A Phase II Trial of Gemcitabine and Erlotinib (GE) plus Proton-chemotherapy (PCT) and CapOx for Locally Advanced Pancreatic Cancer (LAPC)

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Informed Consent Document
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A Phase II Trial of gemcitabine and erlotinib (GE) plus proton-chemotherapy (PCT) and capox for locally advanced pancreatic cancer (LAPC)

INFORMATION AND CONSENT FORM

HUMAN RESEARCH AND INFORMED CONSENT: This is a clinical trial, a type of research study, conducted at Loma Linda University Medical Center. 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.

You are being asked to take part in this study because you have cancer of the pancreas and are not a candidate for surgery.

Please read this consent form carefully and do not hesitate to ask questions about any of the information in it.

PURPOSE OF THE RESEARCH STUDY: You have been diagnosed with pancreatic cancer that is unresectable or borderline resectable and may be eligible to take part in a study that uses proton treatment for pancreatic cancer done at Loma Linda University Medical Center. The standard treatment for this type of cancer has traditionally been a combination of chemotherapy and radiation therapy. This is a phase II study which tests the safety and effectiveness of an experimental treatment**.** The purpose of this study is to evaluate the safety and the effectiveness of proton radiotherapy, rather than standard radiation therapy (standard of care), when given concurrently with standard of care gemcitabine chemotherapy. We are doing this study because we would like to find a better treatment for locally advanced pancreatic cancer; our hope is that patient outcomes can be improved with proton radiation therapy given along with strong, standard-of-care chemotherapy.

DESCRIPTION OF THE RESEARCH STUDY: As part of this study you will receive the following Standard of Care tests and procedures prior to study entry. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will all be done in an outpatient setting:

- Physical exam
- Blood tests for blood counts, electrolytes, and kidney and liver function.
- X-rays and scans (must be done within 4 weeks prior to the start of therapy)

Initials_____

Date _____

Chemotherapy and proton-therapy

Pre- proton-chemotherapy (See Appendix 1, p. 9)
You will receive gemcitabine and erlotinib (standard of care chemotherapy) for 8 weeks prior to proton-chemotherapy; gemcitabine is given intravenously over 30 to 60 minutes weekly in week 1, 2, 3, 5, 6 and 7, and erlotinib is given orally daily for 43 days.

Proton-chemotherapy (See Appendix 2, p. 10)
You will receive proton therapy as part of the research study, rather than standard radiation therapy: 50.4 Gy over 28 fractions (1.8 Gy per fraction) once a day for 5 ½ weeks. You will take Capecitabine (standard of care chemotherapy) orally twice a day on proton therapy day, starting on day 1 of proton therapy until proton therapy completed.

Post-proton-chemotherapy (See Appendix 3, p. 11)
You will start chemotherapy in 2 to 6 weeks after completion of proton-chemotherapy with Oxaliplatin (standard of care chemotherapy) intravenous infusion over 2 hours on day 1 and Capecitabine (standard of care chemotherapy) orally twice a day on day 2 to day 15 every 3 weeks for 4 cycles (see Appendix 4, Study Flow Chart, p.12-14) for study flowchart

Tests during treatment: You will need these tests and procedures (see test schedule Appendices 1 – 3, pages 9,10,11) that are either being tested in this study or being done to see how the study is affecting your body. These tests are part of regular cancer care.

- Physical examination
- Blood tests for blood counts
- Blood tests for kidney function, liver function, and to measure electrolytes
- X-rays and scans

Following treatment: After you are finished with the study treatment, the study doctor will ask you to visit the office for follow-up exams for at least every 3 months from the time you finished the study. It is up to the doctor what tests are performed during these visits. We would like to keep track of your medical condition for the rest of your life. We would like to do this by calling you on the telephone once a year to see how you are doing. Keeping in touch with you and checking on your condition every year helps us look at the long-term effects of the study.

POTENTIAL RISKS: All precautions will be taken throughout your therapy. However, doctors don't know all the side effects that may happen. 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 away soon after you stop treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.

