Local Protocol #: 2012-570

TITLE: A phase II trial of preoperative FOLFIRINOX followed by gemcitabine based chemoradiotherapy in patients with borderline resectable pancreatic adenocarcinoma

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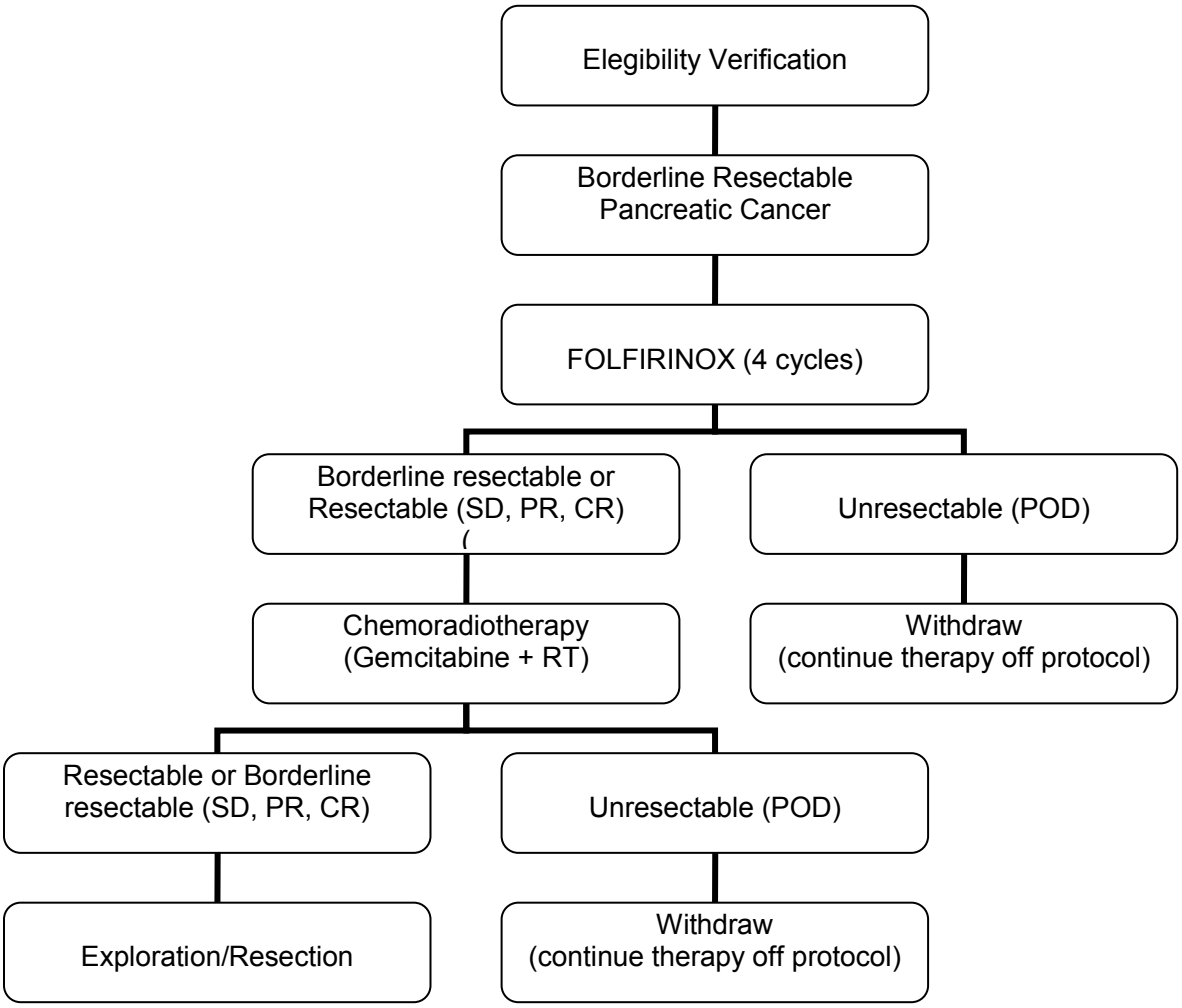
SCHEMA


Elegibility Verification
Borderline Resectable Pancreatic Cancer
FOLFIRINOX (4 cycles)
Borderline resectable or Resectable (SD, PR, CR)
Unresectable (POD)
Chemoradiotherapy (Gemcitabine + RT)
Withdraw (continue therapy off protocol)
Resectable or Borderline resectable (SD, PR, CR)
Unresectable (POD)
Exploration/Resection
Withdraw (continue therapy off protocol)

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1.0 OBJECTIVES

1.1 Primary Objective

To assess the efficacy, measured as the proportion of R0 resections, of FOLFIRINOX chemotherapy regimen followed by gemcitabine based chemoradiotherapy when used as preoperative therapy in patients with borderline resectable adenocarcinoma of the pancreas.

1.2 Secondary Objectives

- To measure the overall response rate (ORR).
- To evaluate overall survival (OS).
- To evaluate progression free survival (PFS).
- To evaluate safety and toxicity associated with chemotherapy and radiotherapy.
- To assess adverse events related to surgery.
- To assess the proportion of patients able to undergo resection.
- To assess proportion of patients requiring vascular reconstruction.

2.0 BACKGROUND

2.1 Pancreatic Cancer

The incidence of pancreatic cancer is 11.7 per 100,000 men and women of all races, being significantly higher in the black population (16.6 per 100,000). It is estimated that 44,000 people will be die of pancreas cancer in 2011. It is the fourth leading cause of cancer deaths; ranking only behind lung, colorectal and breast. It is an aggressive disease with a generally grim prognosis, with a 5-year survival rate of 5.5%. [1-3]. Surgery is the only hope for prolonged survival, however only 7% of cases present with localized disease [2].
The current standard of care for patients with "resectable" and "borderline resectable" disease is resection, generally involving a pancreatoduodenectomy, also known as Whipple procedure. Perioperative therapy is widely accepted as the standard of care for patients undergoing resection, given in the form of chemotherapy or chemoradiotherapy [4]. Ideally, patients should be exposed to all 3 modalities: surgery, radiation and chemotherapy. There is still debate among experts regarding which is the best approach in terms of sequence and combination of these modalities: chemotherapy followed by chemoradiotherapy vs. chemoradiotherapy vs. chemotherapy alone; postoperative (adjuvant) vs. preoperative (neoadjuvant) [5-6].
Besides all these efforts in finding the best strategy, the 2 and 5 year survival rate for patients with pancreas cancer that undergo resection are 40-50% and 15-20%.

2.2 Neoadjuvant therapy in pancreatic cancer

Different strategies of neoadjuvant chemotherapy and neoadjuvant chemoradiotherapy have been used in resectable and borderline resectable pancreatic cancer in an attempt to achieve better outcomes. These treatment strategies demonstrated to be feasible and helped identifying two 2 different groups of patients; 1) patients who respond and tolerate therapy well and will likely benefit from extensive surgery afterwards; and 2) patients who progress rapidly and develop

metastatic disease early on that probably would not have benefited from initial resection.
The use of neoadjuvant therapy is of particular importance in "borderline resectable" pancreatic cancer since this subgroup of patients needs downstaging of the tumor in order increase the chances of achieving clear margins or R0 resections at the time of surgery. Prior trials evaluating neoadjuvant therapy in patients with borderline resectable pancreas cancer were not uniformly done. They analyzed different patient populations (resectable, borderline resectable, unresectable/locally advanced), sometimes including more than one subgroup in a single trial. Also, the definition used to define resectable and borderline resectable tumors varied between the different studies (NCCN, surgeon's decision, and group guidelines). Furthermore, some of studies did not report resection margins (R0/R1) nor differentiate survival between resected or non-resected patients [7-15].
A group of trials conducted by the MD Anderson Cancer Center (MDACC) were done using the same inclusion criteria, making them appropriate for comparison [16-19] (see Table-1). These trials evaluated different chemoradiotherapy regimens in patients with "potentially respectable" (defined in Table-1) disease. The overall survival on patients who received preoperative chemoradiotherapy and underwent surgery was 20-34 months. The best outcomes were reported by Evans et al using a combination of Gemcitabine + RT (30Gy), with an overall survival of 34 months [17] . Patients who completed preoperative therapy but were unable to undergo resection had much worse outcomes with an overall survival of 7-10 months. The overall resection rate was 60-90%, with an R0 resection rate of 70-95%. Among all these trials, the vast majority of patients who underwent resection had distant recurrences (60-80%), mainly in the liver. The local recurrence rate was 10-25%. Surprisingly all the local failures were in patients who had R0 resection margins. The addition of induction chemotherapy followed by chemoradiotherapy (Gem/Cis, followed by Gem/RT) was attempted to decrease the distant recurrences and improve survival. This trial neither demonstrated survival benefit nor decrease in the percentage of distant failure. However, it showed that a longer course of neoadjuvant therapy can be done without compromising definitive therapy, since the resection rates were similar to prior trials in which shorter course of therapy was used [19].
The MD Anderson Cancer Center group also reported a retrospective subset analysis of "borderline resectable" pancreatic subjects treated with preoperative chemoradiotherapy showed that the R0 resection rate was 40% and the median overall survival was 18 months [20].

