Official Title: MR Guided Phase II Radiotherapy Dose Escalation in Unresectable Non-Metastatic Pancreatic Cancer

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Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

MR guided Phase II Dose Escalation in Unresectable Non-metastatic Pancreatic Cancer

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You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

Radiation therapy-high energy radiation from x-rays and other sources used to kill cancer cells and shrink tumors.

Dose escalation Radiation Therapy- radiation therapy given at these higher doses of radiation (dose escalated)

Concurrent Chemotherapy- chemotherapy given during Radiation Therapy.

Capecitabine- is an oral drug taken twice per day on the same day that radiation therapy is given.
Gemcitabine- is an intravenous drug given once per week.

Purpose

This project is being done to find out the effects of giving higher doses of radiation while receiving chemotherapy for controlling pancreas cancer, which surgery is not recommended.

Length

You will be in this research project for about 2- 5 years and then yearly. We will ask you to come into the clinic every three months from the start of maintenance the first 2 years, every 6 months years 2- 5, then annually.

Procedures

Some screening tests will be done first to see if you are eligible.

List of visits:

- Screening Visit
  - Total Number: About 3 visits
  - Total Time: About 3 hours
- Treatment
  - Total Number: About 3 hours

  Total Time: Radiation therapy about 10 minutes. Chemotherapy (Gemcitabine and Capecitabine) about 30-40 minutes.

  Visit- about 30-35 visits
- Follow up visits- about 14 visits for the first 5 years and then yearly.
- Total Time- about 2-3 hours

Procedures that will occur at various visits:

Invasive Procedures

Gemcitabine administration, blood samples, PET, CT & MRI scans.

.Non-invasive Procedures

Full medical history physical exam, guided radiation therapy, oral Capecitabine and chest x-ray.

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

Radiation therapy risks:

- Stomach pain and intestinal discomfort, nausea, vomiting, heart burn
- Fatigue
- Tanning, redness of skin, and hair loss within the radiation area
- Permanently dry skin in the radiation treatment area
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Loss of appetite and weight loss

Gemcitabine:

- Flu-like symptoms of muscle pain, fever, headache, chills and fatigue
- Nausea, vomiting
- Rash
- Hair Loss
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia which may require a blood transfusion
- Muscle weakness
- Blood in urine
- Feeling of “pins and needles” in arms and legs
- Numbness and tingling of the arms and legs
- Tiredness
- Difficulty sleeping
- Hearing loss
- Swelling of arms, legs

Capecitabine:

- Swelling of the body
- Blisters on the skin
- Redness, pain or peeling of palms and soles
- Pain
- Diarrhea, loss of appetite, nausea, vomiting
- Sores in mouth which may cause difficulty swallowing
- Anemia which may require blood transfusions
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Feeling of “pins and needles” in arms and legs
- Tiredness
- Fever

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:

- Joining a different project
- Routine care for this condition.
- Getting no treatment for this condition

If you have more questions about this project at any time, you can call Beth Erickson, MD at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are invited to participate in this research because you have Pancreas cancer for which surgery is not recommended. You will have already received several months of chemotherapy before you are eligible for this research project and there will not have been any detectable spread of your tumor on imaging studies following this chemotherapy course.

A total of about 23 people are expected to participate in this research the Medical College of Wisconsin/Froedtert Hospital/Blood Center of Wisconsin.

The Director of the project is Beth Erickson in the Radiation Oncology. A research team works with Dr. Erickson. You can ask who these people are.

This research is funded by the Department of Radiation Oncology.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

In this project we want to find out more about the efficacy of giving higher doses of radiation with concurrent chemotherapy in controlling unresectable pancreas cancers. We also want to assess the acute and late side effects (problems and symptoms) of radiation therapy given at these higher doses of radiation (dose escalated) following full dose chemotherapy given before the radiation and with concurrent chemotherapy for pancreas cancer. Radiation therapy is given in higher doses that are limited by the proximity of your normal organs to the radiation dose distribution to improve the likelihood of controlling the tumor in the pancreas while minimizing the risk of radiation injury to these organs. There are two chemotherapy drugs, Capecitabine is an oral drug taken twice per day on the same day that radiation therapy is given and Gemcitabine is an intravenous drug given once per week. Everyone in this research will have already received chemotherapy alone first. Everyone in this project will receive radiation therapy and concurrent chemotherapy. We do not know how well this treatment may affect your pancreas cancer.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

Screening procedures:

If you decide to join, some screening tests will be done first to see if you are eligible.

