The effect of chemotherapy and stereotactic body radiation therapy for locally advanced, non-resectable pancreatic cancer

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The effect of chemotherapy and stereotactic body radiation therapy for locally advanced, non-resectable pancreatic cancer

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Table of Contents

Study Schema

To combine chemotherapy with 5 fraction SBRT in patients with locally advanced, non-resectable pancreatic cancer in order to determine treatment toxicity and efficacy.

SYNOPSIS

Name of Sponsor:	James Graham Brown Cancer Center
Title of Study:	The effect of chemotherapy and stereotactic body radiation therapy for locally advanced, non-resectable pancreatic cancer Schema: Eligible primary locally advanced, unresectable pancreatic cancer. Patients will be treated with chemotherapy and SBRT to 4000cGy delivered in 5 fractions over 14 days. Primary objective: To estimate toxicity and efficacy
Protocol No.:	BCC-RAD-13-chemotherapy and SBRT
Investigators:	Neal E Dunlap and Rebecca Redman
Study Center:	James Graham Brown Cancer Center
Study Duration: Approximately 48 months	

1. Background

Pancreatic cancer remains the fourth leading cause of cancer deaths in the United States (1). Despite efforts to improve chemotherapy and radiation treatment regimens, surgical ressection remains the only modality associated with long-term survival (2).

Approximately 40-50% of pancreatic cancer patients present with localized yet unresectable disease with a reported median survival of 6 – 14 months. These results vary based on the patient characteristics, intensity of treatment regimen and those with borderline resectable disease (3-7). Although the Gastrointestinal study group established the standard of care as combined modality treatment with chemotherapy and radiation, the most appropriate method for integrating radiation into the treatment regimen remains unestablished especially with the introduction of newer, more intense chemotherapy regimems. Data using combined modality therapy typically results in locoregional control rates of 40-50%, but the role of multi-modality therapy is not well defined. Recent data from the Eastern Cooperative Oncology Group (ECOG) demonstated that radiation of 50.4Gy in combination with gemcitabine improves median survival compared to gemcitabine alone (8).

Although many people ultimately fail distantly, locoregional control remains an important aspect of treatment due to the significant impact on morbidity and quality of life. Attempts have been made to increase radiaiton dose or hypofractionate radiation dose to improve outcome varying reults. Recent advances in radiation therapy delivery using image-guidance and high dose delivery with stereotactic body radiation therapy have resulted in the potential of dose escalation to the primary tumor. Schellenberg et al. (9) demonstated that single fraction SBRT with gemcitabine showed local control rates of 82% with a median follow up of 22 months. Only 2 patients developed late grade 3 toxicity (12%) in the form of duodenal stricture requiring stent placement. Similarly, Mahadevan et al (10) showed a 3-fraction SBRT regimen in combination with gemcitabine resulted in local control rates of 78% with 14% grade 3 toxicity.

Despite improvements in locoregional control, the impact on overall survival has been limited as the vast majority of patients will ultimately die of metastatic disease. Single-agent gemcitabine and gemcitabine-based doublets were the mainstay of treatment for metastatic pancreatic cancer until recently, although median survival rarely exceeded 8 months and objective response rates were generally less than 20% (11-14). However, a randomized phase III study conducted by Conroy et al. (15) demonstrated that combination chemotherapy consisting of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) significantly improved median survival to 11.1 months as compared to 6.8 months in those treated with single-agent gemcitabine. Treatment-related toxicity was also increased with FOLFIRINOX, primarily gastrointestinal (nausea, vomiting, and diarrhea), cytopenias, and neuropathy. In addition, the objective response rate was 32% as compared to 9% with gemcitabine. As a result of this study, FOLFIRINOX is now widely accepted as a standard first-line therapy for patients with locally advanced and unresectable or metastatic pancreatic adenocarcinoma who have a good performance status. The influence of irinotecan on the efficacy of FOLFIRINOX is unknown as a similar response rate was reported in a single-arm study of 30 patients receiving infusional 5-fluorouracil, leucovorin, and oxaliplatin (16). Since the metabolism of irinotecan is primarily hepatic, FOLFOX is an acceptable alternative, particularly in patients with an abnormal bilirubin. Gemcitabine and nab (nanoparticle albumin bound)-paclitaxel represents an alternative option for first-line treatment based upon results of a multicenter, randomized study

of 861 patients with metastatic pancreatic cancer, which demonstrated superiority of this combination over gemcitabine alone (17). Median overall survival in the gemcitabine and nab-paclitaxel arm was 8.5 months with an objective response rate of 23%. Although median survival was shorter than that reported with FOLFIRINOX, it remains an acceptable alternative for patients with biliary obstruction or for those deemed not to be a candidate for FOLFIRINOX.

The objective of this phase II study is to combine chemotherapy with 5 fraction SBRT in patients with locally advanced, non-resectable pancreatic cancer in order to determine treatment toxicity and efficacy.

