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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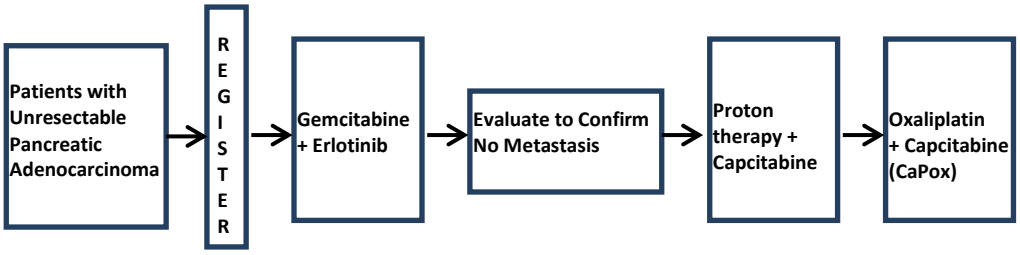
SCHEMA



Pre-Proton-chemotherapy (PCT)
Patients will receive a combination of the agents (Gemcitabine plus Erlotinib) for 8 weeks prior to PCT
Gemcitabine 1000 mg/m2 IV, days 1, 8, 15, 29, 36 and 43
Erlotinib 100 mg po qd days 1-43

PCT
To be started in 4 to 8 weeks after completion of Pre-PCT
Proton therapy: 50.4 Gy/28 fractions *(1.8 Gy per fraction)* once a day for 5 ½ weeks.
Chemotherapy: Capecitabine 825mg/m2 po bid M-F, starting on day 1 of proton therapy until proton therapy completed

Post-PCT
To be started in 4 to 6 weeks after completion of PCT
Oxaliplatin 130 mg/m2, day 1
Capecitabine 1000 mg/m2 po bid on days 2 to 15 for 14 days
The CapOx regimen (Capecitabine plus Oxaliplatin) is repeated every 3 weeks for 4 cycles

ELIGIBILITY: (See Section 3.0 for details)
- Pathologically-confirmed unresectable non-metastatic adenocarcinoma of the pancreas
- Radiographically assessable.
- No prior irradiation to the planned field.
- WBC ≥ 2,000 cells/mm3
- ANC ≥1,500 cells/mm3
- Platelets ≥ 100,000 cells/mm3
- Serum bilirubin ≤ 2.5 mg/dL
- Serum creatinine ≤ 2 x upper limit of normal (ULN), or creatinine clearance (Ccr) ≥ 30ml/min
- ALT ≤ 3 x ULN
- AST ≤ 3 x ULN
- Signed study-specific consent form

Required Sample Size: 43

ELIGIBILITY CHECK
(Y) 1. Does the patient have a pathologically-confirmed adenocarcinoma of the pancreas?
(Y) 2. Does the patient have unresectable disease?
(N) 3. Is there evidence of metastatic disease in the major viscera or peritoneal seeding?
(Y/N) 4. Does the patient have biliary or gastroduodual obstruction?
(Y) If yes, does/will the patient have drainage prior to beginning PCT?
(Y) 5. Does the patient have radiographically measurable disease?
(N) 6. Has the patient had prior radiation to the planned field?
(N) 7. Has the patient had prior chemotherapy?

1.0 INTRODUCTION

1.1 Background

Pancreatic cancer remains a highly lethal malignancy despite advances in treatment. At present, complete surgical resection offers the best chance of cure. However, because of the invasion of major vessels or the presence of metastasis, at initial diagnosis, 50% of patients already present with metastatic disease, 30% present with a locally advanced (unresectable) tumor and only 20% are resectable. The prognosis for locally advanced pancreatic cancer (LAPC), 6-10 months, lies between those for metastatic and resected disease[1].

1.2 The Role of Combined Therapy for Locally Advanced Pancreatic Cancer

The role of combined therapy for LAPC continues to evolve. The goals of radiotherapy in LAPC include improvement in local control and palliation of pain and/or obstructive symptoms. Trials of chemoradiotherapy (CRT) versus chemotherapy alone in LAPC have reported mixed findings regarding survival [2-6]. In a trial conducted by the Gastrointestinal Tumor Study Group[5] the effect of concurrent CRT versus chemotherapy alone in LAPC was evaluated and a benefit in survival from combined modality therapy was noted. The CRT arm consisted of radiation combined with 5-fluorouracil to a total dose of 54 Gy in 1.8 Gy fractions followed by maintenance streptozocin, mitomycin and 5-fluorouracil (SMF). The chemotherapy-only arm was SMF combination chemotherapy for two years or until progression. In this trial, the one-year OS was 41% in the CRT arm compared to 19% in the chemotherapyalone arm ($p<0.02$).

Modern chemotherapy and radiation techniques have been tested in two recent phase III trials evaluating the efficacy of CRT. In the trial by the Eastern Cooperative Oncology Group (E4201), patients with LAPC were randomly assigned to CRT (50.4 Gy in 28 fractions) with concurrent gemcitabine (600 mg/m2 weekly x 6) followed by 5 cycles of gemcitabine alone (1,000 mg/m2 weekly x 3 every 4 wks) versus gemcitabine alone (1,000 mg/m2 weekly x 3 every 4 wks) for 7 cycles. This trial showed that CRTwas associated with a slightly improved survival (11 versus 9.2 months, $p=0.044$) [2].

