

Title: Randomized Phase II Study of Neoadjuvant Chemotherapy (Gemcitabine and Nab-Paclitaxel vs. mFOFIRINOX) and Stereotactic Body Radiation Therapy for Borderline Resectable Pancreatic Cancer

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Table of Contents

<u>Section</u>	<u>Page</u>
Research Protocol Abstract.....	5
1.0. Primary Objective(s).....	9
2.0. Secondary Objectives(s)	9
3.0. Primary endpoint(s)	9
4.0. Secondary endpoint(s)	9
5.0. Background.....	9
6.0. Locally Advanced Disease and Borderline Resectable Disease.....	10
6.1. Chemotherapy for Metastatic Disease.....	10
6.2. Neoadjuvant Chemotherapy for LAD.....	11
6.3. Tumour Markers in Pancreatic Cancer – Role of CA-19.9	12
6.4. Role of Radiation Therapy in Pancreatic Cancer.....	13
6.4.1. Radiation Therapy Locally-advanced Pancreatic Adenocarcinoma	13
6.4.2. Stereotactic Body Radiotherapy (SBRT).....	13
6.4.3. Experience with SBRT at the University of Pittsburgh Cancer Institute.....	14
7.0. Rationale	15
8.0. Patient Selection and Eligibility	15
8.1. Selection of Subjects.....	15
8.2. Number of Subjects.	16
8.3. Inclusion Criteria.	16
8.4. Exclusion Criteria	17
9.0. Investigational Plan and Study Evaluations	17
9.1. Overall Design	17
9.2. Pre-treatment Evaluation.....	17
9.3. Day 0.....	18
9.4. During Study Evaluation.....	18
9.5. Disease Response Evaluation (MDC Evaluation).....	19
9.6. SBRT	19
9.7. Pre-Op.	20
9.8. Surgery.	20
9.9. Post treatment Assessment/Follow Up.....	20
9.10. Treatment	20
9.10. 1. Study Drug and Doses.....	20
10.0. Treatment Plan	22
10.1. Gemcitabine / nab-Paclitaxel.....	22
10.2. mFOLFIRINOX.....	24

11.0. Chemotherapeutic Agents.....	26
11.1. Gemcitabine Hydrochloride (Gemzar®)	26
11.1.1. Description.....	26
11.1.2. Toxicology	26
11.1.3. Pharmacology.....	26
11.2. nab-Paclitaxel (Abraxane™)	27
11.2.1. nab-paclitaxel Packaging, Labelling, and Storage.....	27
11.2.2. nab-paclitaxel (Abraxane™) Administration.....	28
11.2.3. Reconstitution and Use of nab-paclitaxel (Abraxane™)	28
11.3. modified FOLFIRINOX	29
11.3.1. Rounding Drug Doses.....	29
11.3.2. Fluorouracil (5-FU).....	29
11.3.2.1. Clinical Pharmacology	29
11.3.2.2. Precautions: General.....	30
11.3.2.3. Dosage and Administration.....	30
11.3.2.4. Handling and Disposal	31
11.3.3. Irinotecan	31
11.3.3.1. Pharmacology.....	32
11.3.3.2. Pharmacokinetics.....	32
11.3.3.3. Metabolism and Excretion.....	33
11.3.3.4. Administration.....	33
11.3.4. Oxaliplatin	33
11.3.4.1. Dosage and Administration	33
11.3.4.2. Dosage	33
11.3.4.2.1 Preparations of Infusion Solution.....	33
11.3.4.4. Warnings and Precautions.....	34
11.3.4. Gemcitabine.....	35
11.3.4.1. Premedication for Gemcitabine	35
11.3.4.2. Toxicity and Dose Modifications for Gemcitabine.....	35
11.3.6. nab-Paclitaxel (Abraxane™)	36
11.3.6.1. nab-Paclitaxel (Abraxane™).....	36
12.0. Dose Modifications for Chemotherapy.....	37
12.1. mFOLFIRINOX.....	37
12.2. nab-Paclitaxel (Abraxane™) and Gemcitabine (Gemzar®).....	39
13.2.1. Dose Modifications for Gemcitabine and/or Nab-paclitaxel.	39
13.0. Supportive Care	45
13.1. Both chemotherapy Regimen.....	45
13.2. mFOLFIRINOX.....	46
13.2.1. Antidiarrheal Medications.....	46
13.2.2. Irinotecan-related Cholinergic Syndrome	46
13.2.3. Antiemetic Therapy.....	46
13.2.4. Growth Factor Support.....	46
13.2.5. Fever.....	46
13.2.6. Management of Laryngopharyngeal Dysesthesias.....	47
13.3. SBRT Guidelines	47
13.3.1. Tissue Constraints	47
13.3.2. Dose Specification, Homogeneity Considerations & Plan Evaluation	47
13.4. On-Treatment Assessment and Post-treatment Toxicity Evaluation.....	47
13.4.1. Stereotactic Body Radiotherapy Risks	48