2. Objectives and Study Design

The objective of this prospective phase II protocol is to assess the toxicity and efficacy of chemotherapy with 5 fraction SBRT in patients with locally advanced, non-resectable pancreatic cancer in order to document treatment toxicity and estimate efficacy.

2.1 Primary Objective:

2.1.1. To document treatment related toxicities

2.1.2. Establish the efficacy of treatment

2.2 Secondary Objectives:

2.2.1. To estimate progression free survival

2.2.2. To estimate local failure

2.2.3. To estimate overall survival

2.2.4. To estimate quality of life

2.2.5. To explore effects of covariates (demographics, disease and treatment related) on toxicity, local failure, PFS and OS and QOL.

2.2.6. To explore the use of differential scanning calorimetry as a method for monitoring disease status

2.3 Study design:

The study will be a prospective, non-randomized, single center, trial to assess the effects of chemotherapy with SBRT on locally advanced, non-resectable pancreatic cancer. Chemotherapy will be delivered prior to SBRT for 8 weeks. Restaging imaging will occur prior to SBRT delivery. Patients who develop unequivocal evidence of metastatic disease following 8 weeks of first-line chemotherapy will be followed off study for survival, but will not undergo SBRT or additional study-related procedures. SBRT will be delivered using standard stereotactic techniques to a dose of 3200cGy at 650cGy per fraction delivered over 2 weeks. Additional chemotherapy with be delivered at the physician's discretion. Patients will be reassessed both clinically and radiographically at 3 months, 6 months, 9 months and 12 months post-treatment. Quality of life analysis will occur at 3 month intervals after treatment. Blood will be drawn for exploratory biomarker analysis at strategic timepoints during treatment and followup. Following the initial imaging time points, standard surveillance will be employed with clinical assessment and imaging at 3 month intervals for the first 2 years post-treatment.

3. Patient Selection

3.1 Eligibility Criteria

3.1.1 Age >/= 18 years

3.1.2 ECOG performance status 0-2

3.1.3 Pathologic diagnosis of pancreatic adenocarcinoma

3.1.4 Imaging as follows:
-CT scan of the chest, abdomen and pelvis with IV and oral contrast within 8 weeks of registration

3.1.5 Evaluation by a surgical oncologist to determine non-resectability

3.1.6 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential.

3.1.7 CBC/differential obtained within 14 days prior to registration with adequate bone marrow function as follows:
3.1.7.1 ANC $\geq$ 1,500 cell/mm3
3.1.7.2 Platelets $\geq$ 100,000 cells/mm3
3.1.7.3 Hemoglobin $\geq$ 8.0 g/dl (transfusion to obtain this value is permissible)

3.1.8 Additional labs within 14 days prior to registration
3.1.8.1 CA 19-9
3.1.8.2 Creatinine <2mg/dl
3.1.8.3 Bilirubin <3mg/dl
3.1.8.4 AST and ALT $\leq$ 3 x ULN

3.1.9 Patients must provide study specific informed consent prior to study entry.

3.2 Exclusion Criteria

3.2.1. Metastatic disease as defined by the multi-disciplinary team
3.2.2. Prior anti-cancer therapy for a pancreatic tumor
3.2.3. Prior malignancy within the last 3 years
3.2.4. Pregnant women or lactating women
3.2.5. Acquired Immune Deficiency Syndrome (AIDS) based on CDC criteria. However HIV testing is not manditory for this protocol

4. Treatment

4.1 External Beam Radiation

4.1.1. Localization, Positioning and Immobilization:
A volumetric planning CT study will be required to define the gross tumor volume (GTV) and planning target volume (PTV). Each patient will be

positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices of 1-3 mm will be obtained to include the entire treatment volume. The GTV, PTV and normal organs will be outlined on all appropriate CT slices.

4.1.2. 4-D CT: The use of 4-D CT radiation treatment planning is required on all patients. Acceptable methods for acquiring tumor motion include: design of the PTV to cover the excursion of the primary cancer and nodes during breathing such as an ITV approach, a maximum intensity projection (MIP) approach or a gating approach.

4.1.3 Treatment planning: Treatment planning will be performed using either conformal therapy or intensity modulated radiation therapy (IMRT). Cyberknife treatment is allowed. Any combination of coplanar or non-coplanar fields designed to cover the target volumes while limiting dose to critical structures is allowed. Composite dosimetry plans of the prior treatment volume and the new treatment plan will be generated if prior dosimetry is available. Standard SBRT treatment planning should be utilized. Successful treatment planning should attempt to meet the following:

-Normalization: The plan should be normalized such that 100% corresponds to the center of mass of the PTV

-Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the PTV is conformally covered by the prescription isodose surface and 99% of the PTV receives a minimum of 90% of the dose.

