Medical University of South Carolina
CONSENT TO BE A RESEARCH SUBJECT
A Traditional Feasibility study of Gemcitabine, Cisplatin, and ^{90}Y TARE for Unresectable Intrahepatic Cholangiocarcinoma

Study ID: MUSC 102254
Sponsor: Medical University of South Carolina
PI: S. Lewis Cooper, MD

A. PURPOSE AND BACKGROUND:

You are being asked to volunteer for a research study. You are being asked to participate in this study because you have cancer of the bile ducts inside the liver that cannot be removed by surgery. This form contains information about the study, which your doctor will explain so you can decide if you want to participate.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

The study treatments being looked at for this study are gemcitabine, cisplatin and a type of treatment called Yttrium 90 or ^{90}Y TARE. ^{90}Y TARE is a treatment where small glass microspheres (small round particles) containing radioactive yttrium-90 are injected into the artery of the area of the body where there is cancer. The combination of gemcitabine and cisplatin is standard of care chemotherapy for the type of cancer you have. ^{90}Y TARE is approved by the FDA for treatment in unresectable metastatic liver tumors. The use of ^{90}Y TARE in intrahepatic cholangiocarcinoma in combination with chemotherapy is investigational.

The purpose of this study is to find the safe dose when adding ^{90}Y TARE with cisplatin and gemcitabine. This study will also look at the safety and effectiveness of the combination of ^{90}Y TARE with gemcitabine and cisplatin.

Because there may be an interaction between the chemotherapy and the ^{90}Y TARE, this study will start at a lower dose of the gemcitabine than standard for the first two cycles and the ^{90}Y TARE dose will be lower than standard as well. The first several subjects will receive the lowest dose. If the combination does not cause serious side effects, it will be given to other subjects at a higher dose. The doses will continue to increase for every group of subjects until side effects occur that require the dose to be lowered or until the highest dose is safely reached. The study is then stopped.

This research is sponsored by Medical University of South Carolina. The investigator in charge of this study is Dr. Lewis Cooper. Dr. Cooper is responsible for the conduct of this trial. He will not receive compensation for conducting this trial. This study is being done at MUSC and will involve up to 24 subjects.

B. PROCEDURES:

Before you begin the study:

If you decide to participate in this study, and after signing informed consent, you will complete the evaluation process. You will need to have the following exams, tests and procedures to find out if you are eligible for this study treatment. These exams, tests and procedures are sometimes part of regular cancer care and may be done even if you do not join this study. If you have had some of them done recently, they may not need to be repeated. This will be up to your study doctor. These procedures will be done as an outpatient.

- History and Physical Exam with height and body surface area or BSA. Your doctor will also review any medications you are taking.
- Vital Signs (temperature, heart rate, breathing rate, blood pressure and weight)
- Blood Tests to look at blood cell counts (numbers of each type of blood cell), chemistries (elements and minerals in your blood) and how well your blood clots. The amount of blood taken at this blood draw is about 15 ml (or 3 teaspoons).
- Serum (blood) pregnancy test for women who may be able have children (about 1 teaspoon)
- Chest and pelvic CT scan (a series of images taken with x-rays). MRI scan (series of images taken with magnets) of the abdomen. These scans will give a detailed picture of the areas of the body taken from different angles. The procedure for this is described below.

  A CT scan or MRI will be completed before you are enrolled in this study to ensure that you are eligible to participate. For a CT scan, a tourniquet (a device that is used to temporarily constrict an artery of the arm or leg) will be applied to your arm and a dye will be injected which highlights specific areas inside the body and creates a clearer image. During the test, you will lie on your back on an x-ray table. A strap will be placed across the body part to be scanned, to prevent movement. The table will then slide into a large, tunnel-shaped machine. When the CT scan is finished, you may immediately resume your usual activities and diet. A MRI takes pictures of the body created by using magnetic energy rather than x-ray energy. Pictures are taken while you lie in a narrow bed inside of a large magnet.

In addition to the procedures above, the following research procedure may be done at screening:

- We will look at the leftover tissue (tissue not used for your diagnosis) from your original biopsy or surgery to see what genetic mutations may be in your tumor. This will help us

see if there is a difference in how your tumor responds based on the mutation in the tumor.
DNA: Your genes are made up of DNA. **DNA** is short for deoxyribonucleic acid. DNA contains information that determines in part the traits, such as eye color, height, or disease risk, that are passed on from parent to child. **RNA**: RNA is short for ribonucleic acid. RNA is a genetic material that has a major role in making proteins. Proteins: Proteins are the building blocks of your body, cells and organs.

Research to identify genes that cause or contribute to a disease or trait is an increasingly important way to try to understand the role of genes in human disease.