13.4.2. Fiducial Placement Risks	48
13.4.3. CT Risks.....	48
14.0. Statistics	48
15.0. Report of Adverse Reactions	50
15.1. Adverse Event Definitions.....	50
15.2. Reporting of Suspected Adverse Events.....	52
16.0. Data and Safety Monitoring	52
16.1. Subject Removal Criteria	53
17.0. Bibliography.....	54

Abstract

Recent reports indicate that while overall cancer related mortality is decreasing, the incidence of pancreatic cancer continues to rise. In particular, pancreatic cancer is the 4th leading cause of cancer death in the USA with approximately 44,000 new diagnoses in the United States. At the time of presentation, at least 80% of patients are either inoperable due to locally advanced or metastatic disease. Surgery still offers the only chance at 'cure', however only 10-20% of patients are candidates for resection at the time of presentation. Defining the population who should receive resection is perhaps the most important step in treating pancreatic cancer. The Society of Surgical Oncology has established guidelines for the management of unresectable disease, separating the two groups into locally advanced and borderline resectable disease (Callery *et al.* 2009). In general, locally advanced disease (LAD) demonstrates vascular encasement/encroachment but no distant metastases. The subgroup of borderline resectable (BR) disease demonstrates tumor abutment of the visceral vasculature without encasement thereby allowing for the possibility of resection but with added morbidity and a significantly higher rate of relapse compared with resectable patients. With neoadjuvant therapy, it now appears that up to one third of patients who initially present with locally advanced unresectable disease can now proceed to resection (Gillen *et al.* 2010)

In the metastatic setting, effective therapeutic options are limited. Historically, median survival time range from 4 to 6 months with gemcitabine alone to 11 months with newer regimens such as FOLFIRINOX. Until recently, gemcitabine was the standard sole chemotherapeutic agent for treatment of patients with advanced pancreatic cancer following the demonstration that gemcitabine produced improvement in disease-related symptoms and overall survival when compared with 5-FU. Since the establishment of gemcitabine as standard chemotherapy, multiple trials have evaluated the addition of alternate chemotherapeutic agents to gemcitabine with minimal improvement. Recently, data from the MPACT trial has shown a significant increase in one and two year survival for the combination of gemcitabine and nab-paclitaxel (paclitaxel bound protein bound particles (AbraxaneTM)) in the metastatic setting with an overall response rate of 23% in the combination arm (Von Hoff *et al.* 2013). In treatment-naïve patients with metastatic pancreatic cancer, combination therapy demonstrated a statistically significant improvement in overall survival compared to patients receiving gemcitabine alone [(median of 8.5 vs. 6.7 months) (HR 0.72, P=0.000015)] (Von Hoff 2013).

In the metastatic setting, FOLFIRINOX was compared to standard gemcitabine monotherapy in 342 patients with an ECOG PS0 or 1. The primary endpoint was (OS), with a median OS of 11.1 months in the FOLFIRINOX group vs. 6.8 months in the gemcitabine group (HR for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival (PFS) was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (HR for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective RR was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001) (Conroy *et al.* 2011)