Initials_____

Date _____

Risks and side effects related to the **Gemcitabine** include:

Likely	Less Likely	Rare But Serious
• Fatigue (feeling tired) • Loss of appetite • Fever • Flu-like symptoms (fever, aches, pains, chills) • Low white blood cell counts (this may increase your risk of infection or catching other diseases) • Low red blood cell counts (this may cause you to feel tired) • Low platelet counts (these are the cells that help the blood to clot) • Nausea • Vomiting • Diarrhea • Skin rash • Changes in liver function (this may result in abnormal blood tests)	• Mouth sores • Alopecia (hair loss) • Dry eyes, red eyes, eye discomfort • Elevated levels of protein in the urine • Blood in the urine • Swelling • Tingling or numbness in the hands and feet • Redness or swelling at the injection site	• Allergic reaction • A breakdown of red blood cells and kidney failure known as the hemolytic uremic syndrome • Pneumonitis (an scarring of the lungs that can cause shortness of breath) • Heart attack, stroke, changes in heart rhythms, high blood pressure • Death

Risks and side effects related to **erlotinib** include

Likely	Less Likely	Rare But Serious
• Skin rash, including skin rash that looks like acne (pimples) on the face, chest, back, and scalp • Diarrhea (this may be treated with anti-diarrhea drugs) • Nausea • Vomiting • Infection • Weight loss • Loss of appetite • Tiredness, or fatigue • New or worse shortness of breath • Cough	• Dry skin • Itching • Infections associated with skin reactions • Dehydration (loss of too much body fluid) • Dry, red, irritated eyes • Abdominal or stomach pain • Gas, heartburn, or upset stomach • Headache • Depression • Neuropathy (nerve damage resulting in numbness or tingling) • Chest pain • Chills or shakes • Nose bleed • Coughing up blood • Hair loss or thinning • Dry mouth • Mouth sores or mouth ulcers (may cause mouth pain) • Constipation	• Allergic reaction • A breakdown of red blood cells and kidney failure known as the hemolytic uremic syndrome • Pneumonitis (scarring of the lungs that can cause shortness of breath) • Heart attack, stroke, changes in heart rhythms, high blood pressure • Death

Dangerous interaction between erlotinib and warfarin (coumadin): If you are taking warfarin or coumadin (medicine to prevent blood clotting), erlotinib may change the way your blood clots. The interaction

between warfarin and capecitabine is significant and could result in severe bleeding. If you need to take Warfarin, your doctor will regularly check for changes in blood clotting time.

Initials_____

Date _____

Risks and side effects related to <u>capecitabine</u> include those which are:

Likely	Less Likely	Rare But Serious
• Nausea • Diarrhea • Mouth sores • Loss of appetite and weight loss • Weakness • Redness and/or drying of the skin, especially the hands and feet. • Skin or nail darkening • Skin rash or peeling of skin on hands and feet • Low blood counts which could lead to an increased risk of infection, weakness, and/or bleeding/easy bruising • Infection	• Vomiting • Muscle aches • Constipation • Hair loss • Change in liver function that could cause jaundice (yellowing of skin) • Unsteadiness	• Chest pain or irregular heartbeat

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

Risks and side effects related to the <u>Proton Therapy</u> include those which are:

Likely	Less Likely	Rare But Serious
• Stomach pain and intestinal discomfort, which usually occur during the last three weeks of proton therapy and generally go away within 2 months after the treatment is finished • Nausea • Fatigue • Tanning, redness of skin, and hair loss within the radiation area, which is temporary • Loss of appetite and weight loss • Mild muscle aches in the area treated	• Vomiting • Infection • Diarrhea • Low blood counts • Permanently dry skin in the radiation treatment area	• Damage to the liver or kidney • Bowel obstruction, which could result in abdominal pain, nausea and vomiting and may require surgery • Gastric, duodenal or small-bowel ulcer formation that can result in abdominal pain, nausea and vomiting, and bleeding, and may require surgery

Initials_____

Date _____

Risks and side effects related to <u>oxaliplatin and capecitabine</u> include those which are:

Likely	Less Likely	Rare But Serious
• Nausea and vomiting lasting 24-48 hours following completion of the chemotherapy • Diarrhea • Mouth sores • Temporary hair loss • Numbness or tingling in the hands and/or feet • Numbness of the mouth or throat that can be made worse by cold weather or cold drinks • Abdominal pain or cramps • Irritation of intestines • Infection • Dehydration • Loss of appetite • Weakness • Redness and/or drying of the skin, especially the hands and feet. • Skin or nail darkening • Skin rash or peeling of skin on hands and feet • Low blood counts which could lead to an increased risk of infection, weakness, and/or bleeding/easy bruising	• Flu-like symptoms such as fevers, chills, and muscle aches • Watery eyes, nasal stuffiness • Irritation of vein used to administer the drugs • Damage to the liver or kidney • Constipation • Shortness of breath • Headache • Intestinal Blockage • A loss of phosphorous, calcium and/or potassium from the blood • Inflammation of the lungs • Blistering of the palms of the hands and soles of the feet	• Confusion or memory loss • Slurred speech • May affect function of the brain • Build-up of scar tissue in lungs • Stroke • Death. There have been re-ported deaths reported in older patients who had developed weakness, diarrhea, and low blood pressure. These deaths may have been the result of dehydration that was caused by the diarrhea, and an infection. It is important that the occurrence of diarrhea be promptly reported to your physician. • A breakdown of red blood cells and kidney failure known as the hemolytic uremic syndrome • Heart attack or chest pain • Lung failure • Allergic reaction

<u>Reproductive Risks</u> : You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future. For more information about risks and side effects, ask your study doctor.