If your study doctor finds that you do not meet the specific eligibility requirements to be in this study, you will not be able to participate. You will continue to see your regular doctor who will discuss with you additional options for your disease.

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be registered to the study and will begin study treatment.

After you are registered, your study doctor will evaluate you for the ^{90}Y TARE treatment. You will have the following assessments:

- Blood Tests to look at blood cell counts, chemistries, and how well your blood clots. The amount of blood taken at this blood draw is about 15 ml (or 3 teaspoons).
- A procedure called hepatic angiography. For this procedure, you will have a very small tube called a catheter inserted into an artery in your groin or wrist. The Interventional Radiologist will then inject a small amount of a dye to see where blood vessels go into your liver. This is done to see if it is possible to give the Y90. The radiologist will also block off any blood vessels that would cause the Y90 to go to parts of the body that could cause harm. Finally, a small amount of another radioactive substance, Technetium 99m particles, will be injected and then images taken to make sure that the Yttrium 90 will not cause injury to the lung or other organs.

  There is a chance you could have this procedure and then not be able to receive the Y90. If you are unable to receive the Y90, you will be taken off study and will see your regular doctor to discuss additional options for your disease.

<u>During Study Treatment:</u>

Chemotherapy:

You will get Gemcitabine and Cisplatin intravenously (IV, by a needle in the vein) on days 1 and 8 of each treatment cycle. Cisplatin will be given over 1 hour. Gemcitabine will be given over 30 minutes. Each cycle is 21 days. You may have up to 8 cycles of chemotherapy treatment. During the first two cycles of chemotherapy, the dose of

gemcitabine will be lower than you would receive off study. This means there is a chance that it may not be as effective.

^{90}Y TARE:
You will get the ^{90}Y TARE treatment on day 3 or day 4 of cycle 1. You will have another hepatic angiography procedure. Your radiologist will give you ^{90}Y TARE to the parts of the liver that have bile duct cancer.

While on study, you will have the following tests or assessments:

Day 1 before chemotherapy:
- History and Physical
- Vital signs
- Blood Tests to look at blood cell counts and chemistries. The amount of blood taken at each blood draw is about 15 ml (or 3 teaspoons).
- Review of what medications you are taking and any side effects you may be feeling

Day 3 or 4 before ^{90}Y TARE (CYCLE 1 ONLY):
- Blood Tests to look at blood cell counts, chemistries, and how well your blood clots. The amount of blood taken at each blood draw is about 15 ml (or 3 teaspoons).

Day 8before chemotherapy:
- Vital signs
- Blood Tests to look at blood cell counts and chemistries. The amount of blood taken at each blood draw is about 15 ml (or 3 teaspoons).
- Review of what medications you are taking and any side effects you may be feeling.

After cycle 4:
- MRI of the abdomen

End of study visit:

Study treatment will end after cycle 8. After cycle 8, you may have the following tests or assessments. If you end treatment early, before cycle 8, you may also have these assessments.

- History and physical exam
- Blood Tests to look at chemistries. The amount of blood taken at this blood draw is about 15 ml (or 3 teaspoons).
- Review of what medications you are taking and any side effects you may be feeling.
- MRI of the abdomen

After Study Treatment:

After you have finished study treatment you will enter a follow up period. During the follow up period, your doctor may ask you to return to clinic for the following tests or assessments:

- History and Physical
- Vital signs
- Blood Tests to look at chemistries. The amount of blood taken at this blood draw is about 15 ml (or 3 teaspoons).
- MRI of the abdomen
- If you came off study early due to a side effect, a member of the study team may contact you by phone or ask that you come to the clinic until the side effect has gotten better.

The study team will also follow your care and vital status by review of medical records and/or telephone call every 3 months for 2 years and then every 6 months for 4 years. Additionally, the study team may use your social security number to check registries for your vital status.

A table showing the study schedule is on the last page of this informed consent.

C. DURATION:

You may receive study treatment for up to 8 cycles which will take about 6-7 months. After you finish study treatment, you will be followed every 3 months for 2 years and then every 6 months for 4 years after the start of study treatment. The total time on study will be about 6 years.

D. RISKS/DISCOMFORTS:

You may have side effects while on the study. It is important that you tell your physician about any side effects you feel. The physician may reduce the dose or temporarily stop the study medication until the side effect improves. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go way after you stop taking the drugs, however in some cases they can be serious and long lasting. There is also a risk of death.

Risks and side effects related to the specific drugs are listed below. The risk of serious side effects may be higher with Y90 combined with cisplatin and gemcitabine since this has not been tested before. You should talk to your doctor or nurse about these side effects.

