ADULT CONSENT - CLINICAL BIOMEDICAL

Title of this Research Study

Invitation
You are invited to take part in this research study. You have a copy of the following, which is meant to help you decide whether or not to take part:

- Informed consent form
- "What Do I need to Know Before Being in a Research Study?"
- The Rights of Research Subjects

Why are you being asked to be in this research study?
You are being asked to be in this study because you have locally advanced pancreatic adenocarcinoma. Locally advanced means the cancer has spread beyond the pancreas near or involve the major blood vessels around the pancreas and may have spread to the lymph nodes.

If you are pregnant, nursing an infant, or plan to become pregnant during this study, you may not be in this study.

What is the reason for doing this research study?
This study is being done to test the safety and effects (good and bad) of giving a drug called Zometa, before radiation therapy. Zometa is being studied to see if it makes tumor cells more sensitive to radiation.

Zometa is a drug approved by the Food and Drug Administration (FDA), for use in cancer patients to reduce cancer symptoms, but is not approved for use to increase effectiveness of radiation. In this study, Zometa is being studied to determine if it makes tumor cells more sensitive to the radiation.

A total of up to 60 subjects will be able to enter the study at UNMC/the Nebraska Medical Center.

What will be done during this research study?
Your doctors will review your medical history, current medications, and previous treatment for your cancer to determine if you might qualify to participate in the study. If you choose to sign this informed consent form, you will continue with the screening process. Many of the tests were obtained after your recent chemotherapy and will not

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be repeated. Some of these same tests will also be done during your treatment to follow your progress. Additionally, tumor tissue taken at time of diagnosis and at time of surgical resection will be studied and analyzed to determine the effect on tumor cells with Zometa and radiation versus radiation alone.

The screening process will take place over a period of up to 28 days. These may take more than one visit and will include the following:

- A physical examination will be performed.
- Assessment of your health status and your well-being will.
- Blood tests to determine the number of cells in your blood and your liver and kidney function,
- A blood test to measure the amount of a protein called CA19-9 which is sometimes higher in patients with pancreatic adenocarcinoma.
- If you are a women able to have children, a blood test to determine if you are pregnant.
- CT scan to determine the size of your cancer and whether it is locally advanced
- MRI of the abdomen if more information is need
- PET/CT scan (This is done for research purposes and will be repeated prior to surgery. This will be done to provide additional imaging information to evaluate effect of treatment.
- A card you will fill out to describe pain (if any) you have now.

If you qualify for this study and decide to participate, **you will be randomized into one of the study arms described below.** Randomization means that a computer program will assign you by chance in one of the arms. Neither you nor your doctor can choose the group you will be in.

Arm A: Hypofractionated Stereotactic Radiotherapy and Chemotherapy [5-Fluorouracil (5-FU) or Capecitabine]
Your medical oncologist will meet with you to decide which of the 2 chemotherapy drugs is best for you. This part of the treatment is considered "standard of care"

Arm B: Zometa, Hypofractionated Stereotactic Radiotherapy and Chemotherapy (5-FU or Capecitabine)
You will receive Zometa (4mg IV) on day 1 of radiation therapy (2-4 hours prior to radiation therapy) as a single use intravenous infusion over no less than 15 minutes. You will also be given calcium and vitamin D supplements to take daily for 30 days. Zometa can cause the amount of calcium in your blood to fall too low. Calcium and Vitamin D supplements can prevent this. (Vitamin D is needed by the body to help it

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absorb calcium.)

Your medical oncologist will meet with you to decide which of the 2 chemotherapy drugs is best for you. This part of the treatment is considered "standard of care"

After Zometa is given a series of blood samples will be collected to measure the drug level in your blood (only ARM B subjects). Blood samples (about 2 teaspoons each time) will be collected at the following time points:

- the time of infusion
- 1 hour after infusion
- Day 2 of radiation therapy
- Day 3 of radiation therapy
- Day 4 of radiation therapy
- Day 5 of radiation therapy

During this study, you will have the following interventions or procedures:

- ***Marker implantation:***2 to 3 fiducial markers (small metal objects or Calypso Beacons) will be implanted into the tumor. The markers are used to pinpoint the exact location of the pancreatic tumor during the radiation part of the study (image-guided stereotactic radiotherapy).Tthe markers will be placed by Interventional Radiology. The markers are placed using a needle that is inserted into the area of the tumor with the help of computed tomography (CT) or ultrasound (US). Markers prefilled in the needle are then advanced to carefully plotted positions in and around the tumor. You will be given antibiotics to prevent infection.