Table-1: Studies from MDACC using neoadjuvant chemotherapy or chemoradiotherapy in potentially resectable pancreatic cancer

Author	Patient population	Patients	Regimen	Resection Rate (based on all patients)	Median OS		
					All	Resected	Non-resected
Pisters et al, JCO 1998 [16]	*Potentially resectable:* - no metastasis - no ext to SMA or celiac axis - patent SMPV	35	5-FU / RT (30 Gy, 10 Fx)	ORR 57% R0 90% R1 10% R2 0%	-	25 m	7m
Evans et al, JCO 2008 [17]	*Potentially resectable:* - no extrapancreatic disease - no SMA or celiac axis invasion - no occlusion of SMV or confluence of SMV-PV.	86	Gem / RT (30Gy, 10 Fx)	ORR 74% R0 89% R1 11% R2 0%	22.7m	34 m	7.31 m
Pisters et al, JCO 2002 [18]	*Potentially resectable:* - no extrapancreatic disease - no SMA or celiac axis invasion - no occlusion of SMV or confluence of SMV-PV	35	Paclitaxel / RT (30Gy, 10 Fx)	ORR 57% R0 70% R1 30% R2 0%	12 m	19 m	10 m
Varadhachary et al, JCO 2008 [19]	*Potentially resectable:* - no extrapancreatic disease - no SMA or celiac axis invasion - no occlusion of SMV or confluence of SMV-PV.	90	Gem-Cis / RT (30Gy on 10Fx)	ORR 57% R0 96.2% R1 3.8% R2 0%	17.4 m	31 m	10.5 m

Notes:
- OS: overall survival
- ORR: overall resection rate

2.3 FOLFIRINOX chemotherapy regimen

Of particular interest for us is the FOLFIRINOX regimen (oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks), which was initially developed by Dr Conroy and his group in 2003 [21,22].
In a recently published phase III trial, FOLFIRINOX regimen demonstrated a statistically significant improvement in median overall survival in patients with metastatic adenocarcinoma of the pancreas when compared to single agent gemcitabine (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). This clinical benefit was accompanied with significantly higher response rates in the FOLFIRINOX arm (31.6% vs. 9.4%, p = <0.001). In terms of side effects, FOLFIRINOX had higher rates of grade 3 or 4 toxicities. Most common toxicities were myelosupression, nausea, vomiting and diarrhea [23].

2.4 Rationale

Surgery is the only modality that offers prolonged survival and a potential cure for patients with pancreatic cancer. Preoperative chemoradiotherapy is an accepted treatment strategy in patients with borderline resectable disease. Prior reports showed that: 1) selects patients that will likely not benefit from extensive surgery upfront (pancreatoduodenectomy-Whipple), since 10-20% of patients will develop metastasis after preoperative CRT; 2) permits delivery of therapy to a high percentage of patients (>90%). This eliminates the risk of delaying adjuvant therapy due to morbidity associated with upfront surgery.
Prior studies using preoperative chemoradiotherapy showed poor outcomes with resection rates of 60% (50-75%) and a median overall survival of 10-20 months. There are still 25-35% of the participants who never undergo surgical resection due to either development of metastatic disease or because they are found to have unresectable disease at the time of surgery [16-19].
There is an urgent need for more effective preoperative treatment strategies in order to increase the proportion of patients who are able to undergo a potentially curative R0 resection.
To this end we aim to test a preoperative strategy in a group of patients who have borderline resectable pancreatic cancer. We hypothesize that preoperative therapy will: 1) achieve partial responses translating into more R0 resections; and 2) deliver radiation more efficiently since the tumor bed is well oxygenated.
Our rationale to use an aggressive chemotherapy backbone as our initial approach is based on: 1) after neoadjuvant CRT, the majority of recurrences were seen at distant sites, suggesting that a more aggressive chemotherapy regimen should be used to treat micrometastatic disease early; and 2) FOLFIRINOX demonstrated to have the highest reported response rates when used in patients with metastatic disease with manageable toxicities.
We hypothesize that patients borderline resectable disease will achieve similar responses, allowing higher rates of R0 resections. Higher perioperative mortality in patients receiving preoperative chemotherapy was seen in patients requiring vascular reconstructions [24]. We hypothesize that our subgroup of patients will not have such complications, since we will not include patients with locally advanced pancreas cancer, which in general have more invasion of local vascular structures.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria:

- Histologically or cytologically confirmed adenocarcinoma of the pancreas.

- Only patients that have not received any prior treatment for pancreas cancer are eligible for this treatment protocol.

- Patients are not required to have measurable disease by traditional RECIST criteria, as lesions in the pancreas are notoriously hard to measure radiographically. However, patients must have disease which is evaluable for resection.

- Disease should be determined as “Borderline resectable” according to the Expert Consensus Statement published by Callery et al. (5):

- No distant metastasis

- Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.

- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.

- Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.

- Age ≥18 years.

- Life expectancy of greater than 6 months.

- ECOG performance status ≤1 (Karnofsky ≥80%; see Appendix A).

- Patients must have normal organ and marrow function as defined below:

- leukocytes	≥3,000/mcL
- absolute neutrophil count	≥1,500/mcL
- platelets	≥100,000/mcL
- total bilirubin	≤2 mg/dl
- AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
- creatinine	within normal institutional limits
OR	
- creatinine clearance	≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

- Ability to understand and the willingness to sign a written informed consent document.

- Patients may not be receiving any other concurrent chemotherapy, immunotherapy, or radiotherapy.

3.2 Exclusion Criteria:

- Patients who have had prior chemotherapy or radiotherapy for the treatment of pancreas cancer.

- Patients may not be receiving any other investigational agents.

- Evidence of extent of pancreatic cancer beyond that defined as "borderline resectable" above (locally advanced or distant disease). Peripancreatic lymph node involvement, either confirmed or suspected, will not be considered distant disease unless the lymph node involvement extends outside of the field of resection.

- Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to 5-fluorouracil, oxaliplatin, irinotecan or gemcitabine.

- Any concurrent active malignancy other than non-melanoma skin cancers or carcinoma-in-situ of the cervix. Patients with previous malignancies but without evidence of disease for > 3 years will be allowed to enter the trial. Patients with a history of a T1a or b prostate cancer (detected incidentally at TURP and comprising less than 5% of resected tissue) may participate if the PSA remained within normal limits since TURP removal**.**

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- Pregnant women are excluded from this study because 5-fluorouracil, oxaliplatin, irinotecan and gemcitabine are Class D agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated.

- HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with 5-fluorouracil, oxaliplatin, irinotecan and gemcitabine. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and e*thnic groups are eligible for this trial.

4.0 TREATMENT PLAN

This is an open-label, single-arm, phase II trial that evaluates the efficacy (measured as percentage of R0 resections) of preoperative FOLFIRINOX chemotherapy combination (initial phase or first phase), followed by gemcitabine based chemoradiotherapy (second phase) in patients with borderline resectable adenocarcinoma of the pancreas.

The study will evaluate the median overall survival, the median progression free survival, toxicity and safety of this preoperative regimen.

