INFORMED CONSENT DOCUMENT

Project Title: **A Phase Ib study: Treatment of Refractory Pancreatic Adenocarcinoma and Advanced Soft Tissue or Bone Sarcomas Using Decitabine Combined with Gemcitabine**

Principal Investigator: **Varun Monga, MD**

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This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have pancreatic ductal adenocarcinoma (PDAC) or sarcoma (soft tissue or bone) and have had disease progression after one line of treatment.

The purpose of this research study is see if the combination of Decitabine and Gemcitabine is safe in patients with PDAC or sarcoma and how well the combination of drugs are tolerated. We also want to find out the dose of Decitabine that gives the best outcome, and the effects, good and/or bad, that the combination of drugs has on you and on your disease. We will provide a dosing level of Decitabine to 3 subjects, then may adjust the dosing amount up or down for the next group of subjects, depending on how well the drug was tolerated.

Decitabine has been used extensively in the treatment of patients with myelodysplastic syndrome and leukemia with tolerable side effects. Gemcitabine has shown antitumor effects against various diseases including breast cancer, ovarian cancer, lung cancer, pancreatic cancer and refractory sarcoma. However, the combination of Decitabine and Gemcitabine is not FDA approved for treating either PDAC or sarcoma; they are both investigational as used in this research study. Gemcitabine is FDA approved for the treatment of pancreatic cancer.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 42 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement could last indefinitely. This study consists of treatment cycles and each cycle is 28 days long. You will continuously repeat the cycles until you experience disease progression, unacceptable side effects or the investigator decides you are no longer receiving benefit from this study. Once you complete the cycles of this study, you will have an Off Study visit within 30 days.

Visits will range from 1 to 4 hours in length. We may also call you on the telephone monthly for at least 4 months to see how you are doing. If your disease progresses, we will continue to offer follow-up care outside the research study.

WHAT WILL HAPPEN DURING THIS STUDY?

Before you begin the study:
You will need to have the following procedures to find out if you can be in the study. These procedures are part of your regular cancer care and would be done even if you do not join the study:

- A complete physical examination, including assessment of your vital signs (temperature, height, weight, heart rate, blood pressure and respirations or breathing rate).
- Blood tests (approximately 3-4 teaspoons of blood will be drawn and studied for kidney function, liver function, white cells, red cells, and platelets).
- Blood pregnancy test for females of childbearing potential.
- CT scan or MRI scan, if not done within the previous 28 days.

If you are able to continue in the study, you will receive the following study drugs.

Gemcitabine and Decitabine

- An infusion of Gemcitabine will be given through a tube into a vein in your arm. This infusion will take approximately 90 minutes. If you have side effects during the infusion, we will slow the rate of the infusion to try and decrease the side effects. This may result in a longer infusion time. The infusion will be given on Weeks 1, 2 and 3 of each 4-week cycle.
- You will receive 2 doses of Decitabine per week. The dose of Decitabine you receive will depend on how the subjects in the study before you tolerated the drug. The first injection of Decitabine will be given either before, during or after the Gemcitabine infusion and the second one at least 24 hours later. The injections will be given on Weeks 1, 2 and 3 of each 4-week cycle.

  Week 1: Gemcitabine infusion and two Decitabine injections (given at least 24 hours apart)
  Week 2: Gemcitabine infusion and two Decitabine injections (given at least 24 hours apart)

Week 3: Gemcitabine infusion and two Decitabine injections (given at least 24 hours apart)
Week 4: Rest

Weeks 1, 2 and 3 of each cycle:
During the first, second and third weeks of each cycle you will have the following tests and procedures done:

- A complete physical examination, including assessment of your vital signs (temperature, weight, heart rate, blood pressure and respirations or breathing rate). If you had a physical exam within 7 days prior to the visit on Cycle 1, Week 1, this does not need to be repeated. If Decitabine is permanently discontinued but you continue to receive Gemcitabine infusions, the physical examination will only be required on Day 1 of each cycle.
- Blood tests (approximately 3-4 teaspoons of blood will be drawn and studied for kidney function, liver function, white cells, red cells, and platelets). If you had blood drawn for the study within 7 days prior to the visit on Cycle 1, Week 1, this may not need to be repeated.
- Blood drawn for research tests on Days 1, 8 and 15 of Cycle 1, and Day 1 of each cycle thereafter. Approximately 2 teaspoons of blood will be drawn each time. This will only be done for patients with sarcoma.
- Gemcitabine infusion and Decitabine injection. See the information above about the schedule of giving these drugs.
- Starting on cycle 3, week 1, you will have a CT or MRI scan. The scan will be done every odd cycle (i.e., cycles 5, 7, 9, etc.).