In a second recent study by Chauffert et al. reported in 2008, 10 CRT was delivered to a total dose of 60 Gy concurrently with cisplatin (20 mg/m2/day, days 1–5during weeks 1 and 5) and 5-fluorouracil (300 mg/m2/day, days 1–5 for 6 weeks). Thechemotherapy-alone arm consisted of gemcitabine (1000 mg/m2 weekly for 7 weeks).Maintenance gemcitabine (1000 mg/m2 weekly, 3/4 weeks) was given in both arms until disease progression or toxicity. Overall survival in this trial was shorter in the CRT arm (13.0 vs. 8.6 months, p=0.044) and these patients experienced a higher rate of grade 3-4 toxicity compared with the chemotherapy arm (66% vs. 40% respectively; p=0.0008). A potential explanation for increased toxicity is the combination of aggressive chemotherapy delivered with concurrent radiation (60 Gy followed by high-dose weekly maintenance Gemcitabine). Due to inferior survival in the CRT arm, this study was stopped prior to planned enrollment. However, it adds to the growing body of opinion that the benefit of CRT for LAPC is likely confined to a carefully selected group of patients.

1.3 Erlotinib and Gemcitabine in Pancreatic Cancer

The epidermal growth factor receptor (EGFR) is a cell surface receptor for EGF and transforming growth factor-alpha which is over expressed by a number of human tumors. Erlotinib is an oral selective EGFR tyrosine kinase inhibitor, the only drug of its class approved for the treatment for first-line treatment of advanced pancreatic cancer with Gemcitabine.

The FDA approved Erlotinib in combination with Gemcitabine for the treatment of patients with locally advanced, unresectable or metastatic pancreatic carcinoma in 2005. This approval was on the basis of the results of the large, double-blind, randomized, multicenter Phase III trial [7]. This study randomized 569 patients with locally advanced or metastatic pancreatic adenocarcinoma in a1:1 ratio to Gemcitabine with Erlotinib versus Gemcitabine and placebo. The primary end point was overall survival, and secondary end points were progression-free survival, tumor response rate and duration of response, role of EGFR status and survival, and quality of life. Patients in the Gemcitabine and Erlotinib arm had a prolonged median survival of 6.24 months versus 5.91 months in the Gemcitabine and placebo arm, which was statisticallysignificant ($p = 0.038$). One-year survival was 23% in the Erlotinib arm versus 17% in the placebo arm, and progression free survival was also significantly longer in the Erlotinib with Gemcitabine arm than the placebo with Gemcitabine arm (3.75 vs 3.55 months; $p = 0.004$). There was no significant difference between the two arms in global qualityof life scores, and EGFR status did not correlate to response, disease stability or survival.

1.4 Proton Beam Therapy

The beneficial feature of the proton beam is that it produces excellent dose localization to a target compared with photons. The proton beam allows reduction of the irradiated volume and dose given to the normal liver, kidneys and digestive tract, while increasing the dose conformality to the tumor. Several dosimetric and phase I studies have shown that it is effective and feasible in treating pancreatic cancer regardless of the degree of tumor size, and presence or absence of combined therapies[8-12].

For localized pancreatic cancer, dose distribution patterns achievable with proton beam could potentially offer important clinical advantages relative to those achievable with x-rays. Based on this, we believe that this study should be conducted with the modality that offers the best dosimetry achievable at our institution.

1.5 Capecitabine and Oxaliplatin, CapOx

There is no established second-line chemotherapy for patients with pancreatic cancer who have received Gemcitabine-based therapy. A multicenter randomized phase II trial was performed to compare the efficacy and safety of three different chemotherapy doublets in the treatment of advanced pancreatic cancer (PC) [13].At total of 190 patients were randomly assigned to receive Capecitabine plus Oxaliplatin (CapOx), Capecitabine plus Gemcitabine (CapGem) or Gemcitabine plus Oxaliplatin (mGemOx). Treatment cycles were repeated every three weeks. The result of the study showed CapOx, CapGem and mGemOx have similar clinical efficacy. Each regimen has a distinct but manageable tolerability profile. A phase II study from MD Anderson showed the

combination of capecitabine and oxaliplatin is active in Gemcitabine-pretreated patients with LAPC, especially in patients with a good PS and those who have responded to first-line chemotherapy [14].Of the 39 evaluable patients, 1 patient had a partial response and 10 patients demonstrated stable disease.The most common grade 3-4 nonhematologic toxicity was fatigue.

1.6 Correlative Studies

Appropriate identification and validation of biomarkers as well as pharmacogenetics are important in formulating patient-oriented, individualized chemoradiotherapy or biological therapy in cancer patients. These markers can be especially valuable in pancreatic cancer, where high mortality and complex disease biology are frequently encountered.