Patients will be assigned to receive oxaliplatin at a dose of 85 mg/m2, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg/m^2, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180mg/m^2, given as a 90-minute intravenous infusion through a Y-connector. This treatment will be immediately followed by 5-fluorouracil at a dose of 400 mg/m^2, administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg/m^2 over a 46-hour period every 2 week intervals. This will be given for a total of 4 cycles (first phase).
Within 4-6 weeks of termination of chemotherapy, patients that do not have progression of disease by cross sectional imaging (CT scan or MRI) will go into the second phase of the study. During this second phase they will receive chemoradiotherapy with narrow radiation fields (IMRT, 50.4Gy, delivered in 28 fractions, 1.8 Gy per fraction) and weekly gemcitabine given at 400 mg/m^2 (given on days 1, 8 15, 22, 29 and 36).

CHEMOTHERAPY REGIMEN DESCRIPTION				
Agent	***Dose***	***Route***	***Schedule***	***Cycle Length***
Oxaliplatin	*85 mg/m^2 in 500 cc D5W*	*IV over 2 hours, before leucovorin*	*Day 1*	*2 weeks (14 days)*
Leucovorin	*400 mg/m^2 in 250 cc D5W*	*IV over 2 hours, after oxaliplatin*	*Day 1*	
Irinotecan	*180 mg/m^2 in 500 cc D5W*	*IV over 90 minutes, after 30 min of initiation of leucovorin via a Y-connector*	*Day 1*	
5-fluorouracil bolus	*400 mg/m2*	*IV bolus, after irinotecan*	*Day 1*	
5-fluorouracil Infusion	*2400 mg/m^2 in 92 cc NS*	*46 hour infusion, after bolus 5-fluororuacil*	*Days 1-3*	

CHEMORADIOTHERAPY REGIMEN DESCRIPTION

Agent	*Dose*	*Route*	*Schedule*	*Cycle Length*
Gemcitabine	*400 mg/m^2 in 250 cc NS*	*IV over 30 minutes*	*Days 1, 8, 15, 22, 29, 36 of RT*	*35 days*

4.1 Treatment Administration

Treatment will be administered on an *outpatient* basis. Reported adverse events and potential risks for 5-fluorouracil, oxaliplatin, irinotecan and gemcitabine are described in Section 6. Appropriate dose modifications for FOLFIRINOX regimen and gemcitabine are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Before dose administration for each patient, the total dose of each of the drugs (oxaliplatin, irinotecan, 5-fluorouracil, leucovorin, gemcitabine) must be calculated by the following equation:

Dose (mg) = Scheduled Dose (mg/m^2) × Body Surface Area (BSA) (m^2)

BSA will be calculated at the beginning of each cycle, using any method that is accepted and customarily used by the clinical site (e.g., the Mosteller formula):
BSA (m^2) = ([Height (cm) × Weight (kg)]/3600)1/2

4.2 Chemotherapy Agent Administration

4.2.1 Oxaliplatin

Oxaliplatin will be administered as a 2-hour intravenous infusion at a dose of 85 mg/m^2 on day 1 of a 14 day cycle.
For more information about oxaliplatin see appendix B 2.

4.2.2 Leucovorin

Leucovorin will be administered at a dose of 400 mg/m^2, given as a 2-hour intravenous infusion on day 1 of a 14 day cycle. Leucovorin can be replaced by levoleucovorin (Fusilev) due to the current national shortage of the first one. Levoleucovorin will be used at a dose of 200 mg/m^2, given as a 2-hour intravenous infusion on day 1 of a 14 day cycle.

4.2.3 Irinotecan

Irinotecan will be administered as a 90 min. intravenous infusion through a Y connector dosed at 180 mg/m^2 on day 1 of a 14 day cycle. This will be given 30 minutes after finalization of the leucovorin infusion.
For more information about irinotecan see appendix B 3.

4.2.4 5-Fluorouracil

5-fluorouracil will be administered as a 2-5 minute intravenous bolus at a dose of 400 mg/m^2, followed by a 46 hours continuous intravenous infusion of 2400 mg/m^2. Both bolus and infusion will be administered on day 1 of a 14 day cycle. 5-fluorouracil will be administered immediately following the administration of the irinotecan infusion.
For more information about 5-fluorouracil see appendix B 1.

4.2.5 Gemcitabine

Gemcitabine will be administered at a dose of 400 mg/m^2, as a 30 min intravenous infusion of on days 1,8,15, 22, 29, 36 of radiation.
For more information about gemcitabine see appendix B 4.

4.3 Radiotherapy Administration

Patients who did not have disease progression after completion of four cycles of neoadjuvant FOLFIRINOX chemotherapy will receive one course of radiation therapy (RT). Patients will undergo CT-based simulation after completion of neoadjuvant chemotherapy.

The course of RT will be intensity modulated (IMRT) and administered concurrently with gemcitabine, preferably starting within 2-4 weeks after completion of FOLFIRINOX, but no later than 6 weeks after FOLFIRINOX.

External beam radiation therapy using intensity modulated radiation therapy (IMRT) technique

Localization: Fiducial marker placement in the pancreas will be optional for better localization of the tumor. When available, fiducial markers will be used for daily tracking of the target during treatment delivery with kV imaging.

Immobilization: A custom immobilization device with a universal leg rest and a wing board will be used to minimize set-up variability.

Simulation and Planning: The simulation scan will be done with the patient in the supine position with arms raised above the head using a CT-simulator with 2.5 mm slice thickness. All tissues to be irradiated will be included in the CT scan along with additional centimeters of superior and inferior margin for dose calculations. The simulation CT scan will be acquired with the patient in the treatment position using the same immobilization devices as for treatment. Oral and intravenous (IV) contrast agents will be used when possible to help delineate organs on 3D images. An additional 4D CT simulation will be done with respiratory gating to assess the extent of tumor/liver movement. If gated treatment is chosen, three to four gating phases with the least amount of target motion will be selected for generation of plans and treatment delivery. The maximum intensity projection (MIP) image and the average intensity projection (Ave-IP) image will be recorded. The movement of the target due to respiration will be assessed and

motion in superior-inferior, medial-lateral and anterior- posterior directions will be recorded at the center of the primary tumor or fiducial markers. The treatment planning (simulation) CT scan will be used to define gross tumor volume (GTV) and clinical tumor volumes (CTV). The GTV and CTV will be outlined on all CT slices of the MIP image set in which the structures exist. Normal tissues will be outlined on the AVE-IP.

Treatment Planning/Target Volumes

The definition of volumes will be in accordance with the 1993 ICRU Report #50, as follows:

The Gross Tumor Volume (GTV) will be defined as all known gross disease determined from CT scans (plus MRI or PET, if available), clinical information, endoscopic findings and biopsy. There will be two GTVs for node positive patients and one for node negative patients. Target tumor volumes will delineated slice by slice on the treatment planning CT images

- *GTV-primary* will include the gross primary tumor volume (as documented by CT, PET or MRI, if available).
- *GTV-Node* will include all involved nodal regions (as documented by biopsy or imaging) (plan to deliver 50.4 Gy).

The Clinical Target Volume (CTV) will be defined as the areas of subclinical risk around the GTV. Elective nodal irradiation for microscopic disease will not be performed.

The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for treatment set-up uncertainty and internal organ motion. The margin expansion determined from the 4D CT simulation will be used to generate the treatment volume. The PTVs will spare non-target skin surfaces (manually or automatically trimmed to 3-5 mm within the skin surface).

Organs at Risk: Surrounding critical normal structures (small bowel, stomach, duodenum, liver, kidneys, lung and heart) will be delineated on the Ave-IP image set of the 4D CT sim. The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs will be designated as unspecified tissue.

Heterogeneity Corrections: All dose distributions will include corrections for tissue heterogeneities. The method used for heterogeneity calculations will be reported.

Dose Specifications

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram *(*DVH*)* analyses of the planning tumor volume (PTV) and organs at risk. The treatment aim will be dose optimization to the PTV while minimizing dose to uninvolved tissue.

Target prescription dose:

- For N0 disease: The primary tumor PTV (PTV_primary) will receive 50.4 Gy in 28 daily fractions at 1.8 Gy per fraction.
- For N1 disease: The PTV_primary and the positive lymph node PTV (PTV_node) will receive 50.4 Gy in 28 daily fractions at 1.8 Gy per fraction.