- **Chemotherapy:**You will have chemotherapy starting on the evening before day 1 of radiation therapy if you are to receive capecitabine oral chemotherapy (taken orally daily for 4 weeks) or day 1 of radiation therapy if you will receive 5-FU infusional chemotherapy(given as a continuous infusion for 28 days). Chemotherapy will last for 4 weeks total. Premedications for nausea may be given if needed prior to each chemotherapy.

- ***Stereotactic Radiation Therapy:*** The total dose of 40Gy will be delivered in 5 treatments over 5 consecutive days for 1 week.

- ***CT Scan:*** You will need to have a CT scan done before your radiation therapy to plan your radiation therapy. You may also need to have an MRI scan (if CT scan is not sufficient) to plan your radiation therapy. Your skin will be marked or tattooed for daily positioning before receiving radiation therapy.

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Infrared markers may be attached to your chest and abdomen in suitable positions to monitor movements from breathing.

Prior to surgery, you will have a CT scan done (possible an MRI if more information is needed) to determine if you are a surgical candidate. Additionally a PET/CT scan will be done for research purposes to provide additional imaging to determine effect of treatment. If you are, you will have surgery 1-3 weeks after the scans. If you are not a candidate for surgery, you will resume chemotherapy.

- ***Surgery:*** You will have surgery intended to remove of all remaining tumor approximately 4-8 weeks after completing radiation therapy. You will meet with a surgical oncologist to discuss this part of your treatment.

Monitoring During the Study
You will have blood tested monthly during the treatment. Chemotherapy and radiation therapy can lower your blood cell counts. If your counts get too low, the chemotherapy will need to be delayed and or reduced for your safety.

Follow-up Visits
You will be seen in the Department of Radiation Oncology for follow-up every 3 months for the 1st year and every 4 months for the 2nd year, then every six months thereafter. Subjects will be assessed for long term side effects from the combination of Zometa and radiation.

Subjects who go off study at any time during the study will be followed for 30 days after the last treatment or until other disease-related treatment begins.

What are the possible risks of being in this research study?
ZOMETA
Likely:

- Fever
- Fatigue
- Anorexia
- Nausea
- Vomiting
- Constipation and /or abdominal pain
- Low levels of calcium in the blood, which may cause muscle cramps
- Flu-like symptoms including fever, chills, and joint and muscle aches

Less Likely:

- Headaches

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- Insomnia
- Anxiety
- Stomach irritation
- Tachycardia
- Abnormal kidney function tests
- Diarrhea
- Tingling in the fingers and toes
- Bone, back, muscle, and joint pain. In some cases, this pain could be severe and could interfere with the subjects normal activities.
- Allergic reactions, which include itching, flushing, rash, and shortness of breath,
- Low levels of potassium, magnesium, and/or phosphate in the blood. In almost all cases, subjects would not experience symptoms from these effects. If these levels fall to extremely low levels, possible side effects could include muscle twitching, muscle weakness, and abnormal heart rhythm.
- A reaction at the injection site, which might include pain, redness, tenderness, swelling, and/or bruising.

Rare but Serious:

- Kidney failure
- Severe allergic reactions, which could include the inability to breathe and dangerously low blood pressure, which could be fatal
- Permanent damage to the jawbone (osteonecrosis of the jaw) that may be painful and might require surgery to remove the damaged area. This might be more likely to happen in patients who have certain dental procedures.

STEREOTACTIC RADIOTHERAPY

These are the risks of standard radiation therapy. The SRT will have the same risks as the other forms of radiation therapy.

Short term side effects may include:

- Skin reaction
- Hair loss to the area being treated
- Fatigue
- Abdominal pain
- Nausea
- Vomiting
- Diarrhea
- Increasing liver function abnormality
- GI bleeding or perforation which may require surgical intervention.

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Long term side effects are less likely to occur but if they do occur are more likely to be permanent. They include:

- Hair loss in the treated area
- Liver function abnormality
- Diarrhea
- Small bowel obstruction which may require surgical intervention
- Spinal cord injury which could result in paralysis
- Kidney function abnormality.

