Title:	A Phase II Study to Assess the Efficacy and Safety of Preoperative Chemotherapy with Radiation therapy for Patients with Unresectable or Borderline Resectable Adenocarcinoma of the Pancreas
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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
Cal9-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CCTO	Cancer Clinical Trials Office
Cis	Cisplatin
CRF	Case Report Form
CT	Computed Tomography
CXR	Chest X-Ray
DNA	Deoxyribonucleic Acid
EBRT	External Beam Radiation Therapy
FDG	Fluorodeoxyglucose
FU	Fluorouracil
GCP	Good Clinical Practice
Gem	Gemzar
GGT	Gamma-glutamyl transferase
GTV	Gross Tumor Volume
Gy	Gray
H & P	History and Physical
HUS	Hemolytic-uremic Syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver Function Test
MIP	Maximum Intensity Projection
N1	Nodal Stage 1
NCI	National Cancer Institute
NYHA	New York Heart Association

ABBREVIATIONS CONTINUED

OAE	Other Significant Adverse Event
PET	Positron Emission Tomography
PTV	Planning Target Volume
RBC	Red Blood Cells
RNA	Ribonucleic Acid
R0R	Margin-negative Resection
R0RR	Margin-negative Resection Rate
RSC	Research Support Center
RT/XRT	Radiation Therapy
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SMV	Superior Mesenteric Vein
SOP	Standard Operating Procedure
STEAE	Serious Treatment Emergent Adverse Event
T3	Tumor Stage 3
UA	Urine Analysis
UAMS	University of Arkansas for Medical Sciences
ULN	Upper Limits of Normal
US	Ultrasound
WBC	White Blood Count
WHO	World Health Organization

PROTOCOL SUMMARY

The purpose of this phase II clinical trial study is to assess the resection rate among subjects who have been initially diagnosed with unresectable or borderline resectable pancreatic adenocarcinoma. This will be done by providing preoperative treatment that will include alternating cycles of chemotherapy and radiotherapy treatment. In addition, this clinical trial will assess the safety of preoperative chemotherapy with radiation therapy for subjects with unresectable or borderline resectable adenocarcinoma of the pancreas, assess margin-negative resection rates, disease-free survival, assess overall survival rates, and determine patterns of local and distant recurrence.

The study population in this clinical trial will consist of untreated subjects 18 years or older who have a histologically or cytologically confirmed diagnosis of unresectable or borderline resectable adenocarcinoma of the pancreas. The maximum feasible accrual is estimated to be 20 subjects in a one-year period, and the target sample size is thus 20 subjects. We expect to screen approximately 40 subjects in order to achieve our enrollment goal of 20 subjects at the University of Arkansas for Medical Sciences. Once the patient has undergone the necessary tests and the tumor has been staged, the principal investigator or co-investigators will determine if the patient is suitable to be inducted in this clinical trial. The course of preoperative treatment in this study will consist of an alternating combination of 6mg/M² of Gemzar for 24 hours and 7.0 Gy of radiation therapy. The subject will undergo one of these therapies alternating daily for a total of 10 days then the subject will be allowed to rest for 4 weeks before undergoing restaging and surgery. After surgery, the subject will then undergo the conventional chemotherapy regimen consisting of 6 cycles (1 cycle = 28 days) of 1000mg/M² of Gemzar over a 30 minute infusion rate.

The primary outcome of this clinical trial is the margin-negative resection rate. This will be determined by the tumor's response to the pre/post-operative treatment so that the tumor can be removed surgically.. Once the subject has completed the treatment as described in the protocol, he/she will continued to be followed to assess survival and patterns of local and distance recurrence until recurrence and/or death up to five years. The purpose of this clinical trial will be an attempt to provide subjects with a more hopeful alternative to treatment for a disease that otherwise offers a grim prognosis.

BACKGROUND

Survival of patients with pancreatic cancer remains the most depressing among all cancer patients. The main hope for survival hinges on the possibility to resect the tumor but this is not really done to more than a minority of patients due to the pattern of presentation of this tumor. Patients with pancreatic cancer are staged into three groups: Resectable (~20% of total), locally advanced/unresectable (35%–40% of total), and Metastatic (40% of total).

The rationale for pursuing preoperative therapy for patients with unresectable or borderline resectable pancreatic cancer includes: (a) potential for downstaging in order to maximize the chances for a margin-negative resection (R0R) (b) treating micrometastatic disease early, (c) giving "adjuvant" therapy in a "neoadjuvant" setting when it is better tolerated, and (d) using this approach to gauge the aggressiveness of the cancer and thereby select the best patients for surgery who have the greatest likelihood of a favorable postoperative outcome.[1,2] Traditionally

patients with pancreatic cancer were defined as either resectable or unresectable. However, recent National Comprehensive Cancer Network guidelines include a definition of borderline resectability. This definition includes patients with severe unilateral mesenteric/portal vein impingement, tumor abutment on the mesenteric artery, limited involvement of the vena cava, mesenteric vein occlusion with patent vein, and colon or mesocolon invasion.[3] The Stanford criteria of marginally resectable pancreatic cancer are similar and highlights main vessel involvement.[4] The M. D. Anderson Cancer Center criteria of borderline resectability include vessel involvement but also patients with concern for extrapancreatic disease and patients with marginal performance status due to reversible conditions (such as hyperbilirubinemia).[5]

There have been several trials at M.D. Anderson Cancer Center of preoperative chemoradiation for resectable pancreatic cancer. The initial studies used a standard-fractionation treatment schema of preoperative chemoradiation and pancreaticoduodenectomy. In an early study, radiation therapy was delivered 5 days/week over 5.5 weeks with 18-MeV photons.[6] Using a four-field technique, subjects received a total dose of 50.4 Gy prescribed to the 95% isodose at 1.8 Gy/fraction (28 fractions). 5-FU was given concurrently by continuous infusion at a dosage of 300 mg/m2 per day, 5 days/week, through a central venous catheter. This treatment allowed improved locoregional control with preoperative chemoradiation.[6] However, this 5.5-week chemoradiation program was associated with gastrointestinal toxicity (nausea, vomiting, and dehydration) that required hospital admission of one third of the subjects. These findings prompted a change in the delivery of preoperative chemoradiation at M.D. Anderson Cancer Center in favor of rapid-fractionation or short-course EBRT. In future trials at this institution, rapid-fractionation chemoradiation at a total dose of 30 Gy (3 Gy/fraction [10 fractions] 5 days/week) was delivered over 2 weeks with concurrent chemotherapy. Rates of local tumor control and subject survival times achieved were equal to the results obtained with standard-fractionation (5.5 weeks) chemoradiation. Subsequent trials also incorporated Gemzar as the systemic agent with concurrent rapid-fractionation RT.