Recently, several advances have been made to further our knowledge in this specific area of pancreatic cancer. Researchers have identified several potential biomarkers: shorter EGFR intron 1 CA repeat length is associated with worse pancreatic cancer clinical prognosis and in vitro response to Erlotinib. EGFR intron 1 length can be reliably measured in peripheral blood and may translate into a quantitative predictive marker of both pancreatic cancer aggressiveness and Erlotinib sensitivity[15]; the increased level of 14-3-3s protein likely contributes to the poor clinical outcome of pancreatic cancer by causing resistance to radiation and anticancer drugs [16]; methylenetetrahydrofolatereductase (MTHFR) single nucleotide polymorphisms predicted serum folate and plasma homocysteine levels, and, combined, these factors may be important predictors of Capecitabine induced toxicity [17]. Additional markers affect clinical prognosis of patients and treatment toxicities will also be investigated[18] (see Section 10).

1.7 Quality of Life/Patient-Reported Outcomes

1.7.1 Importance of Patient-reported Outcomes in Pancreas Cancer

Patient-reported outcomes, in addition to overall survival, are now accepted by oncologists as an important clinical endpoint in clinical trial design for patients with advanced pancreatic cancer. This is largely based on the landmark randomized trial of Burris et.al, which reported, for patients with advanced pancreatic cancer, a significant increase using Gemcitabine (rather than Fluorouracil) in the "clinical benefit response" that included nontraditional measures related to symptoms, including pain, performance status and weight [19]. To date, there has been limited available literature using formal patient reported measures for patients with pancreatic cancer [20]. This is unfortunate, because the majority of patients with this cancer have incurable disease and palliation and quality of their remaining life become the major goals.

1.7.2 Patient-Reported Fatigue Using FACIT-Fatigue May Predict for Overall Survival in Patients with Pancreatic Cancer

Fatigue has been described as the most frequent and distressing symptom related to cancer and its treatment [21]. The FACIT-Fatigue, version 4, is a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. This questionnaire can be completed by patients in approximately 5 minutes. The FACIT-Fatigue is a psychometrically sound instrument and has been widely used to measure fatigue for patients with various chronic illnesses including cancer [22]. Data has suggested a high baseline FACIT–Fatigue score (> 30), indicating low fatigue, was the best predictor of longer overall survival in a stepwise, Cox proportional hazards multiple-regression analysis (HR, 0.47; CI: 0.30–0.74) [23]. We hypothesize that patients reporting low baseline fatigue, as measured by the FACIT-Fatigue13 item questionnaire, will experience longer overall survival.

1.8 Study Rationale and Potential Significance

The current trend toward using the biology of the disease as it becomes evident over a period of chemotherapy to better select patients who will benefit from CRT seems to be the most pragmatic way to proceed, until we have a better means of predicting tumor behavior and more active systemic agents.This has led to increased interest in treatment regimens incorporating induction chemotherapy with target agent followed by CRT and additional chemotherapy for diseases that carry a high risk for systemic relapse.

The PA.3 trial was the first phase III trial in advanced pancreatic cancer to show a survival advantage with the addition of a second drug, in this case the oral EGFR inhibitor Erlotinib to gemcitabine. The approval provides an important proof of concept regarding the use ofnewer "targeted" therapies in pancreatic cancer [7]. Proton beam therapy may result in lower toxicity, enhanced efficacy and could contribute to improved local control of patients with LAPC. The CAPOX regimen utilized in this trial has been proven to be active in gemcitabine-pretreated patients with advanced pancreatic cancer [14].

The current trial will provide important data on the recurrence rates and patterns of failure using state of the art target agent, chemotherapy and proton beam technology for patients with LPAC. A median survival of 10 months or greater would be considered evidence of a regimen potentially worthy of further study as a new treatment paradigm in one arm in a future phase III trial.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the one-year survival rate

2.2 Secondary Objectives

2.2.1 To evaluate the frequency of serious adverse events (section 9.1.1)
2.2.2 To evaluate disease control rate and progression-free survival
2.2.3 To determine the predictive value of CA 19-9 for prognosis
2.2.4 To evaluate quality of life and clinical benefit response

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologically or cytologically confirmed unresectable non-metastatic adenocarcinoma of the pancreas
3.1.2 AJCC stage I-III with unresectable or borderline unresectable disease as defined by NCCN guidelines
3.1.2.1 Radiological resectability is defined by the following criteria on abdominal imaging:
a) No evidence of tumor extension to the celiac axis, hepatic artery or superior mesenteric artery.
b) No evidence of tumor encasement or occlusion of the superior mesenteric vein (SMV) or the SMV/portal vein confluence
c) No evidence of visceral or peritoneal metastases
3.1.2.2 Borderline and Unresectable cases would be defined as those that do not meet the criteria in section and also show no evidence of distant metastatic or intraperitoneal disease.
3.1.3 Eastern Cooperative Oncology Group performance status of ≤ 2
3.1.4 Age > 18 years
3.1.5 Adequate hematologic reserve, hepatic reserve and renal function
3.1.5.1 WBC > 2,000 cells/mm3
3.1.5.2 ANC > 1,500 cells/mm3
3.1.5.3 Platelets > 100,000 cells/mm3
3.1.5.4 Serum bilirubin ≤ 2.5 mg/dL
3.1.5.6 Serum creatinine ≤ 2 x upper limit of normal (ULN), or creatinine clearance (Ccr) ≥ 30ml/min
3.1.5.6 ALT < 3 times ULN
3.1.5.7 AST < 3 times ULN
3.1.5.8 Albumin > 3.2 g/dl
3.1.5.9 Patient must sign study-specific informed consent