SURGERY

- Delayed healing of the incision site
- Pain at surgery site
- infection
- Bleeding
- Perforation
- Pancreatitis

IMPLANTATION OF MARKERS

- Infection
- Bleeding
- Pancreatitis
- Pain at local area
- Markers may move away from where they were originally implanted.

IMAGING STUDIES

There is small health risk of radiation exposure. If contrast dye is used, there is a small risk of a reaction.

BLOOD DRAWS

There is risk of discomfort, and a small amount of bleeding or bruising at the site where the needle is inserted. There is a small risk of infection or inflammation of the vein.

PREGNANCY RISKS

It is possible that the medicines used in this study could injure a fetus if you, or your partner, becomes pregnant while taking them. You have already been told what is known about this possibility, and you are encouraged to ask further questions.

You may want to discuss this with others before you agree to take part in this study. If you wish, we will arrange for a doctor, nurse, or counselor who is not part of this

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study to discuss the potential risks and benefits with you and anyone else you want to have present.

Because of the potential risks, you, or your partner, must not become pregnant while you are participating in this study. Women must have a negative pregnancy test before entering the study.

If you are sexually active and can get pregnant, or can get your partner pregnant, you must use TWO appropriate method(s) of birth control every time you have sex, or you must not have sex.

Because of the nature of this research, methods of natural family planning are not, by themselves, sufficiently reliable to avoid pregnancy.

You can get additional information about methods to avoid pregnancy by calling the UNMC Research Subject Advocate's Office at (402) 559-6941.

You will need to continue to avoid pregnancy for 3 months after finishing the research.

By signing this and being in the study, you are agreeing to not get pregnant while you are on the study and for 3 months after. Should you become pregnant while on this study, you should immediately notify the study personnel. The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can refuse to provide this information.

It is possible that other rare side effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

What are the possible benefits to you?
If you agree to take part in this study, you may or may not benefit from the treatment. Potential benefits of Zometa may result in greater tumor response and possible prolong survival.

What are the possible benefits to other people?
Information obtained from this study may help patients in the future with the same disease by contributing to the knowledge of whether this treatment offers advantages over other treatments available.

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What are the alternatives to being in this research study?
If you choose not to participate in this study, other therapies are available to you. Other therapies may include surgery, chemotherapy, SRT without Zometa, external beam radiation therapy, a combination of these therapies, or no treatment (such as hospice or supportive care).

What will being in this research study cost you?
You will be responsible for any applicable insurance deductibles and co-payments. If you wish to speak with a financial counselor about your insurance coverage and benefits, let the investigator or other study personnel know. A contact for personal assistance will be made available for you.

The radiation therapy, the chemotherapy drugs (capcitabine, 5-FU) and the chemotherapy administration charges, and surgery as well as all other tests and procedures (laboratory tests, radiology tests, physical examinations) will be your responsibility or your health insurance company's responsibility as these are considered standard cancer treatment. You or your health insurance company might also have to pay for other drugs or treatments that are given to help you control side effects.

Zometa and calcium and vitamin D supplements and PET/CT scan (pre-study treatment and pre-surgery)will be paid by the UNMC/The Nebraska Medical Center Radiation Oncology designated funds and the Fred and Pamela Buffett Cancer Center.

Will you be paid for being in this research study?
You will not be paid to be in this research study.

Who is paying for this research?
This research is being paid for by grant funds from UNMC/The Nebraska Medical Center Radiation Oncology designated funds, the Fred and Pamela Buffett Cancer Center, and the UNMC Research Support Fund.

What should you do if you are injured or have a medical problem during this research study?
Your welfare is the main concern of every member of the research team. If you are injured or have a medical problem as a direct result of being in this study, you should immediately contact one of the people listed at the end of this consent form. Emergency medical treatment for this injury or problem will be available at the Nebraska Medical Center. If there is not sufficient time, you should seek care from a

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local health care provider.

The Institution has no plans to pay for any required treatment or provide other compensation. If you have insurance, your insurance company may or may not pay the costs of medical treatment. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay for the medical treatment.

Agreeing to this does not mean you have given up any of your legal rights.

How will information about you be protected?
You have rights regarding the protection and privacy of your medical information collected before and during this research. This medical information is called "protected health information" (PHI). PHI used in this study may include your medical record number, address, birth date, medical history, the results of physical exams, blood tests, x-rays as well as the results of other diagnostic medical or research procedures. Only the minimum amount of PHI will be collected for this research. Your research and medical records will be maintained in a secure manner.