These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the project. If you have had some of them recently, they may not need to be repeated. This will up to your research doctors. If the screening information shows that you meet the requirements, then you will be able to start.

- Biopsy
- History and physical exam, including weight, performance status and vital signs
- Blood tests, chemistry, CA19 and CEA
- Abdominal/pelvic CT/MRI/PET scan
- Chest CT or x-ray

During the project:
If the exams, tests and procedures show that you can be in the research project, and you choose to take part, then you will need the following tests during the research project. They are part of regular cancer care.

- Physical exam: at investigator discretion (Recommended weekly during radiation treatment, and then at least monthly)
- Blood tests: at investigator discretion (Recommended Weekly)
- Daily image-guided radiation therapy
- Oral Capecitabine twice per day during RT **OR** IV Gemcitabine once per week during RT
- CT/MR or MRI SIM planning mid treatment (weeks 2-5) if necessary.
- Tumor Tissue SMAD 4 testing from your biopsy tissue (if possible)

You will receive radiation therapy daily as an outpatient for about 6-7 weeks, oral Capecitabine twice per day **or** IV Gemcitabine once per week.

When you are finished with treatment you will have the following exams, tests, and procedures that are part of standard cancer care.

- Physical exam: one month, every 3 months the first 2 years, every 6 months until year 5, then annually after year 5.
- Blood tests (standard of care): Performed at investigator discretion (Recommended time points are 30 days post radiation, every 3 months until 2 years, every 6 months years 2-5, then annually after year 5).
- CT abdomen/pelvis one month following completion of radiation.
- Abdominal/MRI: 3 months following completion of radiation. Additional MR scans every 6 months for the first 2 years should be obtained and alternated with CT scans every 6 months. After 2 years, alternating abdominal MR and abdominal CT scans will be obtained every 6 months until year 5 and after year 5, a CT abdomen scan will be obtained annually.
- Chest X-ray, or CT: Every 3 months or until your disease comes back.
- If recommended by your doctor, PET/CT at 3 months post radiation and at additional intervals thereafter, you can discuss with the research team.

- Tumor tissue SMAD 4 testing if your cancer returns and surgery is required.

B2. HOW LONG WILL I BE IN THE PROJECT?

After the treatment is finished, we want to keep in touch with you to follow your health over time. We will ask you to come into the clinic every three months from the start of maintenance the first 2 years, every 6 months years 2- 5, then annually.

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.
The research doctor can tell you about the effects of stopping, and you and the research doctor can talk about what follow-up care would help you the most.

The research doctor may take you out of this project at any time. This would happen if:
- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE PROJECT?

Dangerous interaction with warfarin (Coumadin):
If you are taking warfarin (which is also called Coumadin), a medicine used to prevent blood clotting, capecitabine may change the way your blood clots. The interaction between warfarin and capecitabine is very significant and could result in severe bleeding. If you need to take warfarin, your doctor will regularly check for changes in blood clotting time.

You will also be instructed when you can eat or drink prior to the radiation treatments each day. We would like to keep your stomach empty prior to the radiation treatments to minimize swelling of your stomach. You will be asked to drink a small amount of water prior to each radiation treatment.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may get treatment that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from treatment. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.** If you have an emergency, call Dr. Erickson immediately at 414-805-6700. In an emergency, call 911.

C2. RISKS OF TREATMENT

The research treatment itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away.
Many go away soon after you stop taking the treatment. Drugs can affect individuals in different ways. Complications of some of the side effects below may lead to life-threatening events.

The side effects that other people have experienced so far with the drug are:

Risks and side effects of Radiation Therapy:
Likely

- Stomach pain and intestinal discomfort, which usually occur during the last three weeks of radiation and generally go away within 2 months after the treatment is finished
- Nausea
- Vomiting
- Heart burn
- Fatigue
- Tanning, redness of skin, and hair loss within the radiation area, which is temporary
- Permanently dry skin in the radiation treatment area
- Low blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Loss of appetite and weight loss

Less Likely

- Diarrhea
- Infection
- Mild muscle aches in the area treated

Rare but serious

- Change in liver or kidney function, which is unlikely to cause symptoms.
- Bowel obstruction or perforation, which could result in abdominal pain, nausea and vomiting and may require surgery. Very rarely, death can occur.
- Gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain, heart burn, nausea vomiting, and bleeding, and may require surgery. Very rarely death can occur.