In the neoadjuvant setting a recent retrospective review of 18 LAD patients treated with FOLFIRINOX demonstrated a 44% R0 (margin negative) resection rate (Hosein *et al.* 2012). Acknowledging the limits of a small retrospective trial, this trial suggests that a neoadjuvant approach utilizing FOLFIRINOX is feasible. In a recent study performed at our institution, 25 patients with LAD, 13 (52%) unresectable and 12 (48%) BR were treated with FOLFIRINOX. Following treatment with FOLFIRINOX, 11 underwent surgical resection, of which 4 (31%) were initially unresectable. 36% of resected patients (4 of 11 patients) received additional chemotherapy and/or radiation therapy prior to surgery. The R0 resection rate for borderline resectable patients was 6/8 (75%). Of the 10 initially unresectable patients, 3 (33%) underwent surgical resection, with 2 (20%) R0 resections. The overall R0 resection rate was 38%. A total of 6 patients (55%) demonstrated a significant pathologic response (data to be published). Definition of pCR has been well established and recently retrospective analysis has been done to evaluate pCR that have demonstrated varying results from 2-35% (Evans *et al* 1992, White *et al*, 2009). Given the variability that we have with

pCR and the high rate of pCR we have seen in our feasibility trial, we hope to see a 12% improvement in pCR.

Gemcitabine and *nab*-paclitaxel have been evaluated in the neoadjuvant resectable setting. Our Institution has participated in multi-center feasibility trial of preoperative gemcitabine/*nab*-paclitaxel. Subjects meeting NCCN criteria for potentially-resectable pancreatic cancer received 3 cycles of gemcitabine and *nab*-paclitaxel (1000mg/m² & 125mg/m² – day 1, 8, and 15) followed by surgical resection. The primary endpoint was grade III/IV pathological response in \geq 30% of resected tumor specimens. Of 15 patients that completed all 3 cycles, 6 required dose reduction. 5 patients were unable to complete all 3 cycles of therapy due to serious adverse events (Grade 3 or 4 toxicities). To date, 10 patients have undergone surgical resection. All 10 achieved negative surgical margins (R0 100%) and CA19-9 decrease from baseline (mean 181.7 U/ml) to end of therapy (mean 44.2 U/ml) was also noted (response measured after three cycles). There were no unexpected postoperative complications. A \geq 90% tumor necrosis (Grade III/IV) was seen in 3 patients, with 4 Grade 2, 1 Grade 1, and 2 without effect (obtained from communication with the trial investigators). The data available suggests that gemcitabine/*nab*-paclitaxel is a safe and well tolerated regimen in this population that is highly effective as demonstrated by the data above.

SBRT, modelled after intracranial stereotactic surgery, is technique that combines highly conformal radiotherapy with real-time imaging to deliver high doses of radiation in a small number of fractions. Because of the precise targeting, SBRT has the potential to improve upon the local control achieved with conventional EBRT while minimizing the dose to normal tissue. Most prospective randomized trials of conventionally fractionated EBRT for the treatment of locally-advanced pancreatic cancer have reported local control rates of 35%-55% (39)(40). Koong, et al established the feasibility of using SBRT for locally-advanced pancreatic cancer in a phase I dose escalation study which achieved 100% local control with no treatment limiting toxicities at 25 Gy in a single fraction (41). A follow-up study combined conventionally fractionated 5-FU chemoradiotherapy with an SBRT boost resulting in 94% local control but no improvement in overall survival and an increase in toxicity compared to SBRT alone (42). A recent study combining full dose gemcitabine with single fraction SBRT reported 81% local control and 100% 1-year freedom from local progression. While acute toxicities were minimal, a significant number of subjects (47%) experienced Grade 2 or greater late toxicities, primarily duodenal ulcers (43). It is possible that these late toxicities may be reduced by increasing the degree of conformance of the radiation dose cloud and increasing the number of fractions, as studies comparing conventionally fractionated RT with hypofractionated RT have found increase incidence of late GI toxicities in the hypofractionated group (38).