Who will have access to information about you?
By signing this consent form, you are allowing the research team to have access to your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study at the Institution.

Your PHI will be used only for the purpose(s) described in the section "What is the reason for doing this research study?"

You are also allowing the research team to share your PHI, as necessary, with other people or groups listed below:

- The UNMC Institutional Review Board (IRB)
- Institutional officials designated by the UNMC IRB
- Federal law requires that your information may be shared with these groups:
    - The HHS Office of Human Research Protections (OHRP)
    - The Food and Drug Administration (FDA)
- The HIPAA Privacy Rule requires the following groups to protect your PHI:
    - Your health insurance company
    - The Fred and Pamela Buffett Cancer Center Scientific Review Committee (SRC)

Your PHI may also be shared with the following groups. However, these organizations do not have the same obligation to protect your PHI:

- Data and Safety Monitoring Committee (DSMC)
- The National Cancer Institute's (NCI) Clinical Trial Reporting Program
- Forte Research (Oncore) EDC

You are authorizing us to use and disclose your PHI for as long as the research study is being conducted.

You may cancel your authorization for further collection of PHI for use in this research at any time by contacting the principal investigator in writing. However, the PHI which is included in the research data obtained to date may still be used. If you cancel this authorization, you will no longer be able to participate in this research.

How will results of the research be made available to you during and after the study is finished?
In most cases, the results of the research can be made available to you when the study is completed, and all the results are analyzed by the investigator or the sponsor of the research. The information from this study may be published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

If you want the results of the study, contact the Principal Investigator at the phone number given at the end of this form or by writing to the Principal Investigator at the following address:
Chi Lin, MD
987521 Nebraska Medical Center
Omaha, NE 68198-7521

A description of this clinical trial will be available on 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.

What will happen if you decide not to be in this research study?
You can decide not to be in this research study. Deciding not to be in this research will not affect your medical care or your relationship with the investigator or the Institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

What will happen if you decide to stop participating once you start?
You can stop participating in this research (withdraw) at any time by contacting the

Principal Investigator or any of the research staff.Deciding to withdraw will otherwise not affect your care or your relationship with the investigator or this institution. You will not lose any benefits to which you are entitled.

For your safety, please talk to the research team before you stop taking any study drugs or stop other related procedures. They will advise you how to withdraw safely. If you withdraw you may be asked to undergo some additional tests. You do NOT have to agree to do these tests.

You may be taken off the study if you do not follow instructions of the investigator or the research team.

You may also be taken off the study if:

- your disease gets worse
- If you have an adverse reaction, allergic response or develop of additional medical problems and the doctor decides you need to be off the study.
- If you choose to withdraw from the study.
- If the study doctor decides to stop the study.

Any research data obtained to date may still be used in the research.

Will you be given any important information during the study?
You will be informed promptly if the research team gets any new information during this research study that may affect whether you would want to continue being in the study.

What should you do if you have any questions about the study?
You have been given a copy of "*What Do I Need to Know Before Being in a Research Study?*" If you have any questions at any time about this study, you should contact the Principal Investigator or any of the study personnel listed on this consent form or any other documents that you have been given.

What are your rights as a research participant?
You have rights as a research subject. These rights have been explained in this consent form and in The Rights of Research Subjects that you have been given. If you have any questions concerning your rights or want to discuss problems, concerns, obtain information or offer input, or make a complaint about the research, you can contact any of the following:

- The investigator or other study personnel
- Institutional Review Board (IRB)

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- Telephone: (402) 559-6463.
- Email: IRBORA@unmc.edu
- Mail: UNMC Institutional Review Board, 987830 Nebraska Medical Center, Omaha, NE 68198-7830

- Research Subject Advocate
  - Telephone: (402) 559-6941
  - Email: unmcrsa@unmc.edu

Documentation of informed consent
You are freely making a decision whether to be in this research study. Signing this form means that:

- You have read and understood this consent form.
- You have had the consent form explained to you.
- You have been given a copy of The Rights of Research Subjects
- You have had your questions answered.
- You have decided to be in the research study.
- If you have any questions during the study, you have been directed to talk to one of the investigators listed below on this consent form.
- You will be given a signed and dated copy of this consent form to keep.

Signature of Subject _____
Date _____

My signature certifies that all the elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the subject possesses the legal capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Signature of Person obtaining consent _____
Date _____

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