Gemzar is a potent radiation sensitizer of human pancreatic cancer cells, and laboratory studies suggest that gemzar lowers the threshold for radiation-induced tumor-cell apoptosis. Gemzar is also a systemic agent utilized for advanced pancreatic cancer. In another trial from M.D. Anderson, the Gem-XRT trial, subjects with biopsy-proven, potentially resectable adenocarcinoma of the pancreatic head or uncinate process received 7 weekly infusions of Gemzar (400 mg/m2) and 30 Gy of EBRT (3 Gy/Fx, M-F over 2 weeks beginning 3 days after the first dose of gem).[7] Eighty six subjects were enrolled, all subjects completed the radiation component, and 85 of 86 subjects underwent restaging evaluation. Pancreaticoduodenectomy (PD) was successfully performed in 64 (74%) of 86 subjects. The median overall survival of all 86 subjects was 22.7 months (95% CI 15.9, 29.5); the median progression-free survival was 15.4 months (95% CI 7.8, 23.0). The 5-year survival for all 86 subjects was 27%. Following surgical resection, local recurrences were rare (11%; isolated local recurrence in 3%) and the dominant site of failure was distant metastases, since pancreatic cancer is a systemic disease in most subjects. Therefore, the next trial, Gem-Cis-XRT was designed in response to this pattern of recurrence by delivering more systemic therapy using Gemzar-cisplatin followed by Gemzar-based chemoradiation, since at the time, a Gemzar-cisplatin doublet was showing promising activity in advanced disease. Results from this trial were not superior to those observed with Gem-XRT. The median survival for the 52 subjects who underwent PD after Gem-Cis-XRT was 31 months; less, although not statistically different, than the 34 month median survival observed for the 64 subjects who underwent PD following Gem-XRT (p=0.41).

There was insufficient power to detect differences in survival based upon the sizes of the 2 study populations, and it remains unclear if there were other confounding variables unique to such complicated treatment sequencing in subjects with pancreatic cancer. The higher incidence of local recurrence following surgery in this trial compared to Gem-XRT may be due to the greater proportion of subjects with T3 and/or N1 disease, the location of the primary tumor in relation to the SMA, and the unknown potential for chemotherapy given prior to chemoradiation to enhance radiation resistance. Therefore, to summarize, there have been multiple trials with encouraging results using neoadjuvant therapy for resectable pancreas cancer, but few trials addressing the new criteria of borderline resectability.

A recent phase II study of chemoradiotherapy in the borderline and unresectable population has been performed at the New York University Cancer Institute.[8] The treatment was well-tolerated with only 3 cases of grade-4 toxicity (fever and neutropenia). Four out of 26 subjects in this study were converted from unresectable to resectable status and underwent potentially curative surgery. The only other study to address this population included subjects with less advanced disease, employed a more liberal definition of borderline resectability, and excluded subjects with unresectable disease.[5] In this retrospective study of 160 subjects from M. D. Anderson Cancer Center, 78% of the study subjects completed preoperative therapy and restaging, and 41% underwent pancreatectomy. Vascular resection was required in 18 (27%) of 66 subjects, and 62 (94%) underwent pancreatectomy with a margin-negative resection. A partial pathologic response to induction therapy (< 50% viable tumor) was seen in 37 (56%) of 66 subjects. Median survival was 40 months for the 66 subjects who completed all therapy and 13 months for the 94 subjects who did not undergo pancreatectomy ($p < 0.001$). It remains controversial, however, whether chemo-radiation therapy can convert a subject from borderline or unresectable status to resectable.

Rationale for the design of the current trial for Gemzar as a chemosensitizer in pancreatic cancer:

In-vivo studies using colon and pancreatic cancer cell lines demonstrated that timing and duration of exposure are more important than the dose in determining the radiosensitizing effect of gemcitaibine.[9] Cell kill was the greatest when the cells were incubated with Gemzar for the full 24 hours prior to irradiation. Furthermore, increasing the dose of Gemzar by 100 folds (from 0.1 to 10 μM) in a four-hour-exposure experiment did not increase radiosensitization. In in-vivo studies, the administration of Gemzar between 24 to 60 hours prior to radiation was associated with the longest growth delays of xenografts.[10] Another study showed that the administration of small dose of Gemzar twice weekly during radiation resulted in significantly smaller tumors than one large dose of Gemzar in a xenograft animal model.[11] A clinical study investigating twice a week Gemzar in addition to radiation therapy (50.4 Gy) showed that the maximum tolerated dose was 60 mg/m^2, with gastrointestincal and hematologic toxicities being dose-limiting.[12] The dose of 40 mg/m^2 was chosen to move to phase II clinical trial in locally advanced, non-metastatic pancreatic cancer subjects, and was used in combination with conventional radiation therapy (50.4 Gy in 180 cGy daily fractions over 5.5 wk). The main toxicities from this regimen were nausea and vomiting (44% and 49%) and neutropenia (40%).[13] Median survival was 8.2 months and local recurrence rate was 15% only. Side effects on these trials were attributed to a large radiated volume to encompass the regional nodal basins. Another trial evaluating gemcitabine and radiation in the adjuvant setting reported infrequent grade III/IV gastrointestinal or hematologic toxicities.[14] These trials showed the feasibility of integrating Gemzar and radiation. The encouraging overall survival rates from neoadjuvant trials support the continued

investigation of gemcitabine and radiation therapy.[7] However, neither the optimal dose/schedule of Gemzar nor the appropriate dose/schedule of radiation are fully defined.[15] The schedule dependency of single-agent Gemzar was explored in a phase I study that showed that the maximum tolerated dose in continuous infusion is 8 mg/m^2/d (32 mg/m^2/course over 96 hours) when given every 3 wk, or 6 mg/m^2/d (24 mg/m^2/course over 96 hours) when given every 2 wk.[16]

Based on the pharmacokinetic of Gemzar, its schedule dependency and potential toxicity when combined with radiation therapy, we designed our study to take advantage of the present knowledge to optimize efficacy and minimize toxicity. We propose to administer Gemzar as a continuous infusion at the dose of 6 mg/m^2 over 24 hours on Day One that will be followed by radiation therapy on Day Two. The same treatment will be given for five times over ten days alternating chemotherapy and radiation therapy. (See study calendar).