4.1.4. Critical structures and dose limits: Standard dose constraints to critical structures will be utilized for and SBRT as outlined by Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)

4.1.5. Treatments: 3200cGy delivered in 5 fractions at 650 cGy per faction to the PTV is required. Radiation treatments must be completed within 14 days of initiation of therapy and have a minimum of 36 hours between fractions. Daily image guidance is required with cone beam CT. Respiratory gating or abdominal compression may be utilized as deemed appropriate by the treating physician and physicist.

4.2 Chemotherapy

4.2.1 Patients will receive one of the following chemotherapy regimens at the discretion of the treating physician:

FOLFIRINOX administered intravenously on day 1 of each 14-day cycle for 4 cycles:

- Oxaliplatin 85 mg/m^2 over 2 hours
- Leucovorin 400 mg/m^2 over 2 hours

- Irinotecan 180 mg/m^2 over 90 minutes, concurrent with leucovorin through a Y-connector, started 30 minutes into leucovorin infusion ***(Irinotecan may be omitted at the discretion of the treating physician. Reason for omission should be noted.)***
- Fluorouracil 400 mg/m^2 iv push
- Fluorouracil 2400 mg/m^2 over 46 hours

-OR-

Gemcitabine and nab-Paclitaxel administered intravenously on days 1, 8, and 15 of each 28-day cycle:

- Gemcitabine 1000 mg/m^2 over 30 minutes
- Nab-Paclitaxel 125 mg/m^2 over 30 mnutes

See Appendix A for suggested chemotherapy dose modifications.

4.2.2 Chemotherapy dose rounding allowed per institution protocol as long as rounded dose is within 10% of calculated dose.

4.2.3 BSA should not be capped. Actual weight should be used. Recalculation of BSA and drug doses is required if patient has a 10% or greater change in weight from previously calculated doses.

4.2.4 Antiemetic regimen: A standard, FDA-approved antiemetic regimen will be administered to patients prior to the start of chemotherapy at the discretion of the treating oncologist. An example of such a regimen includes a $5HT_3$ receptor antagonist and dexamethasone.

4.2.5 Growth factor support is recommended with FOLFIRINOX, but not required. If not administered as primary prophylaxis and ANC < 1500 on day 1 of any cycle, the addition of growth factor support and/or dose reduction is strongly encouraged with subsequent cycles.

4.2.6 Supportive therapy will be administered at the discretion of the treating oncologist. Examples include prevention/treatment of delayed nausea, diarrhea, and fever. The prophylactic administration of atropine 0.5 mg IV is strongly encouraged to prevent or decrease symptoms of the cholinergic syndrome associated with irinotecan.

4.2.7 Pharmaceutical Data:

1. Oxaliplatin

4.2.7.1.1 Mechnism of action: Oxaliplatin, a platinum derivative, is an alkylating agent. Following intracellular hydrolysis, the platinum compound binds to DNA forming cross-links which inhibit DNA replication and

transcription, resulting in cell death. Cytotoxicity is cell-cycle nonspecific.

4.2.7.1.2 Preparation/Administration: Do not freeze and protect from light the concentrated solution. A final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions. The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP. After final dilution, protection from light is not required. Oxaliplatin is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.

2. Irinotecan

4.2.7.2.1 Mechanism of action: Irinotecan and its active metabolite (SN-38) bind reversibly to topoisomerase I-DNA complex preventing religation of the cleaved DNA strand. This results in the accumulation of cleavable complexes and double-strand DNA breaks. As mammalian cells cannot efficiently repair these breaks, cell death consistent with S-phase cell cycle specificity occurs, leading to termination of cellular replication.

4.2.7.2.2 Preparation/Administration: Irinotecan should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.

3. Fluorouracil

4.2.7.3.1 Mechanism of action: A pyrimidine analog antimetabolite that interferes with DNA and RNA synthesis; after activation, F-UMP (an active metabolite) is incorporated into RNA to replace uracil and inhibit cell growth; the active metabolite F-dUMP, inhibits thymidylate synthetase, depleting thymidine triphosphate (a necessary component of DNA synthesis).

4.2.7.3.2 Preparation/Administration: Fluorouracil Injection, USP is available for intravenouse use in 10 mL vials. Each mL contains 50 mg (available as 500 mg/10 mL)

of fluorouracil in a colorless to faint yellow aqueous solution. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F and shaking vigorously; allow to cool to body temperature before using. Do not refrigerate or freeze. Protect from light.

4. Leucovorin

4.2.7.4.1 Mechanism of action: Stabilizes the binding of 5-dUMP and thymidylate synthetase, enhancing the activity of fluorouracil.

4.2.7.4.2 Preparation/Administration: Reconstitute the lyophilized vial products with Bacteriostatic Water for Injection, USP (benzyl alcohol preserved), or Sterile Water for Injection, USP. Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute). Leucovorin should not be mixed in the same infusion as 5-fluorouracil, since this may lead to the formation of a precipitate.

5. Gemcitabine

4.2.7.5.1 Mechanism of action: A pyrimidine antimetabolite that inhibits DNA synthesis by inhibition of DNA polymerase and ribonucleotide reductase, cell cycle-specific for the S-phase of the cycle (also blocks cellular progression at G1/S-phase).