4.0 PRETREATMENT EVALUATION

4.1 Required Evaluations

4.1.1 History and physical examination

4.1.2 CT scan of chest, abdomen, and pelvis

4.1.3 CBC, serum chemistries, liver function tests, amylase/lipase, CA 19-9

4.1.4 Histologic confirmation of malignancy

4.1.5 Female Participant Evaluation:
Non-pregnant and non-breast-feeding female participants of child-bearing potential must have a negative urine or serum pregnancy test prior to registration. Perimenopausal participants must be amenorrheic> 12 months to be considered not of childbearing potential. All patients of reproductive potential must agree to use an effective method of birth-control while receiving study therapy.

5.0 REGISTRATION

Patient registration as per LLUMC institutional standards for participation in clinical trials.

6.0 RADIATION THERAPY

6.1 Immobilization and Treatment Planning CT Scan

6.1.1 All patients will be immobilized in a full body immobilization device in the supine position.

6.1.2 A CT scan from T5 to L5/S1 with intravenous and oral contrast will be performed.

6.2 Treatment Planning

6.2.1 The GTV will be the primary tumor and involved regional nodes. There will be no prophylactic elective nodal irradiation

6.2.2 The CTV will be GTV + 1 cm margin

6.2.3 A margin will be created around the CTV to account for proton beam penumbra and setup error.

6.2.4 A multi-field conformal proton beam treatment plan with the 90% isodose covering the CTV will be created.

6.2.5 Critical normal structures to be outlined are: small bowel with duodenum as a distinct volume, spinal cord, kidneys, and liver. DVH data will be generated for these structures and standard normal tissue constraints will be upheld with the exception of the duodenum.

6.3 Dose and Fractionation

Standard fractionation of 1.8 Gy per day will be used for all patients to a total dose of 50.4 Gy.

6.4 Radiation Toxicity

All patients will be seen and examined on a weekly basis during treatment. All acute toxicities will be scored according to the NCI Common Toxicity Criteria v 4.0. Late toxicity will be scored per RTOG guidelines.

6.5 Toxicity Related Radiation Treatment Modification

Radiation is held if chemotherapy is held due to hematologic toxicities. (Section 9)

6.0 DRUG THERAPY

7.1 Gemcitabine

7.1.1 Drug Administration
Gemcitabine is to be administered intravenously over 30 minutes weekly at a dose of 1000mg/m2.

7.1.2 Formulation
Gemcitabine is an antineoplastic agent that is structurally related to Cytarabine. It is a pyrimidine analogue that is cell-cycle specific. Gemcitabine is available commercially as a lyophilized powder in sterile vials containing 200 mg or 1 gram of Gemcitabine as the hydrochloric salt (expressed as the free base) formulated with mannitol and sodium acetate.

7.1.3 Mechanism of Action
Gemcitabine is cytotoxic to cells undergoing DNA synthesis (S-phase) and also blocks the progression of cells through the G1/S- phase boundary. Gemcitabine is converted intracellularly to

gemcitabine-5'-triphosphate, its active form. Steady-state plasma levels of Gemcitabine occur within 15 minutes after starting the infusion. The elimination half-life of gemcitabine ranges from 32 to 638 minutes, depending on the age and gender of the patient and the rate of administration of Gemcitabine.

7.1.4 Toxicities

The major side effects observed with Gemcitabine include leukopenia, thrombocytopenia, anemia, and a collection of signs and symptoms referred to collectively as a flu-like syndrome with fever, headache, rigors, nausea, diarrhea, itchy skin rash, myalgia, and anorexia. Other side effects have included fatigue, peripheral edema, and proteinuria. Less likely side effects include abnormal renal and liver function tests, vomiting, constipation, malaise, and anorexia. Rare side effects include Stevens-Johnson syndrome (severe skin reaction) and shortness of breath, cough, inflammation or scarring of the lung. Rare side effects have included hemolytic uremic syndrome/renal failure and liver failure have occurred following therapeutic gemcitabine therapy. Cardiac dysfunction (myocardial infarction, congestive heart failure, and atrial fibrillation) have been infrequently reported.

7.1.5 Supply

Gemcitabine is commercially available.

7.2 Erlotinib

7.2.1 Drug Administration

Erlotinib should be taken once daily by mouth one hour before or two hours after a meal. Administration through G-tube or J-tube: The tablets required for the dose should be dissolved in 100 mL of sterile water. The dissolved tablets should be shaken vigorously to form a uniform suspension. The suspension should be drawn up into a syringe and administered through the G-tube or J-tube port. Repeat the syringe transfer until the entire volume has been administered. A small volume (40 mL) of sterile water should be added to the container used to dissolve the tablets and the residual suspension should be shaken, aspirated into syringe, and administered. This last step should be repeated to ensure the entire dose is administered. The total volume of delivery/rinse is ~180 mL.

7.2.2 Formulation

Erlotinib is supplied as 25 mg, 100 mg, and 150 mg white filmcoated immediate-release tablets.