OBJECTIVES

Primary Objectives

1. To assess the margin-negative resection rate (R0RR) in subjects with unresectable or borderline resectable adenocarcinoma of the pancreas treated with preoperative chemotherapy with external-beam radiation therapy followed by surgery.

Secondary Objectives

1. To assess the safety of preoperative chemotherapy with radiation therapy for subjects with unresectable or borderline resectable adenocarcinoma of the pancreas
2. To assess disease-free survival
3. To assess overall survival
4. To determine patterns of local and distant recurrence

DESIGN AND METHODS

Subjects with unresectable or borderline resectable pancreatic cancer will be offered participation in the study. Subjects may be inpatient or outpatients. Subjects should have a contrast CT scan within 28 days of enrollment. Unresectability or borderline resectability will be defined based on radiologic (CT scan) and operability will be defined based on clinical criteria (see eligibility criteria), and concurrent chemotherapy and radiation therapy will be administered as defined by the protocol. Chemotherapy will consist of 24-hour-continuous infusion of Gemzar on days 1, 3, 5, 7 and 9, while radiation therapy will consist of 7.0 Gy administered on days 2, 4, 6, 8, and 10. At the completion of this treatment, the subjects will be given a 4-week break before they undergo restaging CT scan. Restaging will define two groups of subjects: those whose disease progressed locally or who developed distant metastatic disease, and those whose disease has responded or remained stable. Subjects whose disease progressed locally or who developed distant metastatic disease will be removed from the study. Subjects whose disease did not progress will proceed to surgery with exploratory laparotomy to assess resectability, and if their cancer is resectable, they undergo pancreatectomy. Within twelve weeks after surgery, subjects will start adjuvant chemotherapy with weekly Gemzar for six months as per standard of care. After completion of study–related treatment, subjects will be followed until recurrence and/or death up to five years.

STUDY CALENDAR																	
	Pre-Treatment Evaluation ≤ 28 days	Screening	Day											Pre-Operative Evaluation Day 35 (+/- 3d)	Surgery Day 38 (+/- 3d)	Post Surgery Evaluation ≤122 d	Survival Follow-up Q 6 months
			T	W	R	F	S	Sun	M	T	W	R	F				
H&P & Concurrent Meds	X					X								X		X	
Consent		X															
Vital Signs[a]	X		X		X	X				X		X		X		X	
Kidney function [b]	X					X								X		X	
Blood Chemistries[c]	X		X											X		X	
Liver Function (LFT's)[d]	X					X								X		X	
CBC[e]	X					X						X		X		X[i]	
Pregnancy Test (urine or serum)	X																
Ca19-9														X			
CT chest, abdomen, and pelvis[f]	X													X		X[j]	X
Adverse Events [g]			X	X	X	X		X	X	X	X	X	X	X	X	X	
Preop XRT				X		X			X		X		X				
Preop chemo			X		X			X		X		X					
Surgery															X		
Tissue for correlative studies															X		
Post operative chemotherapy																X[h]	

*See the Study Calendar Footnotes on the following page.

Study Calendar Footnotes:

a. Vital signs: blood pressure and pulse rate
b. Kidney Function includes BUN and Creatinine
c. Blood Chemistries: Bilirubin, alkaline phosphatase, ALT, AST, , phosphorus, calcium, glucose, total protein, albumin, and electrolytes [sodium, potassium, CO2, chloride, and magnesium]
d. Liver function includes: AST, ALT, GGT, alkaline phosphatase, LDH, and bilirubin.
e. Complete Blood Count (CBC): Hemoglobin, hematocrit, red blood cells [RBC], white blood cells [WBC], platelets, and differential blood cell counts such as: neutrophils, lymphocytes, monocytes, eosinophils, basophils)
f. Biphasic (arterial and venous CT of the abdomen with ≤ 3mm thick axial slices.
g. All adverse events occurring during any part of the study will be reported appropriately to the IRB.
h. Post operative chemotherapy treatment every weeks for 3 weeks and 4^{th} week no treatment
i. CBC will be drawn prior to start of each chemotherapy treatment
j. CT of chest, abdomen, and pelvis prior to start of cycles 1, 3, 5. (1 cycle = 28 days)

Eligibility criteria

Inclusion Criteria:

1. Ages 18 years and above. There will be no upper age restriction.
2. ECOG performance status ≤ 2. (See Appendix A –ECOG Performance Status Scale).
3. Cytologic or histologic proof of adenocarcinoma of the pancreas.
4. Adequate renal, and bone marrow function:
    a. Leukocytes >= 3,000/uL
    b. Absolute neutrophil count >= 1,500/uL
    c. Platelets >= 100,000/Ul
    d. Serum creatinine <= 2.0 mg/dL
5. Hepatic function (endoscopic or percutaneous drainage as needed)
    a. AST (SGOT)/ALT (SGPT) <= 5 X institutional ULN
6. Borderline resectable pancreatic cancer:
    a. Short segment hepatic artery abutment (< 180° involvement)
    b. Tumor abutment (<180°) of superior mesenteric artery
    c. Superior mesenteric/portal vein involvement beyond that of a simple resection and reconstruction
    d. Pancreatitis that obscures the determination of vessel involvement and may preclude an otherwise curative operation
7. Unresectable pancreatic cancer:
    a. Tumors that encase (> 180° involvement) single or multiple arteries and veins (celiac axis, superior mesenteric artery, superior mesenteric/portal vein, hepatic artery)
    b. Occlusion of superior mesenteric/portal vein

Exclusion Criteria:

1. Infections such as cholangitis, pneumonia, or wound infections that would preclude protocol therapy.
2. Women with a positive urine or serum pregnancy test are excluded from this study; women of childbearing potential (defined as those who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months) must agree to refrain from breast feeding and practice adequate contraception as specified in the informed consent. Adequate contraception consists of oral contraceptive, implantable contraceptives, injectable contraceptives, a double barrier method, or abstinence.
3. Subjects cannot have known heptic or peritoneal metastases detected by ultrasound (US), CT scan, or laparotomy/laparoscopy prior to treatment.
4. Subjects with unstable angina or New York Heart Association (NYHA) Grade II or greater congestive heart failure will be excluded (see Appendix B).
5. Known presence of central nervous system or brain metastases
6. Subjects with prior radiotherapy to the upper abdomen or liver will be excluded.
7. Subjects will be excluded if deemed unable to comply with study and/or follow-up procedures.