Treatment Schedule: Treatment will be delivered once daily, 5 consecutive fractions per week (with the exception of holidays). All targets will be treated simultaneously. Breaks in treatment will be avoided as much as possible.

Dose specifications: The prescription isodose surface will encompass at least 95% of the primary and involved nodal PTVs
• No more than 5% of any PTV will receive < 90% of the prescription dose.
• No more than 2% of any PTV will receive < 80% of the prescription dose.
• No more than 2% of the primary PTV will receive > 115% of the prescription dose.

Planning priorities: Target volume prescription goals followed by organs at risk dose constraints will be the most important planning goals.

Treatment Delivery
Megavoltage equipment capable of delivering dynamic intensity modulation will be used with inverse-planned IMRT software. Treatment machine–generated CT images through at least one plane within the PTV, with tumor and critical structures turned on for display, will be used for set-up verification. Reference simulation images used for set-up verification will include the target volumes. Setup verification images will be obtained at levels where cephalocaudad and transverse positioning can be verified. Respiratory gating will be used for treatment delivery only in the phases selected during the treatment simulation.

Critical Structures
Critical normal structures: Dose volume histograms (DVHs) will be generated for all critical normal structures. Effort will be made to achieve the dose constraints to normal tissues listed below. The dose constraints are listed in order from most to least important.
Small bowel:
• No more than 200 cc above 30 Gy
• No more than 150 cc above 35 Gy
• No more than 20 cc above 45 Gy
• None above 50 Gy
Kidney:
• No more than 75% above 12 Gy
• No more than 50% above 15 Gy
• No more than 33% above 18 Gy
Liver:
• No more than 40% above 30 Gy
• No more than 30% above 40 Gy
• No more than 5% above 50 Gy
Lung:
• No more than 20% above 20 Gy
• No more than 5% above 42 Gy
Heart:
• No more than 50% above 35 Gy
• No more than 15% above 40 Gy
• No more than 5% above 50 Gy

Large bowel:
• No more than 200 cc above 30 Gy
• No more than 150 cc above 35 Gy
• No more than 20 cc above 45 Gy

4.4 General Concomitant Medication and Supportive Care Guidelines

All supportive measures consistent with optimal patient care will be given throughout treatment.

Loperamide (Imodium): Patients will be instructed to begin taking loperamide at the earliest signs of a poorly formed or loose stool. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every two hours around the clock until the patient is diarrhea-free for at least 12 hours (not to exceed 16 mg in one day/24hour period).

Antiemetics: Oxaliplatin is emetogenic. All patients should be pre-medicated with an acceptable anti-emetic regimen. Patients may receive dexamethasone 10 mg IV as pre-treatment antiemetic unless there is a relative or absolute contraindication to corticosteroids. Other antiemetics may be used in addition to the suggested regimen, if clinically indicated. As the majority of patients on previous trials have not experienced significant nausea, antiemetics other than decadron are recommended only for those patients who demonstrate nausea and/or vomiting despite treatment with decadron.

Anticoagulants: Patients who are taking warfarin sodium (Coumadin) may participate in this study; however, they must be on a stable, therapeutic dose and have close monitoring of their levels. Subcutaneous heparin is also permitted.

Hypersensitivity: Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, antihistamines, and epinephrine; bronchodilators and vasopressors may be required. Platinum hypersensitivity is an extremely rare event and should be treated promptly. Oxaliplatin hypersensitivity occurs in approximately 0.5% of patients receiving this agent.

Pharyngo-laryngodysesthesias: Oxaliplatin may cause discomfort in the larynx or pharynx associated with dyspnea, anxiety, swallowing difficulty and is exacerbated by cold. Appropriate therapy includes use of anxiolytics, cold avoidance and monitoring.

Growth Factors: Prophylactic use of G-CSF or GM-CSF is permitted on this trial at the investigator's discretion, during the FOLFIRINOX period, but not during chemoradiotherapy part. Therapeutic G-CSF use in patients with serious neutropenic complications may be given at the investigator's discretion and should follow ASCO Guidelines for G-CSF use. Erythropoietin stimulating agents may be used according to ASCO guidelines.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of

the following criteria applies:

- Grade 3 or Grade 4 toxicities that are deemed to be too unsafe to continue with therapy.
- Radiological evidence of disease progression.
- Withdrawal of consent by patient.
- Presence of other medical conditions that prohibit continuation with therapy.
- Failure of the patient to comply with study procedures that compromise safety, despite repeated efforts of the investigator to contact the patient with complete documentation of the circumstances.
- In the opinion of the investigator, it is in the best interest of the patient to be discontinued from therapy.

4.6 Duration of Follow Up

Patients will be followed every 3 months after removal from study. They will be followed every 3 months for 30 months, until death or loss of follow up, whichever occurs first. These visits will include a clinical history for symptom assessment, physical examination and measurement of serum CA 19-9 tumor marker. Imaging studies will be left at the criteria of each investigator based on their clinical suspicion of recurrence. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.7 Criteria for removal from Study

Patients will be removed from study when any of the criteria listed in Section 4.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5.0 DOSING DELAYS/DOSE MODIFICATIONS

All toxicities should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

According to the following tables, the final dose modification should be based upon the worst grade of toxicity experienced. If patients require dose reductions lower than level -2, protocol therapy will be discontinued. Any dose reduction is continued for all subsequent cycles; therefore, dose re-escalation is not allowed following a dose reduction. NOTE: there are no dose reductions for leucovorin; the dose remains fixed at 400 mg/m2 and without modification.

5.1 Dose Modifications for FOLFIRINOX (chemotherapy):

Dose reduction steps: FOLFIRINOX			
	Starting Dose	*Dose Level -1*	*Dose Level -2*
Oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
5-Fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2
5- Fluorouracil bolus	400 mg/m^2	0	0
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2
**leucovorin dose remains fixed at 400mg/m^2*			

The following table describes the recommended dose modifications at the start of each subsequent course of therapy. All dose modifications should be based on the worst preceding toxicity.

Note: Dose modifications must be based on AEs observed during the cycle (column 2) and on the scheduled cycle day 1 (column 3). Dose modifications must be based on the AE requiring the greatest modification. Toxicity NCI CTCAE v4.

Toxicity NCI CTAE v4.0 Grade (value)	**Note: Dose modifications must be based on AE's observed during the cycle (column 2) and on the scheduled cycle day 1 (column 3). Dose modification must be based on the AE requiring the greatest modification.**	
	Worst interval toxicity (modifications for AE's that occurred during a cycle but did note require delay in treatment)	**Day of treatment (modifications for AE's that require a delay in treatment)**
Neutrophils (ANC) Grade 1 (ANC<LLN-1500/mm3) Grade 2 (ANC<1499-1000mm/m3) Grade 3 (ANC<999- 500mm/m3) Grade 4 (ANC<500mm/m3)	 Maintain dose level Maintain dose level Omit bolus 5-FU Omit bolus 5-FU and reduce oxaliplatin and irinotecan one dose level	 If ANC<1000 at start of cycle, hold and check weekly then treat based on worst interval toxicity. If ANC <1000 after 4 weeks, discontinue therapy
Platelets Grade 1 (PLT<LLN-75,000/mm3) Grade 2 (PLT<74,999-50,000mm/m3) Grade 3 (PLT<49,999- 25,000mm/m3)	 Maintain dose level Maintain dose level Omit bolus 5-FU Omit bolus 5-FU and reduce oxaliplatin and irinotecan one dose level	 Grade 4 (PLT<25,000mm/m3) If PLT<60,000 at start of cycle, hold and check weekly then treat based on worst interval toxicity. If PLT <60,000 after 4 weeks, discontinue therapy
Other hematologic toxicities do not require dose modification; however, red blood cell transfusion should be strongly considered for hemoglobin <8g/dl		
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Maintain dose level Omit bolus 5-FU and reduce infusional 5-FU and irinotecan one dose level Omit bolus 5-FU and reduce infusional 5-FU, oxliplatin and irinotecan one dose level.	 Hold if > grade 2 diarrhea is present. Reduce drugs per worst interval toxicity upon resolution of diarrhea. If Grade > 2 after 4 weeks, discontinue therapy.