Risks and side effects related to gemcitabine include those that are:
Possible Side Effects of Gemcitabine

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:

- Flu-like symptoms of muscle pain, fever, headache, chills and fatigue
- Nausea, vomiting

- Rash
- Hair Loss
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia which may require a blood transfusion
- Muscle weakness
- Blood in urine
- Feeling of “pins and needles” in arms and legs
- Numbness and tingling of the arms and legs
- Tiredness
- Difficulty sleeping
- Hearing loss
- Swelling of arms, legs

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Gemcitabine, from 4 to 20 may have:

- Diarrhea, constipation
- Sores in mouth which may cause difficulty swallowing
- Shortness of breath
- Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of ankles
- Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause headache, seizure, blindness

RARE, AND SERIOUS
In 100 people receiving Gemcitabine, 3 or fewer may have:

- Abnormal heartbeat
- Heart failure or heart attack which may cause shortness of breath, swelling of ankles, and tiredness
- Blisters on the skin, which can be life-threatening
- Sores on the skin
- Blood clot
- Liver damage which may cause yellowing of eyes and skin, swelling
- Damage to organs which may cause shortness of breath
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Kidney damage which may require dialysis
- Scarring of the lungs
- Fluid around lungs
- Blockage of the airway which may cause cough

Possible Side Effects of Capecitabine

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Capecitabine, more than 20 and up to 100 may have:

- Swelling of the body
- Blisters on the skin
- Redness, pain or peeling of palms and soles
- Pain
- Diarrhea, loss of appetite, nausea, vomiting
- Sores in mouth which may cause difficulty swallowing
- Anemia which may require blood transfusions
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Feeling of “pins and needles” in arms and legs
- Tiredness
- Fever

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Capecitabine, from 4 to 20 may have:

- Blurred vision, dry or itchy eyes
- Muscle spasms, body aches
- Abnormal heartbeat
- Restlessness, irritability
- Swelling of face, fingers and lower legs
- Constipation
- Confusion
- Difficulty with balancing

RARE, AND SERIOUS
In 100 people receiving Capecitabine, 3 or fewer may have:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Difficulty speaking, walking or seeing
- Internal bleeding which may cause blood in vomit or black tarry stools
- Damage to the heart

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Loss of Confidentiality:

We will do our best to keep your information confidential. Information that identifies you will not be given to anyone, unless required by law. If research results are published, your name and other personal information will not be used.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant

The treatment in this project might affect a baby, before or after the baby is born. We do not know if the treatment cause(s) harm to a baby, so we do not want anyone who might be pregnant to enter the project. You should not become pregnant or nurse a baby while in this project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project during the project. If you become pregnant while receiving treatment, you will be withdrawn from the project. Dr. Erickson will discuss treatment options.

You may not donate eggs during your participation in the project or for 3 months after stopping the treatment.

Risks of fathering a child

You should not father a baby while taking part in this project because it is unknown if treatment could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the research doctor right away if you think your partner is pregnant.

You may not donate sperm during your participation in the project or for 6 months after stopping treatment.

Birth control methods for all subjects

Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use birth control while you are in this project. This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms (“double barrier”)
- Limiting sexual activity to a male partner who has had a vasectomy

Females should continue using birth control for 3 months after stopping the Capecitabine or Gemcitabine and 6 months for males.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

We don’t know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us develop better treatments for Pancreas cancer.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier. Activities / costs that are part of the project will not be billed to you or your insurance company. These are SMAD 4 testing on your biopsy tissue, which will be paid for by this project. Some insurers will not pay for drugs, tests or hospitalization that are part of research, so check with your insurer before you join this project. If you have questions regarding costs, please contact Dr. Erickson.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this project

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Your other choices may include:

- Standard radiation and chemotherapy for pancreas cancer
- Joining a different research project
- The procedure or drug offered to you may also be available without being in any research project.

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information the treatment that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

Clinically relevant results, including individual results, will be disclosed to you, during your treatment and in follow up during a clinic visit.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Dr. Erickson, 414-805-6700.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Erickson at 414-805-6700If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:
Past medical record and records dating from when you join this project until the end of the project.

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital/BloodCenter of Wisconsin employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record or BloodCenter blood donor record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information and tissue specimen, the information and tissue specimen may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Beth Erickson, MD at Department of Radiation Oncology 9200 W. Wisconsin Ave, Milwaukee, WI 53226. The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

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.

You can look up this project by referring to the ClinicalTrials.gov number (NCT#01972919)or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**

*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*