8. Subjects with a known hypersensitivity to Gemzar are excluded.
9. Multiple positive lymph nodes, which will make the radiotherapy treatment volume too large. Peripancreatic involved nodes can be included in the radiotherapy treatment volume if the field of involved nodes is less than 7.5cm.

Informed Consent will be obtained.

Type of Study: Prospective phase II, single institution clinical trial.

Procedures and Treatment Plan

1. **Preoperative Therapy:**
   a. Gemzar: 6 mg/M^2/24 hours on day 1, 3, 6, 8 and 10. External beam radiation therapy will be delivered at 7.0 Gy each on days 2, 4, 7, 9 and 11. Subjects may miss up to 2 doses of chemotherapy and/or 2 treatments of radiation. Subjects missing more than 2 chemotherapy or radiation treatments will be removed from the protocol. If any days of chemotherapy and radiation are missed, these days will be made up prior to day 122. Chemotherapy and radiation therapy will be given in the same sequence as pre-operative treatment.

2. **Postoperative Therapy:**
   a. All subjects will get baseline restaging scans after surgery prior to starting postoperative adjuvant therapy) within 4 weeks prior to beginning adjuvant therapy. Gemzar - 1000 mg/M2 IV over 30 min; Days 1, 8, 15 q 28 days +/- 3 days for 6 cycles beginning within 12 weeks of surgery (repeat restaging scans after every 2 cycles of therapy. Subjects not able to start chemotherapy within 12 weeks of surgery will be removed from the protocol.

Dose Adjustments for Preoperative Gemzar:

(1) Gemzar Dose Adjustment/Modifications for days 5 and 8 of preoperative Gemzar

Table 1: Hematologic Toxicities - Dose Adjustment of Gemzar during a cycle

ANC (x10^3/mcl)	Platelets (x10^3/mcl)	Percent dose of Gemzar[1]
> or = 1.5	And > or = 100	100
1-1.49	Or 75-99	50
<1	Or <75	0
[1.] Percent dosage refers to the dose of drugs on the first day of the cycle.		

Table 2: Non-Hematological Toxicity due to Gemzar (Excluding alopecia, inadequately treated nausea and vomiting)

Worst toxicity during previous cycle	Percent of Gemzar dose from the previous cycle[1]
Grade 0/1	100
Grade 2	75
Grade 3-4	50
[1.] Percent dosage refers to the dose of drugs on the first day of the cycle.	

(2) Gemzar Intracycle Dose Adjustment/Modifications (days 8 and 15 of each postoperative cycle)

Table 3: Hematologic Toxicities - Dose Adjustment of Gemzar during a cycle

ANC ($x10^3$/mcl)	Platelet ($x10^3$/mcl)	Percent dose of Gemzar[1]
> 1.0	And >75	100
0.51-0.99	Or 51-74	50
<0.5	Or <50	0
[1.] Percent dosage refers to the dose of drugs on the first day of the cycle.		

(3) Intra-cycle Dose Adjustments for Non-Hematological Toxicity due to Gemzar (excluding alopecia, nausea, vomiting, and diarrhea, ocular visual and dermatological), based on the NCI- Common Toxicity Criteria v.3, as follows:

Table 4: Non-Hematologic Toxicities - Dose Adjustment of Gemzar during a cycle

Worst toxicity during cycle	Percent dose of Gemzar[1]
0/1	100
2	75
3-4	0
[1.] Percent dosage refers to the dose of drugs on the first day of the cycle	

(3) Dose Adjustments of Gemzar on Subsequent Treatment Cycles (Based on the worst toxicity due to Gemzar on any day of the previous cycle).

Table 5: Hematological Toxicity due to Gemzar

Worst toxicity in previous cycle		Percent in Gemzar dose from the previous cycle[1]
ANC	Platelets	
<0.5	or <50	75
0.5-0.99	or 51- 74	75
>1.0	and >75	100
[1.] Percent dosage refers to the dose of drugs on the first day of the previous cycle.		

Note: The physician should keep reducing doses in subsequent cycles if still faced with significant hematological toxicity. Subject may have a maximum of 2 dose reductions on the protocol. If greater than 2 dose reductions are necessary, the subject will be removed from the protocol.

Table6: Non-Hematological Toxicity due to Gemzar (Excluding alopecia, inadequately treated nausea and vomiting)

Worst toxicity during previous cycle	Percent of Gemzar dose from the previous cycle[1]
Grade 0/1	100
Grade 2	75
Grade 3-4	75
1. Percent dosage refers to the dose of drugs on the first day of the cycle.	

Note: The physician should keep reducing the doses in subsequent cycles if still faced with significant hematological toxicity. Subjects may have a maximum of 2 dose reductions on the protocol. If greater than 2 dose reductions are necessary, the subject will be removed from the protocol.

Radiation Therapy

1. Pre-CT Simulation imaging studies:
    a. Biphasic (arterial and venous) CT of the chest, abdomen, and pelvis with ≤ 3mm thick axial slices.

2. CT-Simulation:
   Subjects are placed in the supine position using an alpha-cradle as an immobilization device. A respiratory gated (4D) CT scan of 2mm slice thickness with oral contrast is obtained for radiotherapy planning.