A retrospective review from our institution evaluated the outcome in 71 subjects with pancreatic cancer treated with SBRT (46). With a median follow-up of 12.7 months the freedom from local progression at 6 months and 1 year was 72% and 49%, respectively. Median overall survival for the entire group was 10.3 months. Treatment-related toxicity was minimal with only 3 patients experiencing acute grade 3 toxicity (4%). There was no recorded late toxicity. Another study from our institution examined outcomes in 24 patients treated post-operatively with SBRT (47). Sixty-six percent of the patients had positive margins and the remainder had close margins of 1-2.5mm. The median follow-up was 1 year. The freedom from local progression at 6 months and 1 year was 95% and 66%. There was no acute or late grade 3-4 toxicity, and two patients (8%) had late grade 1-2 toxicity, again demonstrating that when done properly, SBRT has a low potential for toxicity.

It would appear that both gemcitabine/*nab*-paclitaxel and FOLFIRINOX are effective in the neoadjuvant setting. In our own institution, we demonstrated that patients who initially fail to respond to FOLFIRINOX, when treated with gemcitabine/*nab*-paclitaxel had responses and successfully underwent resection (data to be published, presented at GI ASCO). There are currently no direct comparisons of Gemcitabine/*nab*-paclitaxel vs. FOLFIRINOX in the setting of either the metastatic, LAD or BR pancreatic adenocarcinoma. The preliminary data thus far from utilization of FOLFIRINOX in the locally advanced setting and more

recently Gemcitabine/*nab*-paclitaxel as neoadjuvant treatment for resectable disease have demonstrated promising response rates in the realm of 30-44%. We now wish to formally study the pathological response and ability to obtain R0 resections in this group of patients. The current study seeks to further investigate the impact of up-front systemic therapy in combination with fractionated SBRT for potentially resectable, locally-advanced pancreatic adenocarcinoma

Primary Objective(s)

Characterize the safety and efficacy of neo-adjuvant gemcitabine plus *nab*-paclitaxel in patients receiving SBRT and surgery for borderline resectable pancreatic cancer, using neo-adjuvant mFOLFIRINOX as a control.

Secondary Objective(s)

- To determine R0 resection rates in borderline resectable pancreatic cancer after treatment with gemcitabine/*nab*-paclitaxel or mFOLFIRINOX and SBRT
- To determine the safety and toxicity of preoperative chemotherapy and SBRT
- To determine radiological response rate to therapy
- To determine CA19-9 response to neoadjuvant chemotherapy and other serologic markers of response including HMGB1, sRAGE, DNA by picogreen, and IL-6
- To determine time to progression (TTP) in this population
- To determine predictive factors of response to chemotherapy with the use of correlative factors including SPARC, RM1, and SMAD4
- To assess absolute lymphocyte count at the beginning and end of therapy as potential novel markers of overall survival.
- To determine patients Quality of Life effects during chemotherapy and SBRT

Primary Endpoints

Efficacy: pathological complete response (pCR) *and* R0 resection.

Safety: Grade 4 toxicity.

Secondary Endpoint(s):

- R0 resection rates for patients with BR pancreatic cancer
- Incidence of grade 3 and 4 toxicities according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTAE, v4.0) for the 2 chemotherapy regimens that occur after Cycle 1 Day 1.
- Radiological improvements will be evaluated by determining changes in density of measurable disease on CT pre and post chemotherapy.
- Ca19-9 response to neoadjuvant chemotherapy will be measured during every cycle
- TTP in the group of patients who undergo resection. TTP will be defined as time after surgery to time of first progression as measured on CT scan or Ca19-9
- Measurement of biomarkers (SPARC, RM1 and SMAD4) in tissues that are obtained at screening and in the resected tumour specimen.
- To assess absolute lymphocyte count at the beginning and end of therapy as potential novel markers of overall survival
- Quality of life effects of Chemotherapy on patients receiving chemotherapy and SBRT as measured by the FACT-HB questionnaire.

Study Population

Subjects with primary borderline resectable adenocarcinoma of the pancreas (as defined by SSO criteria; shown in figure 1) will be eligible to participate in this trial.