Mucositis/Stomatitis Grade 1	 Maintain dose level	 Hold until <grade 2, then treat

Grade 2 Grade 3 Grade 4	Maintain dose level Omit bolus 5-FU and reduce infusional 5- FU one dose level Omit bolus 5-FU and reduce infusional 5- FU, irinotecan and oxaliplatin one dose level	based on worst interval toxicity.
Vomiting (despite antiemetics) Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose Maintain dose Reduce oxaliplatin and irinotecan one dose level Reduce oxaliplatin, irinotecan and infusion 5-FU one dose level and omit bolus 5-FU	 Hold until resolved then: Maintain dose Maintain dose Reduce oxaliplatin and irinotecan one dose level Reduce oxaliplatin, irinotecan and infusion 5-FU one dose level and omit bolus 5-FU
Other non-hematologic toxicities	Dose modifications for other nonhematologic adverse events at the start of subsequent cycles of therapy, and at time of retreatment are the same as recommended for vomiting (above) with the following exception: **Omit bolus 5-FU and decrease infusion 5-FU by one dose level for other Grade>3 non-hematologic events**	

5.1.1 Febrile neutropenia

Hold FOLFIRINOX during the febrile neutropenia. Doses missed will be made up at a following date.

Resume FOLFIRINOX at one dose level lower than the dose administered in the last cycle. This dose should be used for all subsequent cycles.

If febrile neutropenia develops in a given cycle, the use of colony stimulating factors is may be instituted at the discretion of the investigator until resolution of febrile neutropenia or septic episode. Growth factors may be considered at the discretion of the investigator on the following cycle of FOLFIRINOX.

5.2 Dose Modifications for Gemcitabine (chemoradiotherapy):

Dose reduction steps: chemoradiotherapy			
	Starting Dose	*Dose Level -1*	*Dose Level -2*
Gemcitabine	400 mg/m^2	320 mg/m^2	250 mg/m^2

Dosage adjustments will be made based on weekly blood counts obtained within 1 day prior to weekly gemcitabine dose:

ANC		Platelets	Last dose level of gemcitabine given	Dose level of gemcitabine to be given
≥ 1000	and	≥ 100,000	Level 0	Level 0
≥ 1000	and	≥ 100,000	Level -1	Level -1
≥ 1000	and	≥ 100,000	Level -2	Level -2
500-999	or	50,000 to 99,999	Level 0	Level -1
500-999	or	50,000 to 99,999	Level -1	Level -2
500-999	or	50,000 to 99,999	Level -2	Hold and recheck in one week
<500	or	< 50, 000	Any	Hold and recheck in one week

Non-hematologic toxicity

Toxicity NCI CTAE v4.0 Grade (value)	Worst interval toxicity (modifications for AE's that occurred during a cycle but did note require delay in treatment)	Day of treatment (modifications for AE's that require a delay in treatment)
Edema Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Maintain dose level Decrease one dose level Hold	If hold: When the toxicity improves to grade < 2, resume gemcitabine at one dose level lower than the previous dose level administered.
Liver toxicity Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Maintain dose level Decrease one dose level Hold	*Patients with grade 4 hepatic toxicity should be evaluated for disease progression. If disease progression is found, discontinue protocol therapy. If no disease progression is found, resume gemcitabine at one dose level lower than the previous dose when toxicity resolves to grade 0-2. If toxicity does not resolve to grade 0-2 within 4 weeks, discontinue protocol therapy. **Patients who have a repeated episode of Grade 3 hepatic toxicity upon resumption of gemcitabine therapy should discontinue gemcitabine
Nausea/vomiting Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Maintain dose level Maintain dose level Hold	For grade 4 **nausea/vomiting** the dose of gemcitabine should be held until it is grade 2 or less, then patient should resume gemcitabine at one dose level lower
Other non-hematological toxicity Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Maintain dose level Decrease one dose level Hold	For other grade 4 non-hematological toxicities the dose of gemcitabine should be held until it is grade < 2 , then patient should resume gemcitabine at one dose level lower

5.3 Dose Modifications/Interruption for radiotherapy

5.3.1 Radiotherapy Interruption

Therapy interruptions will usually not be necessary. However, if radiation is held for any reason, all systemic therapy must also be held. Interruptions may be kept to a minimum by the use of ancillary therapy and vigorous nutritional support. Interruptions are permitted only on the basis of toxicity. Therapy may be interrupted for grade 3 and 4 hematological and non-hematological

toxicity.
Interruption of therapy may continue until the toxicity has regressed to ≥ grade 2 to allow resumption of therapy; however, every effort should be made to limit treatment interruptions to 1-2 weeks.

5.3.2 Radiotherapy Dose Modifications

Every effort must be made to deliver the full 50.4 Gy to all patients. Toxicity may be encountered that is sufficiently severe to require treatment interruption. Once the toxicity has resolved, the patient's therapy should resume and full protocol dose should be delivered. The toxicity that forced any dose reduction must be documented. If interruption of therapy (up to 2 weeks) becomes necessary, radiation therapy should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported. If an interruption of more than 2 weeks is necessary, resumption of treatment is at the discretion of the radiation oncology chairs. The patient's treatment plan will be considered a major deviation, but follow-up will be continued.

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited (via AdEERS) reporting **in addition** to routine reporting.

6.1 Adverse Event List(s) for Commercial Agent(s)

Oxaliplatin
For a comprehensive list of adverse events please refer to the package insert. Appendix B 2 provides an overview of toxicities related to oxaliplatin.

Irinotecan
For a comprehensive list of adverse events please refer to the package insert. Appendix B 3 provides an overview of toxicities related to irinotecan.

5-Fluorouracil
For a comprehensive list of adverse events please refer to the package insert. Appendix B 1 provides an overview of toxicities related to 5-fluorouracil.

Gemcitabine
For a comprehensive list of adverse events please refer to the package insert. Appendix B 4 provides an overview of toxicities related to gemcitabine.

6.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected.

6.3 Adverse events related to surgery.

All adverse effects related to the surgical resection will be documented and graded, based on the Dino-Clavien Scale. See Appendix C.

6.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions.

7.0 PHARMACEUTICAL INFORMATION

See Appendix B.

8.0 STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

	Pre therapy		FOLFIRINOX (4 cycles)			D 15, 29, 43[c]	Restaging (2-6 weeks after cycle 4 of FOLFIRINOX)	Chemoradiotherapy						Restaging (2-6 weeks after CRT)
								Days						
	(Day -28 to start)	(Day -14 to start)	D 1	D 2	D3			1	8	15	22	29	36	
Informed consent	♦													
History and Physical including weight		♦	♦			♦		♦		♦		♦		♦
Toxicity assessment			♦			♦		♦	♦	♦	♦	♦	♦	♦
Vital Signs		♦	♦			♦		♦	♦	♦	♦	♦	♦	♦
Height		♦												
Performance Status		♦	♦			♦		♦		♦		♦		♦
AE/SAE Monitoring			♦			♦		♦		♦		♦		♦
CT scan or MRI[a]	♦						♦							♦
Tumor Measurements	♦						♦							♦
CBC		♦	♦			♦		♦	♦	♦	♦	♦	♦	♦
Chemistry-7		♦				♦		♦		♦		♦		♦
Ca, Mg, Phosphorus		♦	♦			♦		♦						♦
LFT		♦				♦		♦		♦		♦		♦
Beta-HCG		♦												
Ca 19-9		♦				♦		♦				♦		♦
5-Fluorouracil dosing			♦	♦	♦	♦								
Oxaliplatin dosing			♦			♦								
Irinotecan dosing			♦			♦								
Gemcitabine dosing								♦	♦	♦	♦	♦	♦	
Radiation											♦			
Respectability evaluation	♦													♦

[a] :CT abdomen/pelvis should ideally be done with pancreas protocol. Chest imaging with Chest X-ray or CT chest is accepted.

9.0 CLINICAL LABORATORY TESTS AND PROCEDURES

Prior to study treatment each patient will have the following assessments.

Within 4 weeks of study treatment:
Radiologic studies for baseline tumor measurements with CT of the abdomen and pelvis with pancreas protocol or MRI scanning of the abdomen and pelvis. Chest should be imaged with chest X-ray or CT scan of the chest.
Sign the informed consent document.