7.2.3 Mechanism of Action

Direct inhibition of EGFR tyrosine kinase.

7.2.4 Toxicities

In clinical trials, rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache were the most frequently observed undesirable effects following exposure to single-agent Erlotinib. Patients receiving Erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events as with either agent alone. Adverse events considered study drug related that appear to occur more frequently when Erlotinib is administered with chemotherapy, regardless of regimen, include fatigue, nausea, vomiting, stomatitis, and anemia. The skin rash commonly occurs on the face, upper chest and back, but may be more generalized with desquamation and may be accompanied by itching and tenderness and/or burning. Additional expected events include dry skin, nail changes, paronychia, painful fissures or cracking of skin on the hands and feet, hair growth abnormalities (alopecia, thinning hair, eyelash/eyebrow changes, and hirsutism), dehydration, hypotension, electrolyte changes, renal failure, dry mouth, glossodynia, mucositis/stomatitis, constipation, gastrointestinal bleeding, pneumonia, interstitial lung disease, cough, dyspnea including respiratory impairment, infection, sepsis, cellulitis, hemorrhage, subdural hematoma, cerebral hemorrhage, hematuria, hemoptysis, epistaxis, conjunctivitis, keratitis with associated facial rash, corneal ulceration/perforation, uveitis, orbital cellulites, anemia, thrombocytopenia, neutropenia with or without fever, neutropenic sepsis, elevations of PT or INR, stroke, myocardial infarction, liver function abnormalities, hepatic failure, acute renal failure/renal insufficiency, chest pain, bone pain, insomnia, syncope, ileus, hand-foot skin reaction and erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis).

7.2.5 Supply

Erlotinib is commercially available.

7.3 Capecitabine

7.3.1 Drug Administration

The Capecitabine daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. The tablets should be taken with water. Administration of Capecitabine dissolved in water or through a feeding tube was allowed for patients unable to swallow tablets.

7.3.2 Formulation

Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration. Only the 500 mg tablets will be utilized in this study.

7.3.3 Mechanism of Action

Capecitabine is an oral prodrug of 5-Fluorouracil. Metabolized in the liver to 5'-deoxyfluorocytidine, subsequently converted to 5'-deoxy-5-Fluorouridine which is then hydrolyzed to 5-Fluorouracil (active).

7.3.4 Toxicities

Common side effects from Capecitabine include diarrhea (which may be severe), dermatologic effects (hand-and-foot syndrome referred to as palmar-plantar erythodysesethesia), hematologic effects (neutropenia, thrombocytopenia, anemia and lymphopenia), weight gain, gastrointestinal effects (diarrhea, nausea, vomiting stomatitis, abdominal pain and constipation). Uncommon side effects include hepatotoxicitiy (hyperbilirubinemia). Rare side effects may include cardiovascular effects (myocardial infarction, dysrhythmias, cardiomyopathy).

7.3.5 Supply

Capecitabine is commercially available.

7.4 Oxaliplatin

7.4.1 Drug Administration

Oxaliplatin is infused either by peripheral vein or central venous line over 2 hours.

7.4.2 Formulation

Oxaliplatin for injection is presented in the form of a sterile, preservative-free, lyophilized powder contained in clear glass vials, sealed with an elastomeric stopper and flip-off cover. Oxaliplatin is available as 50 mg or 100 mg vials. The lyophilized powder is reconstituted by adding 10 mL (for the 50-mg vial) or 20 mL (for the 100-mg vial) of water for Injection, USP, or dextrose 5% in water for injection (D5W). The reconstituted solution must be further diluted in an infusion solution of 250 mL to 500 mL of D5W.

7.4.3 Mechanism of Action

Oxaliplatin is a platinum derivative in which the platinum atom is complexed with 1,2diaminocyclohexane and with an oxalate ligand as a leaving group. The mechanism of action of Oxaliplatin is similar to that of Cisplatin as well as other platinum (Pt) compounds. Studies conducted to date indicate that the types and percentages of Pt-DNA adducts formed by Oxaliplatin are qualitatively similar to those formed by Cisplatin, but preclinical data suggest several unique attributes of the cytotoxic/antitumor activity of Oxaliplatin. Oxaliplatin demonstrates a broad spectrum of in vitro cytotoxic and in vivo antitumor activity that differs from that of either Cisplatin or Carboplatin. Oxaliplatin is active against several Cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to Cisplatin.