3. Tumor motion evaluation:
   The 4D CT is reconstructed into the 0, 25, 50 and 75% phases of the respiratory cycle for superior-inferior tumor motion evaluation in the coronal plane. For tumors with motion of ≤ 5mm in the superior to inferior plane no respiratory gating is needed to account for tumor motion. In this case a 0 to 90% respiratory phase maximum intensity projection (MIP) axial scan is to be used for target segmentation and the 25% respiratory phase axial scan is to be used for actual treatment planning. For tumor motion larger than 5mm the 35 to 65% respiratory phase MIP axial scan is used for target segmentation and the 50% respiratory phase axial scan is used for planning. Tumor and normal organ segmentation is done in the radiotherapy planning station with capabilities of image fusion.

4. Gross Tumor Volume (GTV) Segmentation:
   To account for all respiratory-associated movement, as well as potential deformation of the tumor during the respiratory cycle, the GTV is contoured on the MIP axial scans. An additional 3 to 5mm circumferential expansion is to be used to create the planning target volume (PTV).

5. Segmentation of nodal regions:
   No prophylactic radiotherapy is to be given to the regional lymph nodes.[17-19]

6. Segmentation of normal structures:

The following normal structures need to be contoured:

a. Stomach
b. Duodenum
c. Bowel
d. Liver
e. Kidney
f. Spinal cord

7. Stereotactic Treatment Planning:
   Intensity modulated stereotactic planning with co- or non-coplanar beams arrangements will be custom designed for each case to deliver highly conformal prescription distributions. Non-opposing, non-coplanar beams are preferable. Typically, ≥ 10 beams of radiation will be used. Generally, more beams are used for larger lesion sizes. In order to obtain acceptable coverage, field aperture and shape should correspond nearly identically (2mm) to the projection of the PTV along a beam's eye view. Prescription lines covering the PTV will typically be the 60-90% (from a maximum dose of 100%). Higher isodoses must be manipulated to occur within the PTV and not in adjacent normal tissue.

8. Prescription dose constraint:
   a. Prescription: 35Gy in five equal fractions, one fraction every other day.
   b. Maximum dose: 100% corresponds to the maximum dose and must exist within the PTV.
   c. Prescription isodose: will be chosen such that 95% of the PTV is conformally covered by the prescription isodose surface and 99% of the PTV recceivs at least 90% of the prescription dose.
   d. Conformality: Conformality of the PTV coverage will be judged such that the ratio of the volume of the prescription isodose to the volume of the PTV is ideally < 1.2.

9. Critical organ dose-volume limits:
   The following table lists recommended maximum dose limits to a point or volume within several critical organs:

ORGAN	DOSE LIMIT
Liver	Average dose: 10Gy (2Gy/fraction)
Kidney	Average dose: 10Gy (2Gy/fraction)
Spinal Cord	Maximum dose: 20Gy (4Gy/fraction)
Stomach	Maximum dose: 28.75Gy (5.75Gy/fraction); 50% of volume 25Gy (5Gy/fraction)
Duodenum	Maximum dose: 28.75Gy (5.75Gy/fraction); 50% of volume 25Gy (5Gy/fraction)
Other Bowel	Maximum dose: 28.75Gy (5.75Gy/fraction); 50% of volume 25Gy (5Gy/fraction)

10. Toxicity
    Adverse events with Gemzar Radiation Therapy:

Likely	Less Likely	Rare but Serious
Nausea and vomiting	Fever	Liver dysfunction
Abdominal pain	Muscle aches	Renal dysfunction
Gastrointestinal discomfort	Rash	Bowel obstruction
Diarrhea	Headaches	Gastric ulceration
Fatigue	Muscle weakness	Duodenal ulceration
Transient skin erythema	Confusion	Small bowel ulceration
Dry skin over treatment area	Constipation	Gastrointestinal bleeding
Low blood counts		
Loss of appetite		
Weight loss		
Loss of hair		

Surgery
Surgery will be planned 28 days (+/- 3 days) after the last dose of chemotherapy. The liver and pancreas will be examined by palpation and inspection. In the absence of metastases, tumor mobilization and surgical resection will be performed with standard surgical technique.

Pathology
Pancreatic transection margin and the bile duct margin (if transected) will be evaluated on frozen section. Recorded on permanent section will be: tumor size, degree of differentiation (well, moderate, poor), margin status, lymph node status, and degree of treatment effect.

Background drug Information

1. Gemzar:
   A chemotherapeutic drug used to treat pancreatic cancer, Non-small cell lung cancer, Bladder cancer, Soft-tissue sarcoma, and Metastatic breast cancer.[20] Gemzar is classified as an antimetabolite. During a certain stage in mitosis pyrimidine is needed to complete the process of cellular division. Gemzar works by interfering with the metabolism of pyrimidine which inhibits cell division and growth.

2. Chemistry:
   Gemzar HCl is 2`-deoxy-2`, 2`-difluorocytidine monohydrochloride (β-isomer).

3. Clinical Pharmacology:
   Gemzar pharmacokinetics is linear, and is described by a 2-compartment model. Population pharmacokinetic analyses of combined single-and multiple-dose studies showed that the volume of distribution of Gemzar was significantly influenced by duration of infusion and gender. Clearance was affected by age and gender. Differences in either clearance volume or distribution based on

subject characteristics or the duration of infusion results in changes in half-life and plasma concentrations. The half-life of Gemzar for short infusions ranged from 32-94 minutes, and the value for long infusions varied from 245-638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The lower clearance in women and the elderly result in higher concentrations of Gemzar for any given dose. The volume of distribution was increased with infusion duration. Volume of distribution of Gemzar was 50 L/m^2 following infusions lasting <70 minutes, indicating that Gemzar, after short infusions, is not extensively distributed into tissues. For longer infusions, the volume of distribution rose to 370 L/m^2, reflecting slow equilibration of Gemzar within the tissue compartments. The maximum plasma concentrations of dFdU (inactive metabolite) were achieved up to 30 minutes after discontinuation of infusions, and the metabolite was excreted in urine without undergoing further biotransformation. The metabolite did not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function. The effects of significant renal or hepatic insufficiency on the disposition of Gemzar have not been systematically assessed.