This schedule of visits and drug administration will continue until you have progression of your disease, or unacceptable side effects.

Dose Expansion

Once both of the doses of Decitabine used in the first part of the study have been determined to be equally safe by the Principal Investigator, you will be randomly assigned to receive either Dose level 1 (0.1 mg/kg) or Dose level 2 (0.2 mg/kg). This means that whichever study treatment you receive will be determined purely by chance, like flipping a coin. You will have a 50/50 chance of receiving either one of the study treatments.

Off-Study Visit:
Within 30 days of your last dose of study drug, you will have an off-study visit, during which the following tests and procedures will be done:

- A complete physical examination, including assessment of your vital signs (temperature, height, weight, heart rate, blood pressure and respirations or breathing rate).
- Blood tests (approximately 3-4 teaspoons of blood will be drawn and studied for kidney function, liver function, white cells, red cells, and platelets).
- CT scan or MRI scan.

We would like to continue to contact you at least once a month for 4 months to see how you are doing

and then every 3 months for the rest of your life. This can be done during a clinic visit or by telephone. We may look at your medical record as well, to see how you're doing.

Blood Storage for Future Use

As part of this study, we are obtaining blood samples from you. We would like to study your blood samples in the future, after this study is over.

The tests we might want to use to study your blood samples may not even exist at this time. Therefore, we are asking for your permission to store your blood samples so that we can study them in the future. These future studies may provide additional information that will be helpful in understanding sarcoma, but it is unlikely that what we learn from these studies will have a direct benefit to you. It is possible that your blood samples might be used to develop products or tests that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

If you agree now to future use of your blood samples, but decide in the future that you would like to have it removed from future research, you should contact Dr. Varun Monga at 319-384-9497. However, if some research with your blood samples has already been completed, the information from that research may still be used.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. There may be side effects due to the combination of these 2 drugs that we do not yet know about.

There are some medications that may have an impact on your liver enzymes and may interact with the study medications. Please discuss any medications you are taking with the study doctor or nurse.

Decitabine

The dose of decitabine you will be receiving in this study is relatively low compared with the doses given for other disease states. The following side effects may potentially occur:

Risks and side effects related to decitabine (given at much higher doses than you will receive in this study) include:

Likely Side Effects:

- Nausea
- Fatigue
- Fever
- Decreased number of a type of white blood cell (neutrophil/granulocyte) which may lead to infection
- Decreased platelet count (which may lead to increased bruising or bleeding)
- Fever with dangerously low levels of a type of white blood cell (neutrophils)
- Bruising, bleeding

Less likely side effects:

- Decreased red blood cells that may cause tiredness or shortness of breath
- Bruising

• Infection
• Abnormal blood tests that could be a sign of liver problems (ALT/AST; bilirubin)
• Abnormal blood test that could be a sign of kidney problems (creatinine)
• Increased blood sugar level
• Decreased blood levels of a protein called albumin that could be a sign of poor nutrition or liver problems
• Decrease in blood potassium that could lead to heart or muscle problems
• Irritation of a vein
• Liver failure
• Belly pain
• Irritation or sores in the lining of the digestive tract
• Bleeding somewhere in the lungs or respiratory tract
• Irritation or sores in the mouth or throat
• Constipation
• Vomiting
• Diarrhea
• Chills
• Swelling in the arms and/or legs
• Pain, including in the chest, back, bone, muscle and/or joints
• Condition where the body's immune system attacks normal tissues
• Loss of appetite
• Pain in the arms and/or legs
• Sleepiness
• Dizziness
• Headache
• Anxiety
• Difficulty sleeping or falling asleep
• Cough
• Shortness of breath
• Hair loss
• Itching
• Rash
• Injection site reaction including redness, pain, warmth at the injection site, tenderness or swelling that may last for several days
• High blood pressure.