Number of Patients for Study

The proportions of patients who attain R0 resection and pCR will be estimated for each arm. A significant difference in the efficacy endpoint between arms is not expected; the proportion of patients achieving R0 resection and pCR is expected to be between 0.10 and 0.15 in both arms. However, the proportion of patients encountering Grade 4 toxicity is expected to be much lower in the gemcitabine plus nab-paclitaxel arm than in the mFOLFIRINOX arm. If the true probability of Grade 4 toxicity is 0.01 with gemcitabine plus nab-paclitaxel and 0.20 with mFOLFIRINOX, a direct comparison on 40 participants randomized 1:1 using Fisher's exact test at $\alpha=0.1$ will have 62% power to reject the null hypothesis. The expected width of 95% confidence intervals around the probabilities of toxicity would be 0.17 (for $\pi=0.01$) and 0.38 (for $\pi=0.20$). While a direct comparison is underpowered, the results will be necessary to motivate and design a definitive Phase III trial.

Study Design and Methodology

This is a prospective, randomized phase II trial. Patients diagnosed with borderline resectable pancreatic adenocarcinoma will be randomly assigned to one of two treatment arms, either mFOLFIRINOX or gemcitabine and nab-paclitaxel. After three cycles of treatment in the gemcitabine/nab-paclitaxel arm and 6 cycles in the mFOLFIRINOX arm, patients will be restaged with CT scans and if they remain borderline resectable or have improvement of their disease. They will then proceed to SBRT followed by surgical resection.

Treatments Administered

Chemotherapy with either gemcitabine/nab-paclitaxel 3 cycles (3 weeks on/ 1 week off) or mFOLFIRINOX (every 14 days for 6 cycles). Upon completion of the chemotherapy they will proceed to SBRT followed by surgical resection.

1.0. Primary Objective

Characterize the safety and efficacy of neo-adjuvant gemcitabine plus nab-paclitaxel in patients receiving SBRT and surgery for borderline resectable pancreatic cancer, using neo-adjuvant mFOLFIRINOX as a control.

2.0. Secondary Objectives(s)

- To determine R0 resection rates in borderline resectable pancreatic cancer after treatment with gemcitabine/nab-paclitaxel or mFOLFIRINOX and SBRT
- To determine the safety and toxicity of preoperative chemotherapy and SBRT
- To determine radiological response rate to therapy
- To determine CA19-9 response to neoadjuvant chemotherapy and other serologic markers of response including HMGB1, sRAGE, DNA by picogreen, and IL-6
- To determine time to progression (TTP) in this population
- To determine predictive factors of response to chemotherapy with the use of correlative factors including SPARC, RM1, and SMAD4
- To assess absolute lymphocyte count at the beginning and end of therapy as potential novel markers of overall survival.
- To determine patients Quality of Life effects during chemotherapy and SBRT
- To determine patients Quality of Life effects during chemotherapy and SBRT

3.0. Primary Endpoint(s)

Efficacy: pathological complete response (pCR) and R0 resection.

Safety: Grade 4 toxicity.

4.0. Secondary Endpoint(s)

- R0 resection rates for patients with BR pancreatic cancer
- Incidence of grade 3 and 4 toxicities according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTAE, v4.0) for the 2 chemotherapy regimens that occur after Cycle 1 Day 1.
- Radiological improvements will be evaluated by determining changes in density of measurable disease on CT pre and post chemotherapy.
- Ca19-9 response to neoadjuvant chemotherapy will be measured during every cycle
- TTP in the group of patients who undergo resection. TTP will be defined as time after surgery to time of first progression as measured on CT scan or Ca19-9
- Measurement of biomarkers (SPARC, RM1 and SMAD4) in tissues that are obtained at screening and in the resected tumour specimen.
- To assess absolute lymphocyte count at the beginning and end of therapy as potential novel markers of overall survival
- Quality of life effects of Chemotherapy on patients receiving chemotherapy and SBRT as measured by the FACT-HB questionnaire.

5.0. Background

Recent reports indicate that, while overall cancer related mortality is decreasing, the incidence of pancreatic cancer continues to rise. In particular, pancreatic cancer is the 4th leading cause of cancer death in the United States with approximately 44,000 new diagnoses. In 2012, approximately 38,000 patients will die from the disease (American Cancer Society, 2012). While there has been a decline in the overall mortality of several other leading cancers, pancreatic cancer survival has not changed in over 40 years and its incidence continues to increase (1). According to the National Cancer Institute, 94% of patient diagnosed with

pancreatic cancer will die within 5 years, of which 75% of patients die in the first 12 months of diagnosis(American Cancer Society, 2012)(SEER Database, 2010).