4.2.7.5.2 Preparation/Administration: Reconstitute in NS without preservatives to yield a concentration of 38 mg/mL; further dilute with NS prior to administration; final concentration may be as low as 0.1 mg/mL. Diluted solution stable at room temperature for 24 hours; do not refrigerate.

6. Nab-Paclitaxel

4.2.7.6.1 Mechanism of action: Promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication.

4.2.7.6.2 Preparation/Administration: Reconstitute in NS, swirl until complete dissolution occurs. Immediately use the reconstituted suspension in the vial or infusion bag, or refrigerate (2 to 8 degrees C) for a maximum of 24

hours. Infuse IV over 30 minutes and use caution to avoid extravasation.

5. Adverse Events

5.1 Radiation Toxicities

5.1.1. The CTEP Common Terminology Criteria for Adverse Events (CTCAE v4.0) will be used. Standard radiation related toxicities are expected. Toxicity will be defined as acute (<3 months from completion), subacute (3-12 months) and late (>12 months). Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, nausea, and gastritis are expected side effects of radiation therapy.

5.2 Chemotherapy Toxicities

5.2.1 Common Terminology Criteria for Adverse Events (CTCAE) v4.0 will be used to document and report adverse events.

5.2.2 The most common grade 3 or 4 adverse events occurring in more than 5% of patients receiving FOLFIRINOX in a multicenter phase II/III study (15) included neutropenia, febrile neutropenia, thrombocytopenia, anemia, fatigue, vomiting, diarrhea, peripheral neuropathy, transaminitis, and thromboembolism. Alopecia, stomatitis, and hand/foot syndrome are also reported. Irinotecan, in particular, causes both early and late diarrhea. The early form (during infusion or shortly thereafter) is often accompanied by abdominal cramping and other cholinergic symptoms (diaphoresis, flushing) and can be attenuated or prevented with the use of atropine, as suggested in this protocol. In addition to acute and chronic sensory neuropathy, oxaliplatin may cause laryngopharyngeal dysesthesias. All chemotherapeutic drugs carry the risk of an infusional reaction, including anaphylaxis.

5.2.3 The most common grade 3 or adverse events occurring in more than 5% of patients receiving gemcitabine and nab-paclitaxel included leukopenia, anemia, thrombocytopenia, fatigue, peripheral neuropathy, and diarrhea. Febrile neutropenia occurred in 3% of patients, with 26% of patients receiving growth factor support.

5.3 Adverse Event Reporting: Adverse events (AE) and serious adverse events (SAE) will be reported in a timely manner through the appropriate channels. The investigator will assess and determine whether the event is related to the study treatment and assign the following category (possible, probable, definite). If possibly/probably related, investigator will specify whether AE/SAE is related to chemotherapy or SBRT. Please see below for definitions of each. Any and all AE/SAEs occuring during and up to 90 days after protocol-specified treatment (up to 90 days post-SBRT) will be reported.

-AE: Any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether

it is considered related to the medical treatment or procedure. (CTEP, NCI guidelines: Adverse event reporting requirements)

-**SAE**: Any adverse experience occurring during any part of protocol treatment and 90 days after that results in the following: death, life-threatening adverse experience, inpatient hospitalization, a persistent or significant disability, or a cognitive anomaly.

- SAE will include any event leading to the following:

- · Death;
- · A life-threatening adverse drug experience;
- · Inpatient hospitalization or prolongation of existing hospitalization;
- · A persistent or significant disability/incapacity;
- · A congenital anomaly/birth defect.

Reporting of Adverse Events

All AEs, regardless of severity and whether or not they occurred during the study treatment or within 90 days following the last treatment, are to be documented by the Investigator appropriately, including date of onset, severity, action taken, outcome, and relationship to study drug. Adverse events occurring between the time of signing informed consent to the time of the first dose will NOT be captured as AEs unless the AE is a direct result of a study-specific procedure or results in death from an event other than PD.

In the case of an SAE, the Investigator must notify the Institutional Review Board and the Co-Chairman of the Data Safety Monitoring Committee within 24 hours of becoming aware of the event.

6. Follow-up and Response Criteria

6. 1. Follow Up

6.1.1. Follow-up: Complete history and physical exam will be performed at each follow-up visit to assess for treatment related toxicity.

6.1.2. Imaging: Imaging will be obtained every 3 months for two years post-treatment. CT of the chest, abdomen and pelvis should be performed using IV and oral contrast. Surveillance CT imaging of the chest will be obtained as recommended by the treating physician.

6.2 Response Criteria

6.2.1. Response determination: Response assessment will follow a modified version of the RECIST criteria guidelines as outlined below. Response will be assessed from the planning CT scan by determining the longest tumor diameter.

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum of LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Does not qualify for a PR or PD

6.3 Quality of life assessment

Quality of life is one of the measures we plan on examining. SBRT offers a compressed treatment regimen and relative few side effects when compared to convential treatment methods in the retreatment setting.