4. Human Toxicity:
    a. ***Hematologic:*** In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with Gemzar, but < 1% of subjects discontinued therapy for either anemia, leucopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of subjects. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of subjects; less than 1% of subjects required platelet transfusions. Subjects should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity.
    b. ***Gastrointestinal:*** Nausea and vomiting were commonly reported (69%) but were usually mild to moderate severity. Severe nausea and vomiting (WHO grade 3/4) occurred in <15% of subjects. Diarrhea was reported by 19% of subjects, and stomatitis by 11% of subjects.
    c. ***Hepatic:*** In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of subjects, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in subjects receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.
    d. ***Renal:*** In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic-Uremic Syndrome (HUS) were reported in 6 of 2429 subjects (0.25%) receiving Gemzar in clinical trials. Four subjects developed HUS on Gemzar therapy, two immediately post-therapy. Diagnosis of HUS should be considered if the subject develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, retculocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of

serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required. HUS and/or renal failure have been reported following one or more dose of Gemzar since Gemzar has been on the market. Renal failure leading to death or requiring dialysis, despite continuation of therapy, has been rarely reported. The majority of cases of renal failure leading to death were due to HUS.

e. ***Fever:*** The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.
f. ***Rash:*** Rash was reported in 30% of subjects. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild-to-moderate severity, involving the trunk and extremities. Pruritus was reported in 13% of subjects.
g. ***Pulmonary:*** In clinical trials, unrelated to underlying disease, has been reported in associated with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions. Parenchymal toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary adema, and adult respiratory distress syndrome (ARDS), has been reported rarely following one or more doses of Gemzar administered to patients with various malignancies. Some subjects experienced the onset of pulmonary symptoms up to 2 weeks after the last Gemzar dose. Respiratory failure and death occurred very rarely in some patients despite discontinuation of therapy.
h. ***Edema:*** Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of subjects discontinued due to edema.
i. ***Flu-like Symptoms:*** "Flu syndrome" was reported for 19% of subjects. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia, were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of subjects discontinued due to flu-like symptoms.
j. ***Infection:*** Infections were reported for 16% of subjects. Sepsis was rarely reported (<1%).
k. ***Alopecia:*** Hair loss, usually minimal, was reported by 15% of subjects.
l. ***Neurotoxicity:*** There was a 10% incidence of mild parasthesias and a <1% rate of severe parasthesias.
m. ***Extravasation:*** Injection-site-related events were reported for 4% of subjects. There were no reports of injection-site necrosis. Gemzar is not a vesicant.

n. ***Allergic:*** Bronchospasm was reported for less than 2% of subjects. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to subjects with a known hypersensitivity to this drug.
o. ***Cardiovascular:*** During clinical trials, two percent of subjects discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these subjects had a prior history of cardiovascular disease. Congestive heart failure and myocardial infarction have been reported very rarely with the use of Gemzar. Arrhythmias, predominantly supraventricular in nature, have been reported very rarely.
p. ***Vascular Disorders:*** Clinical signs of peripheral vasculitis and gangrene have been reported very rarely.
q. ***Skin:*** Cellulitis and non-serious injection site reactions in the absence of extravasation have been rarely reported. Sever skin reactions, including desquamation and bullous skin eruptions, have been reported very rarely.
r. ***Hepatic:*** Increased liver function tests including elevations in aspartate aminotransferase (AST), alaine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, Lactate dehydrogenase (LDH), and bilirubin levels have been reported rarely. Serious hepatotoxicity including liver failure and death has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.
s. ***Injury, Poisoning, and Procedural Complications:*** Radiation recall reactions have been reported.

5. Pharmaceutical Data:
Gemzar is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 g of Gemzar as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate. Drug vials will be reconstituted with normal saline added to the vial to make a solution ideally containing 10 mg/mL or less. The concentration for 200 mg and 1 g vials should be nor greater than 40 mg/mL. An appropriate amount of drug will be prepared with normal saline and administered as a continuous infusion at 6 mg/m^2/24 hours x 5 (on day 1, 3, 5, 7 and 9; total dose 30 mg/m^2/ten days). Once the drug has been reconstituted, it should be stored at room temperature and used within 24 hours.

6. Storage and Stability:
Store at controlled room temperature (20-25^{0}C), should be handled and disposed of in a manner consistent with other anti-cancer drugs.

7. Route of Administration:
Intravenous continuous infusion at fixed dose rate of 6mg/m^2/24h.

8. Supplier:
Gemzar is commercially available from Eli Lilly and Company, Indianapolis, Indiana.

Pretreatment Evaluation
Within 28 Days Prior to Study Enrollment: Subjects must have appropriate lab and radiographic studies (CT chest, abdomen and pelvis); CBC; blood chemistries; liver function tests; kidney function test; and pregnancy test) conducted prior to study enrollment to meet eligibility criteria. A history and physical, concurrent medications, and vitals will also be collected during the pre-treatment evaluation. These studies are considered standard of care in the evaluation and treatment of patients with pancreatic cancer.

Preoperative Evaluation:

1. During therapy, a study investigator or oncology nurse must see each subject before Tuesday and Sunday of pre-operative chemotherapy, +/- 3 days respectively and at the pre-operative evaluation visit.
2. The subject will be assessed as follows:
    a. Complete blood count (CBC: hemoglobin, hematocrit, red blood cells [RBC], white blood cells [WBC], platelets, and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils) before day 1 and 5 of Gemzar.(+/- 2 days)
    b. Blood chemistries (bilirubin, alkaline phosphatase, ALT, AST, phosphorus, calcium, glucose, total protein, albumin, and electrolytes [sodium, potassium, CO2, chloride, and magnesium] on day 1.
    c. Kidney Function: includes BUN and creatinine
    d. Liver function: AST, ALT, GGT, alkaline phosphatase, LDH, and bilirubin.
    e. History and physical and concurrent medications will be collected.
    f. Vital signs (blood pressure and pulse rate)will be collected.
    g. Subjects must have a WBC count greater than or equal to 3000 cells/uL and platelet count greater than or equal to 100,000 cells/IU to meet eligibility criteria.
3. After completion of treatment, subjects will have approximately a 4 week rest period followed by a restaging chest, abdomen, and pelvis CT scan, Ca19-9 and then surgery.