^{90}Y TARE

Common:

- fever

- anemia
- abnormal liver function tests
- nausea and vomiting
- abdominal pain
- diarrhea

Severe side effects

- There is a less than 5% chance of injury to the liver that could be severe or life threatening.
- Stomach pain with bleeding
- Pancreatitis (injury to the pancreas)
- Injury to the lungs with shortness of breath
- Bleeding from the bowel
- Infection that can be severe or life threatening.
- The chance of any injury to an organ other than the liver is about 10%.
- There is a 1-2% risk of death from complications of Yttrium 90

CISPLATIN:

The following side effects have been identified from clinical trials and/or post-marketing surveillance. Since they are reported from a population of unknown size, we cannot make exact estimates of how often they occur. The most common reported side effects for cisplatin are listed below.

Most Common side effects:

- nausea and vomiting
- renal toxicity – damage to the kidneys that may be seen with an elevation of certain urine and blood tests.
- hearing damage including hearing loss at high-frequency range and/or ringing in the ears
- excess of uric acid in the blood, or hyperuricemia
- myelosuppression, a condition where bone marrow activity decreases, which results in low red blood cell, white blood cell and platelet counts.

GEMCITABINE:

Most common:

- decreased number of platelets and white blood counts
- decreased hemoglobin, or anemia
- flu-like symptoms with fever
- headache
- chills
- nausea

- diarrhea
- itchy skin rash
- muscle pain
- loss of appetite
- fatigue or a feeling of tiredness
- peripheral edema which is a swelling of tissue, usually in the lower limbs
- proteinuria, a condition where the urine has an abnormal amount of protein

Less Common

- abnormal renal and liver function tests
- vomiting
- constipation
- feeling of discomfort or uneasiness

Rare

- Stevens-Johnson syndrome, a life-threatening skin condition
- shortness of breath
- cough
- inflammation or scarring of the lung
- hemolytic uremic syndrome, which is a condition that causes the abnormal premature destruction of red blood cells. This may lead to life-threating kidney failure
- liver failure
- cardiac dysfunction including heart attack congestive heart failure, and atrial fibrillation (irregular heart beat)

Hepatic Angiography: Possible risks and complications include bruising at the insertion site and damage to the artery used during the procedure. There is also risk of allergic reaction or damage to the kidneys due to the contrast used during the procedure. You will be asked to sign a separate clinical consent for the hepatic angiography procedure that will fully describe the specific risks of the procedure. You have the right to withdraw from the study if you decide that you do not want to have this procedure.

MRI Scan: There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within your body, you will be excluded from participation in this research study. We will also keep the examining room locked so that no one carrying metal objects can enter while you are in the scanner. Please inform the study staff if you have a history of claustrophobia (extreme anxiety in close spaces). This may also be a contraindication to participation in the study.

CT Scan: You will be exposed to some radiation with this procedure. There is always a slight risk of damage from being exposed to any radiation, including the low amount of x-rays used for the CT scan. If you are especially concerned with radiation exposure, you should discuss this with the study doctor.

Loss of confidentiality: There is a risk of loss of confidentiality since medical records will be reviewed during this study. MUSC and its study team members will take every effort to ensure that your information is kept confidential during this study.

Venipuncture: The risks of drawing blood include temporary discomfort from the needle stick, bruising and infection. Fainting could occur.

Pregnancy: If you are a female of childbearing potential, or a sexually active male, you must agree to use adequate contraception (birth control) for the time you are in the study. You must agree to use two forms of birth control – one of which must be a barrier method. For example, use of spermicide, an intrauterine device (IUD) or oral contraceptive, plus a barrier method such as a condom, diaphragm or cervical cap. Oral contraception must not be used alone. If you get pregnant during the study, you must tell the doctor immediately. You will have to stop taking part in the study. The doctor will advise you about your medical care.

Genetic Research: Genetic research studies may present unique risks to human subjects and their relatives. These involve medical, psychosocial and economic risks, such as the possible loss of confidentiality (private information), loss of insurability and employability, paternity, and social stigmas. Knowledge of one's genetic make-up may also affect one's knowledge of the disease risk status of family members. Genetic research raises difficult questions about informing you and other subjects of any results, or of future results. Some people feel anxious about the possibility of having a defective gene that would place them or their children at risk. Some people want to know what is found out about them; others do not. The risks of knowing include anxiety and other psychological distress. The risks of not knowing what is found include not being aware if there is treatment for the problem being studied. But these risks can change depending on whether there is a treatment or cure for a particular disease and on how clear the results are. If there is a medical reason to seek specific information from you, your doctor will tell you this. A process called "genetic counseling" is often appropriate in such cases; you should ask your doctor or nurse about this if you have any questions.