6.4.1 Function Assessment of Cancer Therapy – Pancreas (FACT-Hep): The FACT-Hep quality of life assessement form (see Appendix B) will be utilized. This is an established tool for measuring patient quality of life both before and after intervention. The form will consist of 41 questions and be administered at the following time points: within 6 weeks of treatment and at 3 month intervals post-treatment. The questionnaire should take approximately 8 minutes to complete.

6.4 Exploratory biomarker analysis

Differential scanning calorimetry (DSC) examines changes in the thermodynamic properties of high abundance plasma proteins. This is highly relevant since it is recognized that proteins and fragments shed from cancer tissue microenvironments enter the circulatory system. Study of the high abundance proteome by DSC might therefore provide new information about pancreatic cancer biology and for monitoring of disease status. Blood will be drawn at strategic timepoints during treatment and follow-up for this exploratory biomarker analysis.

7. Study Calendar

Assessment	Pretreatment	During Chemotherapy	Prior to Radiation	During Radiation	6 weeks post-treatment	3 months post-treatment	6 months post-treatment	Follow-up (Q3 months up to & including 24 months post-treatment
History and physical	Within 4 weeks	Q4wk		x	x	x	x	x

Performance status and weight	Within 4 weeks	Q4wk		x	x	x	x	x
Diagnostic CT	Within 8 weeks		x			x	x	x
4-D CT scan			1 week prior to radiation treatment during simulation					
Tumor Response Evaluation			x			x	x	x
Adverse Event Evaluation		x		x	x	x		
Quality of Life assessment	x				x	x	x	x (at 9 and 12 months post-treatment only)
Biomarker evaluation (drawn with SOC lab)	x	Q2wk	x		x	x	x	x

8. Subject Registration and Data Collection

8.1.1 Subject registration: The informed consent process must be completed prior to initiation of any study required activities. Registration into the study will occur when the following criteria are met:

-Patient meets all inclusion and no exclusion eligibility criteria
-Patient provides written informed consent

8.1.2 Patient study identification numbers will be assigned in ascending order. This patient identifier will be recorded in the Subject Enrollment Log and placed on the header of all case report forms and study related materials to identify the subject. Subject data will be recorded in a secure location and database in the Clinical Trials Office of the Brown Cancer Center.

8.2.1 Data Collection: Data will be collected according to the protocol requirements for all patients registered to the trial, including early termination and patients deemed ineligible.

8.3.1 The study chair and project team will collect monthly reports of the study project and accrual.

9. DSMC Review

An independent committee, called the Data Safety and Monitoring Committee (DSMC) will review the progress of the study and monitor subjects' accrual, serious adverse events and unexpected events. Through this process the DSMC is also assessing the continuing validity and scientific merit of the trial. The DSMC members are from the Study Chair's Institution, the Brown Cancer Center, University of Louisville. Members on the committee view themselves as representing the interests of the study patients and not that of the institution. The DSMC makes written reports summarizing their findings at each review. The DSMC meets quarterly, or more frequently if requested by the Principal Investigator. The study statistician will provide the DSMC interim analysis reports determined by statistical methods noted in this protocol.

10. Ethical and Regulatory Considerations

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice.

- Informed Consent

- The principles of informed consent are described by Federal regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office of protection from Research Risks Reports; protection of Human Subjects (Code of

Federal regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

- Institutional Review; This study must be approved by an appropriate institutional review committee as defined by Federal regulatory Guidelines (Ref. Federal Register Vol. 46, No 17, January 27, 1981, part 56) and the Office for protection from Research Risks Reports; Protection of Human Subjects (Code of Federal regulations 45, CFR 46).

11. Statistical Considerations

11.1 Study Design:

The study will be a single-arm, single center, uncontrolled phase II trial to estimate the safety of the combined treatment and then estimate the efficacy in terms of the ORR, overall response (CR + PR +SD) rate in patients with advanced, non-resectable pancreatic cancer.

11.2 End-Point Definitions:

We will use two main end-points. The primary end-point of interest is the clinical response. The progression-free survival, PFS, is directly related to the sustained response rate and thus the time to the first event will also be monitored. The second end-point will be tolerability/toxicity to treatment. Secondary end-points to be considered are the overall survival, OS, which is the time to first event or death due to any reason, quality of life.

11.3 Sample Size:

There is no data available at the institution to support the sample size justification based on efficacy of this treatment. In the published literature, Conroy et al. (2011) report overall response rate to be around 25%. We expect that the overall response rate should be between 7-30%. Therefore an ORR rate less than 10% should indicate the treatment is not sufficiently promising (P0 = 0.10). We expect the therapy to increase the overall response rate to approximately 25% (P1 = 0.25). Using Simon's two-stage minimax design for phase II trials (Simon, 1989) we plan to enroll a maximum of 28 patients using alpha=5% and power=70%. In first stage, 13 patients will be enrolled. Table S1 gives the details of the justification of this sample size.