Post-surgery Evaluation:
Within 12 weeks after surgery, the subject will have:

1. Complete blood count: hemoglobin, hematocrit, RBC, WBC, platelets), and differential blood cell counts (neutrophils, lymphocytes, monocytes, eosinophils, basophils) before each dose of Gemzar.
2. Blood chemistries (bilirubin, alkaline phosphatase, ALT, AST, BUN, creatinine, phosphorus, calcium, glucose, total protein, albumin, and electrolytes [sodium, potassium, CO2, chloride, and magnesium]) every 4 weeks ± 2 days.
3. Vital signs (blood pressure and pulse rate) on days of infusion prior to treatment.
4. Within 12 weeks (13 to 17 weeks +/- 2 days after enrollment) of completion of surgery, subjects with an adequate performance status will be considered for adjuvant therapy with Gemzar. A restaging scan will be required prior to starting adjuvant therapy and will be repeated prior to cycles 1, 3, and 5 of postoperative therapy.

Survival:

1. The primary endpoint in this study is resection rate. Survival will be followed as a secondary endpoint, as measured from the time of histologic or cytologic diagnosis of pancreatic adenocarcinoma. Patterns of tumor recurrence and survival will be assessed by reviewing routine surveillance CT scans.
2. After completion of Gemzar adjuvant chemotherapy. All subjects will be followed with a CT scan of the chest, and abdomen with/without pelvis approximately every 6 months following surgery for five years.

Criteria for Removal from Study:

1. Inability of subject to comply with study requirements
2. Determination by the investigator that it is no longer safe for the subject to continue therapy
3. Local progression or metastatic disease after chemoradiation.

Statistical Considerations:

1. This is a single-arm phase II study of preoperative chemotherapy (Gemzar) with radiation therapy in subjects with borderline resectable or unresectable pancreatic adenocarcinoma. The primary objective is to assess margin-negative resection rate (R0RR) after preoperative chemotherapy with radiation therapy for subjects with unresectable or borderline resectable adenocarcinoma of the pancreas. R0RR is defined as percentage of subjects with R0R compared to the total number of subjects who entered the trial.
2. Secondary endpoints include an assessment of safety of preoperative chemotherapy and radiation therapy in this population. Other secondary endpoints include disease-free survival, overall survival, and the patterns of recurrence (local, regional, or distant).
3. A total of 20 subjects will be accrued at a rate of 1-2 subjects per month. Approximately 24% of subjects will likely not undergo surgery (from the MD Anderson experience; due to distant metastases on restaging), which results in an estimated total ±margin of error of approximately 15±4 subjects.
4. The UAMS CCTO will collect the data.
5. Statistical Methods: Subjects with pancreatic cancer will undergo an initial "baseline" assessment via CT scan. On the basis of their baseline CT scan, subjects with pancreatic cancer are staged into three groups: Resectable (~20% of total), locally advanced/unresectable (35%–40% of total), and Metastatic (40% of total). The protocol proposes to recruit subjects in the Locally Advanced group, treat them with a combination of Gemzar and radiation, administer another CT scan at Day 37 (±2 days) after treatment commences, and determine from the CT scan the proportion of subjects who have progressed locally or developed metastatic disease. Subjects who have evidence of progression (local progression or metastatic spread) will not be taken to surgery. All the other subjects will be offered exploratory laparotomy for resection. **The maximum feasible accrual is estimated to be 20 subjects in a one-year period, and the target sample size is thus 20 subjects. We expect to screen approximately 40 subjects in order to achieve our enrollment goal of 20 subjects at the University of Arkansas for Medical Sciences.** A 30% R0 resection rate

(R0RR) would be considered evidence of treatment efficacy, whereas a 10% R0RR would not.

6. Statistical Analysis: This is a phase II study designed to obtain preliminary estimate of the R0RR associated with the proposed treatment, for purposes of determining the feasibility of a future larger randomized clinical trial. In this pilot study, the two most important pieces of information will be (1) the "point estimate" or observed proportion of subjects who underwent R0 resection after their treatment, and (2) the "interval estimate" or exact binomial 2-sided 90% confidence interval on the observed proportion R0RR. Twenty subjects with locally advanced pancreatic cancer will be enrolled, treated, and assessed via CT scan then explored for whether their disease has become resectable following treatment. The table below shows the observed proportions, and the upper and lower 90% confidence limits on each observed proportion that we would obtain if from four to seven subjects (out of 20 enrolled) underwent resection with successful R0 outcome following treatment.

Number R0RR	Observed Proportion	90% Lower Conf Limit	90% Upper Conf Limit
4	0.20	0.0714	0.4010
5	0.25	0.1041	0.4556
6	0.30	0.1396	0.5078
7	0.35	0.1773	0.5580

It should be noted that the 90% lower confidence limit will be above 0.10 if the number of R0 resections is 5 or more. Inasmuch as a R0RR of 0.10 represents lack of treatment efficacy, this result indicates that 20 subjects will confer enough precision on the observed proportion R0RR to meet the information-collection goals of this pilot study.

For secondary analyses, overall survival is defined as the time from enrollment to death or last follow-up. Disease-free survival is defined as the time from surgery to progression or death or last follow-up, whichever occurs first. Kaplan-Meier method will be used to estimate the overall survival. Disease-free survival will also be estimated using the Kaplan-Meier method. The Kaplan-Meier method also will be used to generate the curves of the time to local or distant failure.

DATA AND PROTOCOL MANAGEMENT

Study management will be handled by the Cancer Clinical Trials Office (CCTO) in the Winthrop P. Rockefeller Cancer Institute, 4301 West Markham, Slot #724, Little Rock, AR 72205.

After informed consent is obtained, subjects will be registered on the trial by CCTO.

ADVERSE EVENTS REPORTING REQUIREMENTS

Investigators are required to report to the UAMS IRB ALL serious treatment emergent adverse event (STEAE) as soon as possible. The methods for collecting safety data are described below.

Adverse Events

1. Definitions
   The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The principal investigator is responsible for ensuring this.