7.4.4 Toxicities

Neurotoxicity: The occurrence of acute reversible sensory symptoms, described as dysesthesias, is predominantly associated with oxaliplatin administration. This toxicity is generally of mild to moderate intensity and is associated with early onset and brief duration, following Oxaliplatin administration. It is mainly located in the upper extremities, peri-oral and pharyngo-laryngeal areas, and can be exacerbated by cold exposure. The incidence to mild to moderate distal paresthesias is also commonly observed. Hematologic: Oxaliplatin myelotoxicity is modest. Gastrointestinal: Nausea, vomiting, constipation, diarrhea, and stomatitis can occur. Rash: Hand-foot skin reaction and injection site reactions have been seen. Fever: Fever during infusion of Oxaliplatin has been reported. Fever has been associated with the use of Oxaliplatin. Infection: May occur with normal ANC or unknown ANC. Hepatic: Alkaline phosphatase, bilirubin, gamma-glutamyltranspeptidase(GGT), SGOT, ALT, SGPT have all been reported to be elevated. Venoocclusive disease of the liver is a rare event. Renal: Patients may experience some degree of

elevation of serum creatinine. The incidence of grade 3/4 elevations is about 1% in previously treated patients. Pulmonary: Dyspnea and cough have been reported. Oxaliplatin has also been associated with pulmonary fibrosis in < 1% of patients. Anaphylactic reaction: Allergic reaction including fever has been reported. Cardiovascular: There has been reported incidence of thromboembolism.

7.4.5 Supply
Oxaliplatin is commercially available.

8.0 TISSUE/SPECIMEN

8.1 Tumor Tissue

8.1.1 Paraffin embedded tissue sections or cytologic material from patient's initial diagnostic or surgical procedure will be collected for correlative studies of the following molecular markers in relation to treatment response and outcome with methods such as immunohistochemistry [24-30].

8.1.1.1 Equilibrative nucleoside transporter (ENT1)
8.1.1.2 DPC4/Smad4
8.1.1.3 Vimentin
8.1.1.4 E-cadherin
8.1.1.5 BAX
8.1.1.6 Survivin
8.1.1.7 COX-2
8.1.1.8 S100A2
8.1.1.9 p16(INK4A)
8.1.1.10 14-3-3σ

8.2 Peripheral Blood

8.2.1 Ten-ml peripheral blood will be collected before and during treatment. Each ten-ml peripheral blood will be divided equally into two purple-top vacutainer containing EDTA anticoagulant, and the tubes are inverted five times to ensure adequate mixing of the anticoagulant. DNA will be extracted from leukocytes for pharmacgenomic study to analyze polymorphisms in genes (as below) which encoded proteins are involved in chemotherapy drug metabolism. The results of genetic study will be compared to treatment efficacy and toxicity [31-39].

8.2.1.1 EGFR intron 1
8.2.1.2 Cytidinedeaminase
8.2.1.3 ENT1
8.2.1.4 RRM1
8.2.1.5 ERCC1
8.2.1.6 MTHFR
8.2.1.7 Thymidylate synthase
8.2.1.8 XRCC1
8.2.1.9 RecQ1
8.2.1.10 RAD54L
8.2.1.12 ATM
8.2.1.12 xCT

9.0 TOXICITY RELATED THERAPY ADJUSTMENT

9.1 Dosing Delays/Modifications:

9.1.1 The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

9.1.2 Once a dose of chemotherapeutic agent has been reduced, it should not be increased at a later time. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in progress notes.

9.1.3 No dose reductions or interruptions will be required for anemia as it can be satisfactorily managed by transfusions.

9.1.4 Standard medical supportive care for nausea/vomiting should be provided prior to considering dose modification.

9.1.5 For patients who have had dosing delays, all subsequent evaluations will be correspondingly delayed.

9.2 Dose Levels for Gemcitabine and Erlotinib

Dose level	Gemcitabine	Erlotinib
0	1000 mg/m2	100 mg
-1	750 mg/m2	75 mg
-2*	500 mg/m2	50 mg

***** Two dose reductions are allowed for either Gemcitabine or Erlotinib. If a third reduction is required, treatment with that drug should be discontinued.

9.3 Dosing Delays/Modifications for Gemcitabine

Hematological toxicity			
ANC		**Platelets**	**Gemcitabine dose level**
≥1000	and	≥50,000	Maintain dose.
500-999	or	25,000 – 49,999	Reduce dose by 1 dose level.
<500	or	<25,000	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.
Febrile neutropenia*			Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.
Not recovered by 14 days			Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.
Not recovered by 28 days			Discontinue Gemcitabine chemotherapy. May continue Erlotinib.

*Febrile neutropenia: ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.

Non-hematologic toxicity		
Adverse event	**CTCAE toxicity grade**	**Gemcitabine dose level**
Hepatic (AST, ALT, bilirubin)	0-2	Maintain dose.
	3	Reduce dose by 1 dose level.
	4	Hold until resolved to grade 0-2 then restart at 1 dose level lower than previous. Discontinue if not resolved within 28 days.
Edema	0-2	Maintain dose.
	3	Reduce dose by 1 dose level.
	4	Hold until resolved to grade 0-2 then restart at 1 dose level lower than previous. Discontinue if not resolved within 28 days.
Other non-hematologic toxicity (except nausea/vomiting)	0-2	Maintain dose.
	3	Reduce dose by 1 dose level.
	4	Reduce dose by 1 dose level.
	Not improved from grade 3-	Hold until resolved to grade 0-2 then

	4 toxicity within 14 days	restart at 1 dose level lower than previous.
	Not improved from grade 3-4 toxicity within 28 days	Discontinue Gemcitabine. May continue Erlotinib..