Table S1. Sample size justification P0 =0.10, P1=0.25, alpha=5% and power =70%

MiniMax Two Stage Design	MiniMax Design
First Stage Sample Size (n1)	13
Upper Limit For 1st Stage Rejection of Drug (# of ORR)	1
Maximum Sample Size (n)	28
Upper Limit for 2nd Stage Rejection of Drug (# of ORR)	5
Expected Sample Size If Po = 0.10	19

Probability of Early Termination at Po=0.50	0.62

11.4 Accrual and Follow-up:

Based on our experience we plan to enroll 15 patients per year. It will take approximately 2.0 years to complete the enrollment of 28 patients. Depending on the combination treatment's performance we may not need to enroll all 28 participants. The live patients will be followed two additional years after the completion of the treatment.

11.5 Statistical Analysis:

Patients receiving treatment will be presented. Patients receiving treatment who are found not to have fully met the eligibility criteria will also be presented. On-study protocol violations will also be presented. Patients who do not complete the required observations will be listed and evaluated separately as necessary. Reasons for study discontinuation and date of withdrawal from study will be presented.

Descriptive statistics related to the participant characteristics, treatment, and prognostic factors will be reported. Clinical response rates (complete, partial, and sustained) along with 95% confidence intervals will be estimated (Yuan and Rai 2011). The progression-free survival and overall survival will be estimated by Kaplan-Meier method (Kaplan and Meier 1958). Differences in survival will be evaluated through the estimated hazard rates using the un-weighted log-rank tests. The PFS time will be determined as the time from enrollment until the first adverse event (i.e., disease progression or death due to any cause). The OS time will be determined as the time from enrollment until death or last follow-up evaluation. In order to examine the significant prognostic factors, we will use the Cox proportional hazards regression models in both univariable and multivariable settings (Cox 1972; Cantor 2003; Kalbfleisch and Prentice 2002). Descriptive statistics associated with the toxic events will be reported. Logistic regression model will be used to find association with the presence of higher grade toxicity and clinical and demographic factors (Fleiss 1986, Fleiss et al 2003; Dmitrienko et al. 2005). For longitudinal measures such as quality of life (QOL) mixed model approach will be used (Diggle et al. 2002; Littell 2006). The differential scanning calorimetry (DSC) will be used to predict the response outcome using the method of Rai and others (2013). The factors to be analyzed are ethnicity, gender, age, pathological subtype, etc. The various factors will be placed into categorical variables. All calculations will be performed with SAS statistical software (SAS, 2003).

11.6 Monitoring Rule:

Safety monitoring of the accumulated outcomes data is designed to ensure the continuing safety of the currently enrolled participants and participants not yet enrolled. This is achieved by stopping the trial early to reduce the number of participants exposed to a harmful or ineffective treatment.

11.7 Non-efficacious Treatment (Futility):

In the first stage we will enroll 13 participants and if we observe at most 1 ORR we will not enroll any new participants. If we observe 2 or more ORR in the first stage, then we plan to enroll an additional 15 patients. In order for the treatment to be declared effective there has to be ORR in at least 6 patients. If the ORR is only 7%, we will have 62% chance of stopping the study early and, at most, 19 patients will be treated on the potentially ineffective therapy.

11.8 Toxic Treatment (Safety):

The cumulative number of grade 3 or 4 toxic events will be monitored after each person is enrolled (Ray and Rai, 2011). If the cumulative number of toxic events produces enough evidence to conclude that the true toxicity rate is greater than or equal to 33% (Pt0 = 0.33) then the trial will be stopped early for safety reasons. The cumulative number of toxic events after each is person is treated will be compared to the boundary values in Table S2. If the cumulative number of toxic events after person i is treated is greater than or equal to the associated boundary value bi then the combination treatment is rejected for safety considerations. With this rule, there is only a 5% chance of stopping the trial early for lack of safety if the true toxicity rate is less than 33%. Continual assessment of the toxic events ensures we do not expose an undue number of patients to a harmful treatment.

Table S2. Toxicity Boundaries, N = 42, Pt0 = 0.33, and alpha=0.05

Minimum Number of Subjects	Maximum Number of Subjects	Number of Toxicities
4	4	4
5	6	5
7	7	6
8	9	7
10	11	8
12	14	9
15	16	10
17	18	11
19	19	12
20	22	13
23	23	14
24	27	15
28	28	16

The combined procedure has similar operating characteristics to the Simon 2-Stage design (Ray and Rai, 2011). The probability of stopping early under the null hypothesis of low response or high toxicity is 67.8% with an expected sample size of 27.9 patients.