Within 2 weeks of study treatment:
Medical history and physical examination, including clinical measurement of tumor lesions.
Demographics including measurements of height and weight.
Evaluation of performance status (ECOG).
Vital signs (blood pressure, pulse rate and temperature)
HIV testing
Hematology – CBC with differential
Chemistry – Chem-7 (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose)
LFT – (total bilirubin, direct bilirubin, total protein, albumin, AST, ALT, alkaline phosphatase)
Other chemistry - Calcium, LDH, Magnesium, Phosphorus.

10.0 MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be reevaluated for response 2 times: 1) after 4 cycles of FOLFIRINOX chemotherapy. 2) after finalization of gemcitabine base chemoradiotherapy.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

10.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with FOLFIRINOX chemotherapy.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

> Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 10 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and

neck tumors and those of extremities usually require specific protocols.

Ultrasound (US) When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

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 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): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

10.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	
Any	PD*	Yes or No	PD	no prior SD, PR or CR
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

10.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

11.1.1 Primary Endpoint:

The primary endpoint of this study is to examine the proportion of R0 resection rate in participants receiving at least one cycle of FLOFIRINOX chemotherapy. We will test the R0 resection rate by one-sided one sample Z test for proportion with null hypothesis set at 40%.

This phase II study will use the Simon two-stage design. This design was chosen to allow early rejection of an ineffective treatment. The protocol will be open to patients with borderline resectable pancreatic cancer who did not receive any prior therapy.
The null hypothesis is that FOLFIRINOX chemotherapy, followed by gemcitabine based chemoradiotherapy has an R0 resection rate 40%. This is based on prior report from Katz et al where patients with borderline resectable pancreatic cancer treated with preoperative therapy had an R0 resection rate of 40% [20]. This phase II study will use the Simon two-stage design. This design was chosen to allow early rejection of an ineffective treatment. The protocol will be open to patients with borderline resectable pancreatic cancer who did not receive any prior therapy.
The null hypothesis is that FOLFIRINOX chemotherapy, followed by gemcitabine based chemoradiotherapy has an R0 resection rate 40%. This is based on prior report from Katz et al where patients with borderline resectable pancreatic cancer treated with preoperative therapy had an R0 resection rate of 40% [20]. This study will achieve a 80% power to test the null hypothesis that R0 resection rate <=0.4 versus the alternative that resection rate R0>=0.6 at 5% level of significance. If the treatment is actually not effective, there is a 0.049 probability of concluding that it is (the target for this value was 0.050) and if the treatment is effective, there is a 0.199 probability of concluding that it is not (the target value was 0.2). The new treatment will be tested on 16 patients in the first stage, the trial will be terminated if 7 or fewer R0 resections are achieved. If the total number of R0 resections is less than or equal to 23, the new treatment will be rejected. This study will enroll 50 patients within 36 months.

11.2 Sample Size/Accrual Rate

This study will accrue 50 patients. The estimation is that will accrue 1-2 patients a month,

completing accrual in 36 months.

11.3 Analysis of Secondary Endpoints

11.3.1 Secondary Endpoints:

- The overall response rate (assessed by RECIST criteria) will be examined using one sample Z-test for proportion.
- Overall Survival: The overall survival rate in the study will be examined for survival probabilities using Kaplan-Meier procedure and association of clinical covariates with overall survival status will be examined using log-rank test and Cox regression procedure. Median overall survival with confidence interval will be presented.

Progression free survival (PFS): The time to progression will be analyzed using Kaplan–Meier procedure followed by log-rank tests and Cox regression model to investigate the association between clinical covariates and progression free survival. Median progression free survival will be presented. Brookmeyer and Crowley method will be used to estimate a 95% confidence interval for median PFS and median OS.

- Toxicity (evaluated by NCI CTCAE v4.0). Toxicity will be evaluated every clinic visit (on day 1, 8, 15, 22, 28, 35 or radiotherapy, after restaging and after pancreatoduodenectomy). We will tablet the toxicity outcome.
- Adverse events related to surgery (evaluated by Dino-Clavien scale). We will tablet the toxicity outcome.
- Proportion of patients able to undergo resection. We will tablet resection rate with appropriate 95% confidence interval.
- Proportion of patients requiring vascular reconstruction. We will tablet vascular reconstruction rate with 95% confidence interval.

11.4 Reporting and Exclusions

11.4.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment. This analysis will include patient that received at least 1 one cycle of FOLFIRINOX chemotherapy.

11.4.2 **Evaluation of response.** All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in

exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

12.0 REFERENCES

1. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, Altekruse SF, Feuer EJ, Huang L, Mariotto A, Miller BA, Lewis DR, Eisner MP, Stinchcomb DG, Edwards BK (eds).
2. SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.
3. Jemal A, Murray T, Ward E, et al. Cancer Statistics, 2005. CA: Cancer J Clin;55:10–30, 2005.
4. National Comprehensive Cancer Network Website 2011. http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf.
5. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol (2009) 16:1727–1733.
6. Abrams RA, Lowy AM, O´Reilly AM, et al. Combined Modalty Treatment for Resectable and Borderline Resectable Pancreas Cancer: Expert Consensus Statement. Annals of Surg Oncol: 16:1751–1756, 2009.
7. Pilepich MV, Miller HH, erta al. Preoperative irradiation in carcinoma of the pancreas. Cancer; 46:1945, 1980.
8. Brunner TB, Grabenbauer GG, Kastl S, et al. Preoperative Chemoradiation in Locally Advanced Pancreatic Carcinoma: A Phase II Study. Onkologie 23:436–442, 200.
9. Kastl S, Brunner T, Herrmann O, et al. Neoadjuvant radio-chemotherapy in advanced primarily non-resectable carcinomas of the pancreas. European Journal of Surgical Oncology 26: 578–582, 2000.
10. Palmer DH, Stocken DD, PhD, Hewitt H, et al. A Randomized Phase 2 Trial of Neoadjuvant Chemotherapy in Resectable Pancreatic Cancer: Gemcitabine Alone Versus Gemcitabine Combined with Cisplatin. Annals of Surgical Oncology 14(7):2088–2096, 2007.
11. Satoi S, Yanagimoto H, Toyokawa H, et al. Surgical Results After Preoperative Chemoradiation Therapy for Patients With Pancreatic Cancer. Pancreas 38, 282-288, 2009.
12. Takai S, Satoi S, Yanagimoto H, et al. Neoadjuvant Chemoradiation in Patients With Potentially Resectable Pancreatic Cancer. Pancreas 36; 26-32, 2008.
13. Turrini O, Viret F, Moureau-Zabotto L, et al. Neoadjuvant 5 Fluorouracil-Cisplatin Chemoradiation Effect on Survival in Patients with Resectable Pancreatic Head Adenocarcinoma: A Ten-Year Single Institution Experience. Oncology 76:413–419, 2009.
14. Hoffman JP, Lipsitz S, Pisansky T et al. Phase II Trial of Preoperative Radiation Therapy and Chemotherapy for Patients With Localized, Resectable Adenocarcinoma of the Pancreas: An Eastern Cooperative Oncology Group Study. J Clin Oncol 16; No 1: 317-323, 1998.
15. Evans DB, Rich TA, Byrd DR, et al. Preoperative Chemoradiation and Pancreaticoduodenectomy for Adenocarcinoma of the Pancreas. Arch Surg 127:1335-1339, 1992.
16. Pisters PWT, Abbruzzese JL, Janjan NA, et al. Rapid-Fractionation Preoperative Chemoradiation, Pancreaticoduodenectomy, and Intraoperative Radiation Therapy for