<u>POSSIBLE BENEFITS OF THE RESEARCH</u>: It is not possible to predict whether any personal benefit will result from the use of the study treatment program. The information, which is obtained from this study may be scientifically useful, and in the future may benefit others with pancreatic cancer.

The possible benefits of this study treatment may include improved tumor control, with less damage to

surrounding healthy tissues, compared with standard radiotherapy or surgery, but this is not guaranteed.

Initials_____

Date _____

VOLUNTARY NATURE OF PARTICIPATION: Your decision to participate in this research is voluntary. You are free to choose either to enter the research study or not to enter the study. There will not be any penalty or loss of benefits for you if you decide not to participate.
Before you make your decision, one of the research staff will give you a chance to ask any questions you have about the research study. You will not sign this form unless you have had the chance to ask questions and have received satisfactory answers to your questions.
Even after agreeing to take part in this research, you may withdraw from the research at any time. If you do decide to withdraw from the research, there will be no penalty or loss of benefits for you. After withdrawal, you will be offered available care that suits your needs and medical condition. Before withdrawing from this research, you should notify one of the persons involved with the research that you wish to withdraw. This notice will allow that person or someone else supervising the research to inform you if there are medical risks of withdrawal.

NEW INFORMATION ARISING DURING THE RESEARCH: During this research study, the investigators may know new information regarding the risks and benefits of the study. If this occurs, they will tell you about this new information. New information may show that you should no longer participate in the research. If this occurs, the persons supervising the research will stop your participation in it. In either case, you will be offered available care that suits your needs and medical conditions.

ALTERNATIVE PROCEDURES OR TREATMENTS: Alternatives which could be considered in your case include standard radiation therapy with Fluorouracil chemotherapy, standard radiation therapy with reduced doses of Gemcitabine, Gemcitabine chemotherapy alone, or supportive care with pain management and other comfort measures.

IMPARTIAL THIRD PARTY CONTACT: If you wish to contact an impartial party not associated with this study regarding any complaint you may have about the study, you may contact the Office of Patient Relations, Loma Linda University Medical Center, Loma Linda, CA 92354, 909-558-4647 for information or assistance.

CONFIDENTIALITY: The records relating to your participation in the study will be main- tained with your medical records. However, authorized research investigators and agents of the Food and Drug Administration and the Department of Health and Human Services have the right to inspect the records of research done by faculty at Loma Linda University Medical Center. Other health care providers will have access to research related information contained in your medical record. Privacy and confidentiality of the record will be protected to the extent provided by law. The results of this research may be published. Published reports will not include your name or any other information that would identify you.

COSTS: You or your insurance company will be financially responsible for all costs incurred as part of your cancer treatment program, including physician's fees and diagnostic studies to evaluate your disease status, as well as hospital costs while you are a patient in the hospital. Regular physician visits

and diagnostic tests are considered part of good standard medical care. A financial representative will contact your insurance company to inquire if they will pay for proton therapy.

Initials_____

Date _____

PAYMENT FOR PARTICIPATION: There will be no payment for participation in this study.

PERSONS TO CONTACT: Study Doctors include Gary Yang, MD, principal investigator, and Radiation Medicine study doctors. If you have additional questions regarding your treatment or follow-up according to this study you may speak with Dr. Yang at (909) 558-4243. If you have an after-hours emergency, report to Loma Linda University Medical Center Emergency Room or call (909) 558-4000 and ask for the Radiation Medicine doctor on call.

RESEARCH RELATED INJURY: Your study doctors will be monitoring your condition throughout the study, and precautions will be taken to minimize the risks to you from participating. If you are injured or become ill from taking part in this study:

- If the situation is a medical emergency **call 911** or go to the nearest emergency room. Then, notify the study doctor as soon as you can.
- For a non-emergency injury or illness, notify your study doctor as soon as you can.
- To contact Dr. Gary Yang during regular business hours, dial (909) 558-4243. After hours, call (909) 558-4000 and ask for the Radiation Medicine doctor on call, and identify yourself as a subject in this study.