12. References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics (2006). CA Cancer J Clin 56: 106.
2. S.F. Sener, A. Fremgen, H.R. Menck et al. Pancreatic cancer: A report of treatment and survival trends for 100,313 patients diagnosed from 1985–1995, using the National Cancer Database J Am Coll Surg, 189 (1999), pp. 1–7
3. E. Ben-Josef, A.F. Shields, U. Vaishampayan et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer Int J Radiat Oncol Biol Phys, 59 (2004), pp. 454–459
4. A. Brade, J. Brierley, A. Oza et al. Concurrent gemcitabine and radiotherapy with and without neoadjuvant gemcitabine for locally advanced unresectable or resected pancreatic cancer: A phase I-II study Int J Radiat Oncol Biol Phys, 67 (2007), pp. 1027–1036
5. J.D. Earle, J.F. Foley, H.S. Wieand et al. Evaluation of external-beam radiation therapy plus 5-fluorouracil (5-FU) versus external-beam radiation therapy plus hycanthone (HYC) in confined, unresectable pancreatic cancer. (1994). Int J Radiat Oncol Biol Phys, 28: 207.
6. M. Hoyer, H. Roed, L. Sengelov et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma Radiother Oncol, 76 (2005), pp. 48–53.
7. P. Li, Y. Chao, K.H. Chi et al. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: Gemcitabine versus 5-fluorouracil, a randomized controlled study Int J Radiat Oncol Biol Phys, 57 (2003), pp. 98–104.
8. Loehrer, P. J., Feng, Y., Cardenes, H., Wagner, L., Brell, J. M., Cella, D., ... & Benson, A. B. (2011). Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *Journal of Clinical Oncology*, *29*(31), 4105-4112.
9. Schellenberg, D., Goodman, K. A., Lee, F., Chang, S., Kuo, T., Ford, J. M., ... & Koong, A. C. (2008). Gemcitabine chemotherapy and single-fraction stereotactic body radiotherapy for locally advanced pancreatic cancer. *International Journal of Radiation Oncology* Biology* Physics*, *72*(3), 678-686.
10. Mahadevan, A., Jain, S., Goldstein, M., Miksad, R., Pleskow, D., Sawhney, M., ... & Vollmer, C. (2010). Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. *International Journal of Radiation Oncology* Biology* Physics*, *78*(3), 735-742.
11. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, …& Neoptolemos JP. (2009). Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *Journal of Clinical Oncology*, 27(33):5513.
12. Colucci G, Labianca R, Di Costanzo F, Gebbia V, Carteni G, Massidda B, … & Perrone F. (2010). Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *Journal of Clinical Oncology,* 28(10):1645.
13. Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, … & Benson AB III. (2009). Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology

Group. *Journal of Clinical Oncology,* 27(23):3778.
14. Stathopoulos GP, Syrigos K, Aravantinos G, Polyzos A, Papakotoulas P, Fountzilas G, … & Georgoulias V. (2006). A multicenter phase III trial comparing irinotecan-gemcitabine with gemcitabine monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *British Journal of Cancer*, 95(5):587.
15. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, … & Ducreux M. (2011). FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *New England Journal of Medicine,* 364(19):181.
16. Ghosn M, et al. FOLFOX-6 combination as the first-line treatment of locally advanced and/or metastatic pancreatic cancer. Am J Clin Oncol 2007; 30(1): 15.
17. Von Hoff DD, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. NEJM 2013; 369(18): 1691.
18. Garbet NC, Miller JJ, Jenson AB, Chaires JB. Calorimetry outside the box: a new window into the plasma proteome. Biophys J 2008; 94: 1377-83.
19. GarbetNC, Mekmaysy CS, Helm CW, Jenson AB, Chaires JB. Differential scanning calorimetry of blood plasma for clinical diagnosis and monitoring. Exp Mol Pathol 2009; 86: 186-91.
20. Garbett NC, Merchant ML, Helm CW, Jenson AB, Klein JB, Chaires JB. Detection of Cervical Cancer Biomarker Patterns in Blood Plasma and Urine by Differential Scanning Calorimetry and Mass Spectrometry. PLOS ONE 2014; 9(1):e84710.

Statistical References:

21. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled clinical Trials, 10:1-10, 1989.
22. Yuan, X and Rai, SN. Confidence Intervals for Survival Probabilities: A Comparison Study. Communications in Statistics – Simulation and Computation, 40(7): 978-991, 2011.
23. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. Journal of American Statistical Association, 53:457-481, 1958.
24. Cox DR. Regression and life-tables. J R Stat Soc B. 34:187-220, 1972.
25. Kalbfleisch JD and Prentice RL. The Statistical Analysis of Failure Time Data, 2nd ed. New York: Wiley & Sons, 2002.
26. Dmitrienko A, Molenberghs G, Chuang-Stein, C and Offen W. Analysis of Clinical Trials Using SAS®: A practical Guide. Cary, NC, USA: SAS Institute Inc., 2005.
27. Fleiss, JL. Design and Analysis of Clinical Experiments. New York: John Wiley and Sons, 1986.
28. Fleiss JL, Levin, B and Paik MC. Statistical Methods for Rates and Proportions, 3rd Edition. New York: John Wiley and Sons, 2003.
29. Diggle PJ, Heagerty PJ, Liang KY and Zeger SL. Analysis of Longitudinal Data. 2nd Edition. New York: Oxford University Press, 2002.
30. Littell RC, Milliken GA, Stroup WW, Wolfinger R and Schabenberger O. SAS® for Mixed Models 2nd Edition, Cary, NC: SAS Institute Inc., 2006.
31. The SAS System V9, Cary, NC: SAS Institute Inc., 2003.