9.4 Dosing Delays/Modifications for Erlotinib

Hematological toxicity		
Adverse event	**Erlotinib dose level**	
ANC < 500 (grade 4), platelets < 50,000 (grade 3 or 4), febrile neutropenia	Hold until resolved to < grade 2 or febrile neutropenia is resolved. May reduce dose by 1 dose level if toxicity is felt to be possibly related to erlotinib.	
Non-hematologic toxicity		
Adverse event	**CTCAE toxicity grade**	**Erlotinib dose level**
Rash	3	Hold until resolved to grade 2 or less then restart at 1 dose level lower than previous. Discontinue if not resolved within 14 days.
	4	Discontinue erlotinib.
Diarrhea	0-2	Maintain dose.
	3-4	Hold until resolved to grade 1 or less then restart at 1 dose level lower than previous. Discontinue if not resolved within 14 days.
Pulmonary toxicity	any	Hold temporarily pending diagnosis. Discontinue if pneumonitis or pulmonary infiltrate is confirmed and considered to be related to Erlotinib.
Hepatic (AST, ALT, bilirubin)	0-2	Maintain dose.
	3-4	Hold until resolved to grade 2 or less then restart at 1 dose level lower than previous. Discontinue if not resolved within 14 days.
Other non-hematologic toxicity	0-2	Maintain dose.
	3-4	Hold until resolved to grade 2 or less then restart at 1 dose level lower than previous. Discontinue if not resolved within 14 days.

9.5 Dosing Delays/Modifications for Capecitabine and Radiation

Hematological toxicity	
Adverse event	**Capecitabine dose level**
ANC > 1000 and platelets > 75,000	No dose modification
ANC 500-999 and/or platelets 50,000-75,000	Continue radiation. Hold capecitabine until ANC > 1000 and platelets > 75,000, then resume at permanent 25% dose reduction
ANC < 500 and/or Platelets < 50,000	Hold Capecitabine and radiation until ANC > 1000 and platelets > 75,000 then resume radiation and restart Capecitabine at permanent 25% dose reduction.
NOTE: Patients who have required three dose reductions and who experience a fourth episode of ANC <	

1000 and platelets < 75,000 will complete radiation and but will not receive additional Capecitabine.

Non-hematologic toxicity	
Adverse event	**Capecitabine dose level**
Grade 2 palmar-plantar erythrodysesthesia (hand-foot) syndrome	Hold Capecitabine until resolves to ≤ grade 1, then resume at permanent 25% dose reduction
Grade 3 palmar-plantar erythrodysesthesia syndrome	Hold Capecitabine until resolves to ≤ grade 1, then resume at permanent 50% dose reduction
Grade 3 oral mucositis	Hold Capecitabine until resolves to ≤ grade 2, then resume at permanent 25% dose reduction
Grade 4 oral mucositis	Hold Capecitabine until resolves to ≤ grade 2, then resume at permanent 50% dose reduction
Other grade 3 or 4 AE, 1st occurrence	Hold Capecitabine and radiation until toxicity has resolved to ≤ grade 2, then resume radiation and Capecitabine with a permanent 25% dose reduction
Other grade 3 or 4 AE, 2nd occurrence	Hold Capecitabine and radiation until toxicity has resolved to ≤ grade 2, then resume radiation and Capecitabine with a permanent 25% dose reduction
Other grade 3 or 4 AE, 3rd occurrence	Hold Capecitabine and radiation until toxicity has resolved to ≤ grade 2, then resume radiation and capecitabine with a permanent 25% dose reduction
Other grade 3 or 4 AE, 4th occurrence or grade 3 or 4 AE that persists for > 4weeks	Discontinue Capecitabine and radiation permanently

9.6 Dose levels, Dosing delays/Modifications for Oxaliplatin and Capecitabine

Dose level	Oxaliplatin	Capecitabine
0	130 mg/m2	1000 mg/m2 bid
-1	100 mg/m2	Reduce original daily dose by one 500-mg tablet
-2	75 mg/m2	Reduce original daily dose by two 500-mg tablets

Hematological toxicity				
ANC		**Platelets**	**Oxaliplatin dose level**	**Capecitabine dose level**
≥1000	and	≥50,000	Maintain dose.	Maintain dose.
500-999	or	25,000 – 49,999	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.
<500	or	<25,000	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.
Febrile neutropenia			Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous
Not recovered by 14 days			Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1 dose level lower than previous.
Not recovered by 28 days			Discontinue Oxaliplatin. May continue Capecitabine.	Hold until ANC ≥1500 and platelets ≥75,000. Restart at 1

		dose level lower than previous.