Gemcitabine

Risks and side effects related to gemcitabine include:
Likely Side Effects:
- Nausea and vomiting
- Anemia or lowered red blood cells
- Lowered white blood cells, which may make you more likely to get an infection
- Lowered number of a specific type of white blood cells called neutrophils
- Abnormal liver function laboratory results which may indicate irritation of the liver
- Protein in your urine

- Fever. Fever was frequently associated with other flu-like symptoms and was usually mild.
- Blood in your urine
- Rash
- Lowered platelets
- Diarrhea
- Hemorrhage or loss of blood
- Increased concentration of nitrogen in the blood (elevated BUN lab)
- Infection
- Loss of Hair
- Increased bilirubin or jaundice, which is yellowing of the skin, mucous membranes or eyes which can come from bilirubin, a byproduct of old red blood cells
- Stomatitis (mouth inflammation)
- Somnolence (drowsiness)
- Paresthesia (a sensation of burning, prickling, tingling, or creeping on the skin)

Less likely side effects
- Itching
- Constipation
- Loss of muscle or nerve function which may cause weakness or numbness (similar to having your hand or leg "fall asleep," and which may be associated with some clumsiness of movement)
- Allergic reaction
- Fluid collection (including swelling of the legs and/or arms), and narrowing of the air passages of the lung
- Radiation recall (changes to the skin in previously irradiated areas)
- Inflammation of the lung tissue (pneumonitis)

Risks and Side Effects from other study procedures

Blood Draw:

You will have your blood drawn during the study. Possible side effects of having blood drawn are tenderness, pain, bruising, bleeding and/or infection where the needle goes into the skin and blood vein. Having your blood drawn may also cause you to feel nauseated and/or lightheaded.

Computerized Tomography (CT scan):

A CT scan is a specialized x-ray test that takes images of the body. You may feel some discomfort or anxiety when lying inside the scanner.
- If contrast material (iodine) is used during the CT scan there is slight risk of developing an allergic reaction. The reaction can be mild (itching, rash) or severe (difficulty breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled using medication. Be sure to tell your doctor if you have allergies of any kind (such as hay fever, iodine allergy, eczema, hives, or food allergies) or have had a previous reaction to medications or contrast material.

- The contrast material used during CT scanning can cause water loss or damage to the kidneys that may lead to kidney failure. This is a concern if you have poor kidney function, dehydration, or diabetes, especially if you take Glucophage® (metformin) to control your diabetes.

Magnetic Resonance Imaging (MRI):

MRI scans use strong magnetic fields and radio waves to produce an image of the inside of the body. There are no known harmful effects from the strong magnetic field used in MRI scans. However, the magnet is so powerful that it can affect any unsecured metal objects, which can be pulled towards the magnet. The magnet may affect pacemakers, artificial limbs, and other medical devices or implants that contain metal. You should discuss any devices in your body with the study staff. You may feel some discomfort or anxiety when lying inside of the scanner.

- If contrast material is used during the MRI scan there is slight risk of developing an allergic reaction. However, most reactions are mild and can be controlled using medication.

For patients that need an MRI scan and have reduced kidney function there is a chance of developing "Nephrogenic Systemic Fibrosis", a condition that can cause thickening and itchiness of the skin, stiffening of the joints and possible reduction in the ability to move around. This condition is related to the MRI contrast agent gadolinium and occurs mostly in patients with severe kidney disease. The risk to patients with mild kidney impairment is thought to be small.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because of the knowledge gained about pancreatic ductal adenocarcinoma and sarcoma.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could have another chemotherapy treatment or other investigational treatments. You also have the option of receiving no treatment for your cancer, but receiving care that will make you as comfortable as possible during the course of your disease. Please talk to your doctor about these other options.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You may have additional costs for being in this research study.

The cost of the study drug, Decitabine, will be paid for by the study. However, the cost of the administration of the drug will be the responsibility of you or your insurance carrier. The cost of Gemcitabine will be the responsibility of you and/or your insurance carrier.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The University and the research team are receiving no payments from other agencies, organizations, or companies to conduct this research study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- the U.S. Food and Drug Administration
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will use unique identification code numbers only on data forms, have locked storage areas, and use password-protected computer files. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your medical record chart that you are participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires your health care provider to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study and for your treatment. Once your health care provider has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies and the University of Iowa Institutional Review Boards and support staff.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes your health care provider to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

Varun Monga, MD
University of Iowa Hospitals and Clinics
200 Hawkins Drive, C32 GH
Iowa City, Iowa 52242

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If

you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

If you decide to leave the study early, we will ask you to talk with your doctor so any risks from the study treatment can be evaluated to make sure that safety is addressed. You should also discuss what follow-up will occur and what testing would be most helpful for you.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because the researcher decides it is in your best medical interest, the study is stopped, a better treatment becomes available, your condition worsens, or you have severe side effects from the study drugs.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Varun Monga, MD at 319-384-9497. If you experience a research-related injury, please contact: Varun Monga, MD at 319-384-9497. If you are calling during non-business hours, please call 319-356-1616 and ask the operator to page the hematology/oncology fellow on call. Tell the operator you are a research subject in one of Dr. Monga's studies

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 10/09/20.

_____ _____
(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)