Pancreatic cancer is rarely diagnosed early and is usually already metastatic or unresectable by the time of diagnosis. Only 15-20% of patients who are newly diagnosed can undergo potentially curative surgical resection (Varadhachary GR, 2006). Even those who are able to successfully undergo pancreaticoduodenectomy (Whipple's procedure), only about 15-20% have a 5 year overall survival (Ferrone CA, 2008)(Pelzer U, 2011). Ferrone et al. (2008) reported that AJCC stage and negative margins were the only significant predictors of long term survival.

6.0. Locally Advanced Disease and Borderline Resectable Disease

At the time of presentation, at least 80% of patients are considered inoperable due to locally advanced or metastatic disease. Surgery still offers the only chance at 'cure'; however only 10-20% of patients are candidates for resection at the time of presentation (Gillen S, 2010). Defining the population that should receive resection is perhaps the most important step in treating pancreatic cancer. The Society of Surgical Oncology has established guidelines for the management of unresectable disease, separating the two groups: locally advanced and borderline resectable disease (Callery MP, 2009)(NCCN , 2011 V2.2011). Borderline resectable is defined in **Figure 1**. With neoadjuvant therapy, up to one third of patients who initially present with locally advanced unresectable disease can now proceed to resection (Gillen S, 2010).

Figure 1: Definition of Borderline Resectable Pancreatic Cancer and Locally Advanced (Varadhachary et al, 2006)

Vessel	Resectable	Borderline resectable	Locally advanced
SMA	No extension; normal fat plane between the tumor and the artery	Tumor abutment $\leq 180^\circ$ (one half or less) of the circumference of the artery; periarterial stranding and tumor points of contact forming a convexity against the vessel improve chances of resection	Encased ($> 180^\circ$)
Celiac axis/hepatic artery	No extension	Short-segment encasement/abutment of the common hepatic artery (typically at the gastroduodenal origin); the surgeon should be prepared for vascular resection/interposition grafting	Encased and no technical option for reconstruction usually because of extension to the celiac axis/splenic/left gastric junction or the celiac origin
SMV/PV	Patent	Short-segment occlusion with suitable vessel above and below; segmental venous occlusion alone without SMA involvement is rare and should be apparent on CT images	Occluded and no technical option for reconstruction

SMA, superior mesenteric artery; SMV/PV, superior mesenteric vein/portal vein; CT, computed tomography.

6.1. Chemotherapy for Metastatic Disease

In the metastatic setting, effective therapeutic options are limited and optimal regimens are not clearly established. Historically, median survival time ranges from 4 to 6 months with gemcitabine, a nucleoside analogue, to 11 months with newer regimens like FOLFIRINOX (Conroy T D. F.-B.-A.-V., 2011). Gemcitabine became the standard chemotherapy backbone for treatment of advanced pancreatic cancer after it was demonstrated to produce improved overall survival and disease related symptoms when compared to 5-FU (5.6 vs. 4.4 months, P=0.002)(Burris HA III, 1997)(DiMarco MC, 2009) Since the establishment of gemcitabine as a standard chemotherapy for pancreatic adenocarcinoma, multiple trials have evaluated the addition of alternate chemotherapeutic agents to gemcitabine. However, they have all failed to demonstrate improved OS. Recently, there has been evidence to suggest that over expression of epidermal growth factor leads to poor prognosis in pancreatic cancer. With this mind, Erlotinib (a tyrosine kinase inhibitor of epidermal growth factor) has been tested widely in combination with gemcitabine. Moore et al. (Moore MJ, 2007) first demonstrated a small but statistically significant, improvement in survival with this combination leading to its approval. Since then, several other studies have aimed to reproduce these with variable results. A meta-analysis summarizing the available evidence on the efficacy and safety of gemcitabine plus erlotinib

showed a small but meaningful additive effect of the combination regimen compared to gemcitabine alone (Yang ZY, 2013).