Appropriate medical treatment will be made available to you. However, you and your insurance company will be billed at the usual charge for the treatment of any research-related injuries, illnesses, or complications. You might still be asked to pay whatever your insurance does not pay. Also, no funds have been set aside, nor any plans made to compensate you for time lost for work, disability, or other discomforts resulting from your participation in this research.

RIGHT TO WITHDRAW: Even after agreeing to take part in this research, you may withdraw from the research at any time. If you do decide to withdraw from the research, there will be no penalty or loss of benefits for you. After withdrawal, you will be offered available care that suits your needs and medical condition. Before withdrawing from this research, you should notify one of the persons involved with the research that you wish to withdraw. This notice will allow that person or someone else supervising the research to inform you if there are medical risks of withdrawal. Should developments occur that indicate this treatment is no longer in your best interest, you will be withdrawn from the study, and further treatment options will be discussed.

Initials_____

Date _____

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INFORMED CONSENT

I have read the contents of the consent form and have listened to the verbal explanation given by the investigator. My questions concerning this study have been answered to my satisfaction. I have received a copy of the California Experimental Subject's Bill of Rights and have had these rights explained to me. Signing this consent document does not waive my rights nor does it release the investigators, institution or sponsors from their responsibilities. I may call Dr. Gary Yang during routine office hours at (909) 558-4243 or during non-office hours at (909) 558-4000 and ask for the Radiation Oncologist on call if I have additional questions or concerns. I understand that if I am enrolled in an in-patient study, my primary care physician may be notified of my participation, for proper coordination of care. I hereby give voluntary consent to participate in this study.

I understand I will be given a copy of this consent form after signing it.

Signature of Subject Printed Name of Subject

Date *For inpatient studies, add Time* AM / PM

I attest that the requirements for informed consent for the medical research project described in this form have been satisfied – that the subject has been provided with a copy of the California Experimental Subject's Bill of Rights, that I have discussed the research project with the subject and explained to him or her in non-technical terms all of the information contained in this informed consent form, including any risks and adverse reactions that may reasonably be expected to occur. I further certify that I encouraged the subject to ask questions and that all questions asked were answered. For in-patient studies, I understand that it is my responsibility to notify the subject's primary care physician of study participation, as needed, for proper coordination of care. I will provide the subject or the legally authorized representative with a signed and dated copy of this consent form.

Signature of Investigator

Printed Name of Investigator

Date

Appendix 1

Pre-proton-chemotherapy

Pre-Proton-Chemotherapy (PCT)									
Required studies	Pre-study (within 4 weeks)	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Post-chemotherapy/ pre-proton
Evaluations									
H&P, vitals, weight & PS	X	X	X	X		X	X	X	X
AE assessment	X (baseline)	X	X	X		X	X	X	X
Quality of Life Assessments	X (baseline)								X
Laboratory and imaging									
CBC/diff	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X
CA 19-9	X								X
PT-INR and PTT	X								
Whole blood for correlative study	X					X			X
X-rays & scans as needed for disease assessment	X								X
Treatment									
Gemcitabine		X	X	X		X	X	X	
Erlotinib		Daily from day 1 to day 43							

Appendix 2

Proton chemotherapy (PCT)

PCT							
Required studies	Day 1	Day 8	Day 15	Day 22	Day 29	Day 36	Post-proton
Evaluations							
H&P, vitals, weight & PS	X	X	X	X	X	X	X
AE assessment	X	X	X	X	X	X	X
Quality of Life Assessments							X
Laboratory and imaging							
CBC/diff	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X
CA 19-9							X
Whole blood for correlative study					X		X
X-rays & scans as needed for disease assessment							X
Treatment							
Capecitabine	825mg/m2 po bid on days of radiation, starting on day 1 of proton therapy until proton therapy is completed.						
Proton	50.4 Gy/28 fractions (1.8 Gy per fraction) once a day for 5 ½ weeks.						

Appendix 3

Post-proton chemotherapy (begins 4-6 weeks after proton therapy)

Post-proton	Cycle 1			Cycle 2			Cycle 3			Cycle 4			
Required studies	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Post-chemotherapy
Evaluations													
H&P, vitals, weight & PS	X			X			X			X			X
AE assessment	X			X			X			X			X
Quality of Life Assessments													X
Laboratory and imaging													
CBC/diff	X	X	X	X	X	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X	X	X	X	X	X
CA 19-9	X			X			X			X			X
Whole blood for correlative study	X			X			X			X			X
X-rays & scans as needed for disease assessment													X
Treatment													
Oxaliplatin	X			X			X			X			
Capecitabine	Day 1-14			Day 1-14			Day 1-14			Day 1-14			

Appendix 4

Patient Chart

The chart below shows what will happen to you during treatment as explained previously. The left-hand column shows the day in the treatment and the right-hand column tells you what to do on that day. These treatments and tests will all be done in an outpatient setting.