2. Adverse Event (AE)
   An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), or signs (e.g., tachycardia, enlarged liver). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

3. Serious Adverse Event (SAE)
   A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills one or more of the following criteria:
   a. Results in death
   b. Is immediately life-threatening
   c. Requires in-subject hospitalization or prolongation of existing hospitalization
   d. Results in persistent or significant disability or incapacity
   e. Is a congenital abnormality or birth defect in the offspring of the subject
   f. Is an important medical even that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

   Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening, or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

   The causality of SAEs (i.e., their relationship to study treatment) will be assessed by the investigator(s), who in completing the relevant case report form must answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the drug?”

4. Other Significant Adverse Event (OAE)

OAEs will be identified by the Drug Safety Physician and if applicable also by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative may be written and included in the Clinical Study Report.

Recording of Adverse Events:
Any detrimental change in a subject's condition, subsequent to the subject entering the study should be considered an AE.

Method of detecting AE/SAE:
At each visit the method of detecting AE and SAEs in this study will be by:

1. Information volunteered by the subject, or caregiver
2. Open-ended and non-leading verbal questioning of the subject at every visit such as the following: *How are you feeling? Have you had any (other) medical problems since your last visit*
3. Observation by the investigational team, other care providers or relatives

AUDITS AND INSPECTIONS

Regulatory authorities or the Institutional Review Board (IRB) may perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

TRAINING OF STAFF

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). Dr. Makhoul will ensure that appropriate training relevant to the study is given to all study staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

A Site Initiation Visit will be conducted at the University of Arkansas for Medical Sciences for UAMS staff.

CHANGES TO THE PROTOCOL

Study procedures will not be changed without approval from the IRB. If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (Amended Protocol) must be approved by the UAMS IRB, and if applicable, by

the local regulatory authority, before implementation. Local and federal (Food and Drug Administration [FDA]) requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB and study sponsor is required before the revised form is used.

The principal investigator is responsible for the distribution of these documents to the sub-investigators and staff involved with the study.

ETHICS

Ethics Review:
The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by the UAMS IRB. The principal investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually.

Ethical Conduct of the Study:
The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

Written Informed Consent:
The principal investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator must store the original, signed Written Informed Consent Form in the subject's medical record as well as his/her study subject file. A copy of the signed Written Informed Consent Form must be given to the subject. The consent process will be documented in the subject's medical records.

Subject Data Protection:
The Written Informed Consent Form will explain that for data verification purposes, a regulatory authority, and the IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

EMERGENCY PROCEDURES

Procedures in Case of Medical Emergency:
The principal investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study.

Procedures in Case of Overdose:
There is currently no known antidote for Gemzar. The treatment of AEs associated with overdose should be supportive for the underlying adverse symptoms.
Doses of study treatment in excess of that specified in the clinical study protocol are considered to be an overdose. Overdose, with or without associated symptoms should be handled in the same way as a deviation and sent to IRB. Signs or symptoms of an overdose that meet the criteria of serious should be reported as a SAE in the appropriate timeframes and be documented as clinical sequelae to an overdose.

DATA SAFETY MONITORING PLAN

The principal investigator and all research staff associated with this trial have received training and certification in human subject protections research and are ultimately responsible for monitoring the safety of this trial.

The PI will continuously monitor this trial and more frequently safety related data. This trial will also be reviewed periodically by physicians and research staff at the Gastrointestinal Malignancy Group meeting.

Monitoring will be provided by the Research Support Center (RSC) for this clinical trial. The monitor will assure that the rights and well – being of human subjects are protected and the data are accurate, complete and verifiable from source documents and the trial is conducted in compliance with currently approved protocol/amendments, with good clinical practice (GCP) and the applicable regulatory requirements.

The monitor will be familiar with the protocol, the informed consent form, any other information provided to the subjects, the standard operating procedures (SOP), GCP and applicable regulatory requirements.

Monitors will have access to subject medical records and other study-related records. The principal investigator agrees to cooperate with the monitor (s) to ensure that any problems detected in the course of these monitoring visits are resolved. Personal contact between the monitor and the investigator will be maintained throughout the clinical trial to assure that the investigator is fulfilling his obligations and the facilities used in the clinical trial remain acceptable.

Investigational Products:
Gemzar is the current standard of care for the treatment of pancreatic cancer. The doses used in this protocol are much smaller than usual for this drug. Radiation therapy for unresectable pancreatic cancer is also considered standard of care. The total dose used here is below usual too. The only difference with standard of care in the use of these therapeutic methods is the shortened schedule of chemoradiotherapy administration. In addition, we are attempting to perform margin negative surgery on subjects initially felt to be borderline or unresectable.

Monitoring Report:
After each monitoring visit a separate monitoring report will be generated and submitted to the principal investigator and project manager. This report will include significant

findings related to deficiencies and deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements and actions taken to prevent recurrence of the detected deviations. The report will make recommendations for actions to be taken to secure compliance.

Continuing Review:
An annual report will be compiled and sent to the IRB to report on number of subjects enrolled in the study and safety events and accrual schedule.

DATA QUALITY ASSURANCE AND DOCUMENTATION

CRF's should be filled by qualified personnel, reviewed, dated and signed by the investigator. The forms have to be completed in a neat and legible manner with black or blue ballpoint pen. No entries should be erased or over written or correction fluid or white out be used. Corrections can only be crossed out with a single line and should have the date and initials of the person making the change.

Source Documents are defined as original documents with original observations and information about the clinical investigation. All electronic source documents should be 21 CFR 11 compliant. Source documents will include progress notes, computer print outs, laboratory data and all recorded data from automated instruments. Monitor will review CRF's against source documentation for accuracy of the information. Subject Confidentiality will be maintained. CRFs will not include any personal identification information such as name etc. Subjects will be identified with Initials and subject study number only.

RETENTION OF RECORDS

All documentation related to this trial will be retained for 2 years after the investigator is complete.

TISSUE BANKING

All tissue samples will be collected according to UAMS Tissue bank SOPs. The subject will be asked to give permission for the storage of their pancreatic tumor tissue for future correlative studies that will include DNA, RNA or protein studies.

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Ref Type: Internet Communication

Appendix

A: ECOG Performance Scale

ECOG Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

B: New York Heart Association Class Scale

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.