Resectable Pancreatic Adenocarcinoma. J Clin Oncol 16; 12; 3843-3850, 1998.
17. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative Gemcitabine-Based Chemoradiation for Patients With Resectable Adenocarcinoma of the Pancreatic Head. J Clin Oncol 26:3496-3502, 2008.
18. Pisters PWT, Wolff RA, Janjan NA, et al. Preoperative Paclitaxel and Concurrent Rapid-Fractionation Radiation for Resectable Pancreatic Adenocarcinoma: Toxicities, Histologic Response Rates, and Event-Free Outcome. J Clin Oncology, Vol 20, No 10; 2537-2544, 2002.
19. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative Gemcitabine and Cisplatin Followed by Gemcitabine-Based Chemoradiation for Resectable Adenocarcinoma of the Pancreatic Head. J Clin Oncol 26:3487-3495, 2008.
20. Katz M, Pisters P, Evans D, et al. Borderline Resectable Pancreatic Cancer: The Importance of This Emerging Stage of Disease. J Am Coll Surg. 2008 May;206(5):833-46; discussion 846-8. Epub 2008 Mar 17.
21. Ychou M, Conroy T, Seitz JF, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/5-fluorouracil every 2 weeks in patients with advanced solid tumors. Annals of Oncol 14: 481–489, 2003.
22. Conroy T, Paillot B, francois E, et al. Irinotecan Plus Oxaliplatin and Leucovorin-Modulated Fluorouracil in Advanced Pancreatic Cancer—A Groupe Tumeurs Digestives of the Fédération Nationale des Centres de Lutte Contre le Cancer Study. J Clin Oncol 23(6); 1228-1236, 2005.
23. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med; 364: 1817-25, 2011.
24. Allendorf JD, Lauerman M, Bill A et al. Neoadjuvant Chemotherapy and Radiation for Patients with Locally Unresectable Pancreatic Adenocarcinoma: Feasibility, Efficacy, and Survival. J Gastrointest Surg; 12:91–100, 2008.
25. Callery PM, Chang KJ, Fishman EK et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol; 16:1727–1733, 2009.

13.0 APPENDICES

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

1. 5- fluorouracil

Other names:
Adrucil®

Classification:
Antimetabolite

Mode of action:
A pyrimidine antimetabolite that interferes with DNA synthesis by blocking the methylation of deoxyuridylic acid; fluorouracil inhibits thymidylate synthetase (TS), or is incorporated into RNA. The reduced folate cofactor is required for tight binding to occur between the 5-FdUMP and TS.

Storage and stability:
Store at room temperature 15° to 30°C (59° to 86°F). Protect from light. Retain in carton until time of use.

Preparation:
No dilution necessary for usual injection formulation

Route of administration:
I.V. bolus as a slow push or short (5-15 minutes) bolus infusion, or as a continuous infusion. Doses >1000 mg/m^2 are usually administered as a 24-hour infusion, although some protocols may be continuous infusion with lower doses. Toxicity may be reduced by giving the drug as a constant infusion. Bolus doses may be administered by slow IVP or IVPB.

Incompatibilities/Interactions:
Stable in D_5LR, D_5W, NS, bacteriostatic NS; incompatible with concentrations >25 mg/mL of fluorouracil and >2 mg/mL of leucovorin calcium (precipitation occurs).

Availability:
5-fluorouracil is commercially available in the USA. Is an FDA approved agent for the treatment of patients with adenocarcinoma of the pancreas. However, when used in combination as directed by this protocol, the agents are classified as “unapproved use of an agent” and, by definition, are considered investigational. While this combination is not currently approved by the FDA, the use in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2 (b).

Side effects:

Cardiovascular: Angina, myocardial ischemia.
Central nervous system: Acute cerebellar syndrome, confusion, disorientation, euphoria, headache, nystagmus.
Dermatologic: Alopecia, dermatitis, dry skin, fissuring, palmar-plantar erythrodysesthesia

syndrome, pruritic maculopapular rash, photosensitivity, vein pigmentations, nail changes.
Gastrointestinal: Anorexia, bleeding, diarrhea, esophagopharyngitis, nausea, sloughing, stomatitis, ulceration, vomiting.
Hematologic: Myelosuppression (nadir: 9-14 days; recovery by day 30), agranulocytosis, anemia, leukopenia, pancytopenia, thrombocytopenia.
Local: Thrombophlebitis.
Ocular: Lacrimation, lacrimal duct stenosis, photophobia, visual changes.
Respiratory: Epistaxis.
Miscellaneous: Anaphylaxis, generalized allergic reactions, nail loss.

2. Oxaliplatin

Other names:
Eloxatin®

Classification:
Alkylating agent

Mode 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.

Storage and stability:
After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

Preparation:
The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

Route of administration:
Administer as I.V. infusion over 2 hours. Flush infusion line with D_5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion (may exacerbate acute neurological symptoms).

Incompatibilities/Interactions:
Incompatible with alkaline solutions (e.g., fluorouracil) and chloride-containing solutions. Flush infusion line with D_5W prior to, and following, administration of concomitant medications via same I.V. line.

Availability:
Oxaliplatin is commercially available in the USA. Is an FDA approved agent for the treatment of patients with adenocarcinoma of the pancreas. However, when used in combination as directed by this protocol, the agents are classified as "unapproved use of an agent" and, by definition, are considered investigational. While this combination is not currently approved by the FDA, the use in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2 (b).

Side effects:
>10%:
Central nervous system: Fatigue (61%), fever (25%), pain (14%), headache (13%), insomnia (11%). Gastrointestinal: Nausea (64%), diarrhea (46%), vomiting (37%), abdominal pain (31%), constipation (31%), anorexia (20%), stomatitis (14%).
Hematologic: Anemia (64%; grades 3/4: 1%), thrombocytopenia (30%; grades 3/4: 3%), leukopenia (13%).
Hepatic: AST increased (54%; grades 3/4: 4%), ALT increased (36%; grades 3/4: 1%), total bilirubin increased (13%; grades 3/4: 5%).
Neuromuscular & skeletal: Peripheral neuropathy (may be dose limiting; 76%; acute 65%; grades 3/4: 5%; persistent 43%; grades 3/4: 3%), back pain (11%).
Respiratory: Dyspnea (13%), cough (11%)

1% to 10%:
Cardiovascular: Edema (10%), chest pain (5%), peripheral edema (5%), flushing (3%), thromboembolism (2%). Central nervous system: Dizziness (7%).Dermatologic: Rash (5%), alopecia (3%), hand-foot syndrome (1%).
Endocrine & metabolic: Dehydration (5%), hypokalemia (3%).
Gastrointestinal: Dyspepsia (7%), taste perversion (5%), flatulence (3%), mucositis (2%), gastroesophageal reflux (1%), dysphagia (acute 1% to 2%).
Genitourinary: Dysuria (1%).
Hematologic: Neutropenia (7%).
Local: Injection site reaction (9%; redness/swelling/pain).
Neuromuscular & skeletal: Rigors (9%), arthralgia (7%).
Ocular: Abnormal lacrimation (1%).
Renal: Serum creatinine increased (5% to 10%).
Respiratory: URI (7%), rhinitis (6%), epistaxis (2%), pharyngitis (2%), pharyngolaryngeal dysesthesia (grades 3/4: 1% to 2%).
Miscellaneous: Allergic reactions (3%); hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope: grades 3/4: 2% to 3%); hiccup (2%).

<1%:
Acute renal failure, alkaline phosphatase increased, anaphylactic/anaphylactoid reactions, anaphylactic shock, angioedema, aphonia, ataxia, colitis, cranial nerve palsies, deep tendon reflex loss, deafness, diplopia, dysarthria, dysphonia, eosinophilic pneumonia, extravasation (including necrosis), fasciculations, gait abnormal, hematuria, hemolysis, hemolytic anemia (immuno-allergic), hemolytic uremia syndrome, hemorrhage, hepatic failure, hepatitis, hepatotoxicity, hypertension, hypomagnesemia, hypoxia, ileus, INR increased, interstitial lung

diseases, interstitial nephritis (acute), intestinal obstruction, intracerebral bleeding, Lhermittes' sign, metabolic acidosis, muscle spasm, myoclonus, neutropenic fever, neutropenic sepsis, nodular regenerative hyperplasia, optic neuritis, pancreatitis, peliosis, prothrombin time increased, ptosis, rectal hemorrhage, rhabdomyolysis, seizure, sepsis, thrombocytopenia (immuno-allergic), trigeminal neuralgia, tubular necrosis (acute), veno-occlusive liver disease (sinusoidal obstruction syndrome and perisinusoidal fibrosis), visual disturbance (acuity decreased, field disturbance, transient loss).

3. Irinotecan

Other names:
Camptosar®;

Classification:
Topoisomerase I inhibitor

Mode 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.

Storage and stability:
The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates.