Pre-proton-chemotherapy

Day	*What you do*
Before starting treatment	• Sign informed consent • Chest X ray or CT scan • Routine and research blood test • Physical examination
Day 1 (week 1)	• Routine blood test • Physical examination • Get chemotherapy drug gemcitabine • Take chemotherapy pill erlotinib every day
Day 8 (week 2)	• Routine blood test • Physical examination • Get chemotherapy drug gemcitabine • Take chemotherapy pill erlotinib every day
Day 15 (week 3)	• Routine blood test • Physical examination • Get chemotherapy drug gemcitabine • Take chemotherapy pill erlotinib every day
Day 22 (week 4)	• Routine blood test • Take chemotherapy pill erlotinib every day
Day 29 (week 5)	• Routine and research blood test • Physical examination • Get chemotherapy drug gemcitabine • Take chemotherapy pill erlotinib every day
Day 36 (week 6)	• Routine blood test • Physical examination • Get chemotherapy drug gemcitabine • Take chemotherapy pill erlotinib every day
Day 43	• Routine blood test

(week 6)	• Physical examination • Get chemotherapy drug gemcitabine • Take chemotherapy pill erlotinib until day 43

Proton-chemotherapy Appendix 4, Patient Chart, continued

Day	*What you do*
Before starting proton-chemotherapy	• Chest X ray or CT scan • Routine and research blood test • Physical examination
Day 1 (week 1)	• Routine blood test • Physical examination • Receive proton therapy on Monday to Friday • Take chemotherapy pill Capecitabine on Monday to Friday
Day 8 (week 2)	• Routine blood test • Physical examination • Receive proton therapy on Monday to Friday • Take chemotherapy pill Capecitabine on Monday to Friday
Day 15 (week 3)	• Routine blood test • Physical examination • Receive proton therapy on Monday to Friday • Take chemotherapy pill Capecitabine on Monday to Friday
Day 22 (week 4)	• Routine blood test • Physical examination • Receive proton therapy on Monday to Friday • Take chemotherapy pill Capecitabine on Monday to Friday
Day 29 (week 5)	• Routine and research blood test • Physical examination • Receive proton therapy on Monday to Friday • Take chemotherapy pill Capecitabine on Monday to Friday
Day 36 (week 6)	• Routine blood test • Physical examination • Receive proton therapy on Monday to Friday • Take chemotherapy pill Capecitabine on Monday to Friday
After proton-chemotherapy	• Chest X ray or CT scan • Routine and research blood test • Physical examination

Post-proton-chemotherapy Appendix 4, Patient Chart, continued

Day	***What you do***
Cycle 1 day 1 (week 1)	• Routine and research blood test • Physical examination • Get chemotherapy drug Oxaliplatin • Take chemotherapy pill Capecitabine every day
Cycle 1 day 8 (week 2)	• Routine blood test • Take chemotherapy pill Capecitabine every day
Cycle 1 day 15 (week 3)	• Routine blood test
Cycle 2 day 1 (week 1)	• Routine and research blood test • Physical examination • Get chemotherapy drug Oxaliplatin • Take chemotherapy pill Capecitabine every day
Cycle 2 day 8 (week 2)	• Routine blood test • Take chemotherapy pill Capecitabine every day
Cycle 2 day 15 (week 3)	• Routine blood test
Cycle 3 day 1 (week 1)	• Routine and research blood test • Physical examination • Get chemotherapy drug Oxaliplatin • Take chemotherapy pill Capecitabine every day
Cycle 3 day 8 (week 2)	• Routine blood test • Take chemotherapy pill Capecitabine every day
Cycle 3 day 15 (week 3)	• Routine blood test
Cycle 4 day 1 (week 1)	• Routine and research blood test • Physical examination • Get chemotherapy drug Oxaliplatin • Take chemotherapy pill Capecitabine every day
Cycle 4 day 8 (week 2)	• Routine blood test • Take chemotherapy pill Capecitabine every day
Cycle 4 day 15 (week 3)	• Routine blood test
After treatment	• Chest X ray or CT scan • Routine and research blood test • Physical examination