32. Ray HE and Rai SN. An evaluation of a Simon 2-stage phase II clinical trial design incorporating toxicity monitoring. Contemporary Clinical Trials, 32:428-436, 2011.
33. Rai SN, Pan J, Cambon A, Chaires JB and Garbett NC. Group Classification in High-Dimensional Data: Application to Differential Scanning Calorimetry Plasma Thermogram Analysis of Cervical Cancer and Control Samples. *Open Access Medical Statistics*, 3:1-9, 2013.

13.Appendices

Appendix A

FOLFIRINOX Suggested Dose Modifications*

Hematologic Toxicity

Absolute neutrophil count <1500/mm^3	**Occurrence**	**Fluorouracil**	**Irinotecan**	**Oxaliplatin**
Hold treatment until ≥ 1500/mm3, then resume treatment with dose modifications Add growth factor if not used with previous cycle(s)	1st	Delete bolus; maintain continuous infusion at 100%	150 mg/m^2	85 mg/m^2
	2nd	Same as above	150 mg/m^2	60 mg/m^2
	3rd	Discontinue	Discontinue	Discontinue

Platelet count < 75,000/mm^3	**Occurrence**	**Fluorouracil**	**Irinotecan**	**Oxaliplatin**
Hold treatment until ≥ 75,000/mm^3, then resume treatment with dose modifications	1st	Bolus 300 mg/m^2; continuous infusion 1800 mg/m^2 over 46 hours	180 mg/m^2	60 mg/m^2
	2nd	Same as above	150 mg/m^2	60 mg/m^2
	3rd	Discontinue	Discontinue	Discontinue

Gastrointestinal Toxicity

Diarrhea grade 3-4	**Occurrence**	**Fluorouracil**	**Irinotecan**	**Oxaliplatin**
Hold treatment until recovered to ≤ grade 2, then resume with dose modifications Verify patients are using loperamide	1st	Delete bolus; maintain continuous infusion at 100%	150 mg/m^2	85 mg/m^2
	2nd	Continuous infusion 1800 mg/m^2 over 46 hours	150 mg/m^2	60 mg/m^2
	3rd	Discontinue	Discontinue	Discontinue

Other Toxicity

Grade 3-4 toxicities justify a dose reduction of the responsible chemotherapy drug at the discretion of the treating oncologist.

Gemcitabine/nab-Paclitaxel Suggested Dose Modifications*

Dose Level	Gemcitabine	Nab-Paclitaxel
Full dose	1000 mg/m^2	125 mg/m^2
-1	750 mg/m^2	100 mg/m^2
-2	500 mg/m^2	75 mg/m^2

Chemotherapy should be discontinued in subjects requiring more than 2 dose reductions.

Hematologic Toxicity

Day	ANC (cells/mm^3)		Platelet count (X1000 cells/mm^3)	Gemcitabine dose	Nab-Paclitaxel dose
1	<1000	*or*	<75	Hold until ANC>1000 *and* plt >75	Hold until ANC>1000 *and* plt >75
8	500-999	*or*	50-74	-1	-1
	<500	*or*	<50	Hold	Hold
15	>1000	*and*	>75	Previous dose or -1 if day 8 held	Previous dose or -1 if day 8 held
	500-999	*or*	50-74	-1	-1
	<500	*or*	<50	Hold	Hold

Other Toxicity

Grade 3-4 toxicities: Withhold chemotherapy until ≤ grade 1, then resume at next lower dose level.

Renal Impairment (All drugs)

No dose adjustments are required for creatinine clearance (CrCl) >30mL/min as calculated by Cockcroft-Gault:

CrCl = (140 - age) x IBW / (Scr x 72) (x 0.85 for females)

Hepatic Impairment (All drugs)

Consider delaying treatment to exclude biliary obstruction.

	Bilirubin 1.5-3 mg/dL	Bilirubin >3 mg/dL
Irinotecan	75% of dose	Use not recommended
Nab-Paclitaxel	Reduce dose to 80 mg/m^2	Use not recommended
Gemcitabine	Initial dose of 800 mg/m^2; may increase as tolerated	Initial dose of 800 mg/m^2; may increase as tolerated

Oxaliplatin	No dosage adjustment necessary
Fluorouracil	No dosage adjustment necessary for bilirubin <5 mg/dL

**Dose adjustments are ultimately made at the discretion of the treating oncologist.*

APPENDIX B: FACT-HEP QUESTIONNAIRE

FACT-Hep (Version 4)

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 past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4