Preparation:
CAMPTOSAR Injection (irinotecan hydrochloride) must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL.

Route of administration:
Administer by I.V. infusion, usually over 90 minutes. Premedication with dexamethasone and a 5-HT_3 blocker is recommended 30 minutes prior to administration; prochlorperazine may be considered for subsequent use. Consider premedication of atropine 0.25-1 mg I.V. or SubQ in patients with cholinergic symptoms (e.g., increased salivation, diaphoresis, abdominal cramping) or diarrhea.

Incompatibilities/Interactions:
Stable in D_5W, NS.
Y-site administration: Compatible: Leucovorin calcium; Incompatible: Gemcitabine.

Availability:
Irinotecan is commercially available in the USA. Is an FDA approved agent for the treatment of patients with metastatic colorectal cancer. However, when used in combination as directed by this protocol, the agents are classified as "unapproved use of an agent" and, by definition, are considered investigational. While this combination is not currently approved by the FDA, the use in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2 (b).

Side effects:
>10%:
Cardiovascular: Vasodilation (9% to 11%).
Central nervous system: Cholinergic toxicity (47% - includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing and intestinal hyperperistalsis); fever (44% to 45%), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%).
Dermatologic: Alopecia (46% to 72%), rash (13% to 14%).
Endocrine & metabolic: Dehydration (15%).
Gastrointestinal: Diarrhea, late (83% to 88%; grade 3/4: 14% to 31%), diarrhea, early (43% to 51%; grade 3/4: 7% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), mucositis (30%), weight loss (30%), flatulence (12%), stomatitis (12%).
Hematologic: Anemia (60% to 97%; grades 3/4: 5% to 7%), leukopenia (63% to 96%, grades 3/4: 14% to 28%), thrombocytopenia (96%, grades 3/4: 1% to 4%), neutropenia (30% to 96%; grades 3/4: 14% to 31%).
Hepatic: Bilirubin increased (84%), alkaline phosphatase increased (13%).
Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%).
Respiratory: Dyspnea (22%), cough (17% to 20%), rhinitis (16%).
Miscellaneous: Diaphoresis (16%), infection (14%).

1% to 10%:
Cardiovascular: Edema (10%), hypotension (6%), thromboembolic events (5%).
Central nervous system: Somnolence (9%), confusion (3%).
Gastrointestinal: Abdominal fullness (10%), dyspepsia (10%).
Hematologic: Neutropenic fever (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (grades 3/4: 1% to 2%).
Hepatic: AST increased (10%), ascites and/or jaundice (grades 3/4: 9%).
Respiratory: Pneumonia (4%).

<1%:
ALT increased, amylase increased, anaphylactoid reaction, anaphylaxis, angina, arterial thrombosis, bleeding, bradycardia, cardiac arrest, cerebral infarct, cerebrovascular accident, circulatory failure, colitis, dysrhythmia, embolus, gastrointestinal bleeding, gastrointestinal obstruction, hepatomegaly, hyperglycemia, hypersensitivity, hyponatremia, ileus, interstitial lung disease, intestinal perforation, ischemic colitis, lipase increased, lymphocytopenia, megacolon, MI, myocardial ischemia, pancreatitis, paresthesia, peripheral vascular disorder, pulmonary embolus; pulmonary toxicity (dyspnea, fever, reticulonodular infiltrates on chest x-ray); renal failure (acute), renal impairment, thrombophlebitis, thrombosis, typhlitis, ulcerative colitis.

4. Gemcitabine

Other names:
Gemzar®

Classification:
Antimetabolite (Pyrimidine Analog)

Mode of action:
Gemcitabine is an antimetabolite of the pyrimidine analog type. Gemcitabine is cell cycle–specific for the S phase and for the G 1/S phase. Gemcitabine is phosphorylated intracellularly by deoxycytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate. Gemcitabine diphosphate inhibits the enzyme responsible for catalyzing synthesis of deoxynucleoside triphosphates required for DNA synthesis, and gemcitabine triphosphate competes with endogenous deoxynucleoside triphosphates for incorporation into DNA. The gemcitabine diphosphate–induced reduction in intracellular concentrations of deoxynucleoside triphosphates results in increased incorporation of gemcitabine triphosphate into DNA and, consequently, in inhibition of DNA synthesis. DNA polymerase epsilon is unable to remove the incorporated gemcitabine triphosphate and repair the DNA strands.

Storage and stability:
Gemcitabine vials are stored intact at room temperature of 20°C to 25°C (68°F to 77°F). Reconstituted vials are stable for up to 35 days and infusion solutions diluted in 0.9% sodium chloride are stable up to 7 days at 23°C when protected from light; however, the manufacturer recommends use within 24 hours for both reconstituted vials and infusion solutions. Solutions of reconstituted Gemcitabine should not be refrigerated, as crystallization may occur. The compatibility of Gemcitabine with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets. Caution should be exercised in handling and preparing Gemcitabine solutions. The use of gloves is recommended. If Gemcitabine solution contacts the skin or mucosa, immediately wash the skin thoroughly with soap and water or rinse the mucosa with copious amounts of water. Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Preparation:
To reconstitute, 5 mL of 0.9% Sodium Chloride Injection will be added to the 200 mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1 g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200 mg vial or 1.3 mL for the 1 g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride to concentrations as low as 0.1 mg/mL.

Route of administration:
Gemcitabine will be administered intravenously over 30 minutes.

Incompatibilities/Interactions:
Preclinical and clinical studies have shown that Gemzar has radiosensitizing activity. Toxicity associated with this multimodality therapy is dependent on many different factors, including dose of Gemzar, frequency of Gemzar administration, dose of radiation, radiotherapy planning technique, the target tissue, and target volume.

Availability:
Gemcitabine is commercially available in the USA. Is an FDA approved agent for the treatment of patients with locally advanced and metastatic pancreatic cancer. However, when used in combination as directed by this protocol, the agents are classified as "unapproved use of an agent" and, by definition, are considered investigational. While this combination is not currently approved by the FDA, the use in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2 (b).

Side effects:
>10%:
Hematologic: Anemia (65% to 73%; grade 4: 1% to 3%), leukopenia (62% to 71%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 47%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3/4: <1% to 2%); myelosuppression is the dose-limiting toxicity
Cardiovascular: Peripheral edema (20%), edema (13%)
Central nervous system: Pain (10% to 48%), fever (30% to 41%), somnolence (5% to 11%
Dermatologic: Rash (24% to 30%), alopecia (15% to 18%), pruritus (13%)
Gastrointestinal: Nausea/vomiting (64% to 71%; grades 3/4: 1% to 13%), constipation (10% to 31%), diarrhea (19% to 30%), stomatitis (10% to 14%)
Hepatic: Transaminases increased (67% to 78%; grades 3/4: 1% to 12%), alkaline phosphatase increased (55% to 77%; grades 3/4: 2% to 16%), bilirubin increased (13% to 26%; grades 3/4: <1% to 6%)
Renal: Proteinuria (10% to 45%; grades 3/4: <1%), hematuria (13% to 35%; grades 3/4: <1%), BUN increased (8% to 16%; grades 3/4: 0%)
Respiratory: Dyspnea (6% to 23%)
Miscellaneous: Flu-like syndrome (19%), infection (8% to 16%; grades 3/4: <1% to 2%)

1% to 10%:
Local: Injection site reactions (4%)
Neuromuscular & skeletal: Paresthesia (2% to 10%)
Renal: Creatinine increased (2% to 8%)
Respiratory: Bronchospasm (<2%)

<1%:
Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arrhythmias, bullous skin eruptions, cellulitis, cerebrovascular accident, CHF, chills, cough, desquamation, diaphoresis, gangrene, GGT increased, headache, hemolytic uremic syndrome (HUS), hepatotoxic reaction (rare), hypertension, insomnia, interstitial pneumonitis, liver failure, malaise, MI, peripheral

vasculitis, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, rhinitis, sepsis, supraventricular arrhythmia, weakness.

APPENDIX C

Dino-Clavien Scale

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological. *III-A:* intervention not under general anesthesia *III-B:* intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU-management. IV-A: single organ dysfunction (including dialysis) IV-B: multi organ dysfunction
Grade V	Death of a patient