the research team. (If checked, a witness, other than the translator, must sign the witness line.)