Non-hematologic toxicity		
Adverse event	**Oxaliplatin dose level**	**Capecitabine dose level**
Grade 2 palmar-plantar erythrodysesthesia (hand-foot) syndrome	Maintain dose.	Hold Capecitabine until resolves to ≤ grade 1, then resume at 1 dose level lower than previous.
Grade 3 palmar-plantar erythrodysesthesia (hand-foot) syndrome	Hold Oxaliplatin until resolves to ≤ grade 1, then resume at 1 dose level lower than previous.	Hold Capecitabine until resolves to ≤ grade 1, then resume at 2 dose levels lower than previous.
Grade 3 oral mucositis	Maintain dose.	Hold Capecitabine until resolves to ≤ grade 2, then resume at 1 dose levels lower than previous.
Grade 4 oral mucositis	Hold Oxaliplatin until resolves to ≤ grade 2, then resume at 1 dose level lower than previous.	Hold Capecitabine until resolves to ≤ grade 2, then resume at 2 dose levels lower than previous.
Grade 2 peripheral neuropathy	Reduce 1 dose level than previous	Maintain dose.
Grade 3 peripheral neuropathy	Hold Oxaliplatin until resolves to ≤ grade 1, then resume at 2 dose levels lower than previous.	Hold Capecitabine until resolves to ≤ grade 2, then resume at 1 dose levels lower than previous.
Grade 3 or 4 allergic reaction	Discontinue permanently if due to Oxaliplatin	Discontinue permanently if due to Capecitabine
Other grade 3 or 4 AE	Hold until resolves to ≤ grade 2, then resume at 1 dose level lower than previous.	Hold until resolves to ≤ grade 2, then resume at 1 dose level lower than previous.

10.0 PATIENTASSESSMENTS

10.1 Patient Evaluation Timing

10.1.1 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							

10.1.2 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.						

10.1.3 Post-PCT (begins 4-6 weeks after protontherapy)

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			

10.2 Toxicity Definitions

Late toxicities defined per the CTCAE v. 4.0 will be defined as those occurring 3 months or greater after the completion of radiation treatment. All toxicities occurring prior to that time period will be scored as acute. If there is any fatal treatment morbidity, the event will be reported to the study chairs and the IRB for review.

10.3 Assessment of Treatment Response

The tumor response will be determined by comparison of the pre- and post-treatment CT scans and assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

10.4 Quality of Life Assessments

Patients should complete the FACIT-Fatigue at baseline before therapy initiation, after completion of each phase of therapy, pre-PCT, PCT and post-proton chemotherapy, as well as at 9, 12, and 24 months from start of therapy. FACIT-Fatigue, version 4, is a 13-item questionnaire that assesses self-reported tiredness, weakness, and difficulty conducting usual activities due to fatigue. A 5-point intensity type of rating scale (from "not at all" to "very much") is used. This questionnaire can be completed by patients in approximately 5 minutes (Appendix)

11.0 STATISTICS

11.1 Study Endpoints

11.1.1 Primary Endpoint

One-year overall survival rate (failure: death due to any cause).

11.1.2 Secondary Endpoints

11.1.2.1 Frequency of patients developing serious adverse events (section 9.1.1) attributable to protocol treatment.

11.1.2.2 Progression-free survival (failure: local, regional or distant progression or death due to any cause).

11.2 Sample Size

11.2.1 Sample Size Derivation

The primary objective of this study is to estimate the one-year overall survival rate. In the previous RTOG protocol for unresectable pancreatic cancer (RTOG 98-12), a one-year survival rate of approximately 43% was observed[40]. There were 109 analyzable patients on RTOG 98-12 with 61 still at risk for death at one year. Using the method of Dixon and Simon[41], a sample size of 39 analyzable patients followed over 12 months will ensure at least 90% probability of detecting a minimum of 17% improvement in the one-year survival rate compared to RTOG 98-12 at the 0.10 significance level (with a one-sided test). Adjusting this figure by 10% to allow for patient ineligibility or loss, a total sample size of 43 patients will be required for this study.

11.2.2 Patient Accrual

Based upon an accrual rate of at least 1 patient per month, and allowing 6 months for institutional IRB review and approval, accrual should be completed in approximately 49 months. If the average monthly accrual is less than 1 case per month, the study will be re-evaluated with respect to feasibility.

11.3 Analysis Plan

11.3.1 Interim Reports

Interim reports will be prepared every six months until the primary endpoint has been presented. In general, these reports include:

11.3.1.1 The patient accrual rate with projected completion date

11.3.1.2 Institutional accrual

11.3.1.3 Pretreatment characteristics

11.3.1.4 Compliance rates of treatment delivery with respect to the protocol prescription

11.3.1.5 The frequency and severity of reported adverse events

11.3.2 Analysis for Reporting the Initial Treatment Results

The major analysis for reporting the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are:

11.3.2.1 Tabulation of all cases entered, and any patients excluded from the analysis with reasons for exclusion

11.3.2.2 Institutional accrual

11.3.2.3 Patient accrual rate

11.3.2.4 Distribution of important prognostic baseline other pretreatment variables

11.3.2.5 Observed results with respect to the endpoints described in Section 11.1

The estimated survival will be tested against the RTOG 98-12 trial with a one-sided log-rank test. Estimates of the median and one-year progression-free and overall survival rates will be estimated using the Kaplan-Meier method.

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Appendix I Staging System

American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (2010)

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ**
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Appendix II - **FACIT Fatigue Scale Questionnaire**

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>**.

	Not at all	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless ("washed out")	0	1	2	3	4
I feel tired.....	0	1	2	3	4
I have trouble starting things because I am tired.....	0	1	2	3	4

I have trouble finishing things because I am tired	0	1	2	3	4
I have energy.....	0	1	2	3	4
I am able to do my usual activities.....	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat.....	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do...	0	1	2	3	4
I have to limit my social activity because I am tired.....	0	1	2	3	4