South Carolina law mandates that your genetic information obtained from any test or from this research, be kept confidential. Our state law prohibits an insurer using this information in a discriminatory manner against your or any of your family in issuing or renewing insurance coverage for you or your family. Our state law further prohibits our sharing your genetic information with anyone except in a few narrow circumstances, one of these being a research project of this type, approved by the Institutional Review Board and then we must take all steps to protect your identity. You will still be responsible for paying for health care, however. The Medical University of South Carolina will not be responsible for such costs, even if care is needed for a condition revealed during research or clinical testing.

GENETIC INFORMATION NONDISCRIMINIATION ACT (GINA)

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this new federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance, nor does it protect you against genetic discrimination by all employers.

E. BENEFITS:

There may or may not be a direct benefit to you from participating in this study. However, it is hoped that the information gained from the study will help in the treatment for future subjects with conditions like yours.

F. COSTS:

The mutation analysis of your biopsy will be paid for by the study. You or your insurance company will be billed for all drugs, procedures, and labs completed for this study. Some insurance plans will not pay for the standard of care services you receive while participating in a clinical trial. Please check with your insurance company to find out if your plan will pay. If your insurance plan will not pay, you will be responsible.

G. PAYMENT TO PARTICIPANTS:

You will not be paid for participating in this study.

H. ALTERNATIVE TREATMENT

Participation in this study is voluntary. Other treatment options include:

- Receiving treatment for your cancer without participating in a clinical trial

- Receive palliative care (comfort care) which will not directly treat cancer but aims to make subjects as comfortable as possible.

I. NEW INFORMATION:

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

J. STUDENT PARTICIPATION

Your participation or discontinuance will not constitute an element of your academic performance nor will it be part of your academic record at this Institution.

K. EMPLOYEE PARTICIPATION

Your participation or discontinuance will not constitute an element of your job performance or evaluation nor will it be part of your personnel record at this Institution.

L. PATIENT WITHDRAWAL

You can decide to stop participating in this study at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

The study doctor may stop you from taking part in this study at any time if he or she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

M. CLINICAL TRIAL REGISTRY DATABANK

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.

Results of this research will be used for the purposes described in this study. This information may be published, but you will not be identified. Information that is obtained concerning this research that can be identified with you will remain confidential to the extent possible within State and Federal law. The sponsor and the Food and Drug Administration (FDA) will receive copies of the research records. The investigators associated with this study, employees of the sponsor, the FDA, and the MUSC Institutional Review Board for Human Research will have access to identifying information. All records in South Carolina are subject to subpoena by a court of law.

In the event of a study related injury, you should immediately go to the emergency room of the Medical University Hospital, or in case of an emergency go to the nearest hospital, and tell the physician on call that your are in a research study. They will call your study doctor who will

make arrangements for your treatment. If the study sponsor does not pay for your treatment, the Medical University Hospital and the physicians who render treatment to you will bill your insurance company. If your insurance company denies coverage or insurance is not available, you will be responsible for payment for all services rendered to you.

Your participation in this study is voluntary. You may refuse to take part in or stop taking part in this study at any time. You should call the investigator in charge of this study if you decide to do this. The data collected on you to this point remains part of the study database and may not be removed. Your decision not to take part in the study will not affect your current or future medical care or any benefits to which you are entitled.

The investigators and/or the sponsor may stop your participation in this study at any time if they decide it is in your best interest. They may also do this if you do not follow the investigator's instructions.

Volunteers Statement

I have been given a chance to ask questions about this research study. These questions have been answered to my satisfaction. If I have any more questions about my participation in this study or study related injury, I may contact Dr. Lewis Cooper at (843) 792-4271. I may contact the Medical University of SC Hospital Medical Director (843) 792-9537 concerning medical treatment.

If I have any questions, problems, or concerns, desire further information or wish to offer input, I may contact the Medical University of SC Institutional Review Board for Human Research IRB Manager or the Office of Research Integrity Director at (843) 792-4148. This includes any questions about my rights as a research subject in this study.

I agree to participate in this study. I have been given a copy of this form for my own records.

If you wish to participate, you should sign below.

Signature of Person Obtaining Consent	Date	Signature of Participant	Date

	Pre-Study	Y90 Evaluation	Cycle 1			Cycles 2-4		After Cycle 4	Cycles 5-8		After Cycle 8	Follow Up
			D1	D3 or D4	D8	D1	D8		D1	D8		
Physical Exam and Medical History	X		X			X			X		X	X
Vital Signs	X		X		X	X	X		X	X		X
Review of medications	X		X	X	X	X	X		X	X	X	
Blood tests	X	X	X	X	X	X	X		X	X	X	X
MRI Scan	X							X			X	X
Tumor tissue analysis	X											
Treatment												
^{90}Y TARE				X								
Cisplatin			X		X	X	X		X	X		
Gemcitabine			X		X	X	X		X	X		