Secreted protein acidic and rich in cysteine (SPARC), an albumin-binding protein, was found to be over-expressed in pancreatic adenocarcinomas (Neuzillet C, 2013). Nab-Paclitaxel, a 130-nm albumin-bound formulation of paclitaxel particles (Celgene, Summit, NJ), has shown antitumor activity in various advanced cancer types that over express SPARC (Neuzillet C, 2013). VonHoff et al. (Von Hoff DD E. T., 2013) looked at dose escalation of nab-paclitaxel in combination with gemcitabine and demonstrated an overall response rate of 48%, with a 12.2 median months and 48% 1-year survival when 125mg/m² of nab-paclitaxel was used in combination with Gemcitabine 1000mg/m² given weekly for 3 weeks every 28 days (Von Hoff DD R. R.-S., 2011). Major dose limiting toxicities found were sepsis and neutropenia. In addition, they also showed that decreases in CA19-9 levels were correlated with increased response rate, progression-free survival, and OS (Von Hoff DD R. R.-S., 2011).

Recently, a larger phase III study built on these phase I/II data, the MPACT trial was performed. It demonstrated a significant increase in one and two year survival for the combination of gemcitabine and nab-paclitaxel (paclitaxel bound protein bound particles (AbraxaneTM) compared to gemcitabine alone, in the metastatic setting with an overall response rate of 23% in the combination arm (Von Hoff DD E. T., 2013). In treatment-naïve patients with metastatic pancreatic cancer, combination therapy demonstrated a statistically significant improvement in overall survival compared to patients receiving gemcitabine alone [(median of 8.5 vs. 6.7 months) (HR 0.72, P=0.000015)] (Von Hoff DD E. T., 2013). The safety profile of this combination in this study was well tolerated. This has now prompted the option of using gemcitabine/nab-paclitaxel in this group of patients.

More recently, FOLFIRINOX (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) was compared to standard gemcitabine monotherapy in 342 metastatic patients with an ECOG PS=0 or 1 (Conroy T D. F.-B.-A.-V., 2011). The primary end point was overall survival (OS), with a median OS of 11.1 months in the FOLFIRINOX group vs. 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001). Median progression-free survival (PFS) was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group (hazard ratio for disease progression, 0.47; 95% CI, 0.37 to 0.59; P<0.001). The objective response rate (RR) was 31.6% in the FOLFIRINOX group versus 9.4% in the gemcitabine group (P<0.001). Despite more adverse events at 6 months in the FOLFIRINOX group, including a neutropenia, febrile neutropenia, diarrhea, neuropathy and LFT abnormalities, 31% of the patients in the FOLFIRINOX group had a definitive degradation of the quality of life versus 66% in the gemcitabine group (hazard ratio, 0.47; 95% CI, 0.30 to 0.70; P<0.001). These results demonstrate clear advantages to the use of FOLFIRINOX over gemcitabine and have resulted in the adoption of FOLFIRINOX as the standard of care for newly diagnosed metastatic patients with an excellent performance status (PS). Recently, a study conducted at Emory University demonstrated in 60 patients that with the elimination of the 5FU bolus the overall response rate was 30%. Off the 60 patients, there were 2 CR and 27 SD, demonstrating the efficacy of this combination despite the omission of the 5FU bolus without the hematological complications (Conroy T G. C., 2013).

6.2. Neoadjuvant Chemotherapy for LAD

Several other solid malignancies such as breast and rectal cancer have been treated neoadjuvant with chemotherapy or in combination with radiation. These neoadjuvant treatment regimens achieve improved margin negative resection rates, potential early treatment of micrometastatic disease and allow for improvement in the patient selection for which resection may offer a survival benefit. Several studies have been conducted in pancreatic cancer that looked at combination of external beam radiation therapy (EBRT) with chemotherapy; however, while these provide symptom alleviation and local pain control, survival

benefit and local disease control remains an issue. Two meta-analyses (Gillen S, 2010)(A Sultana, 2007) have been done that compared the use of chemotherapy with chemoradiotherapy. A survival benefit was demonstrated for the use of chemoradiation compared to radiotherapy alone; however the chemoradiation did not yield a survival advantage over chemotherapy alone (A Sultana, 2007).

In the neoadjuvant setting a recent retrospective review of 18 locally advanced pancreatic adenocarcinoma patients treated with FOLFIRINOX followed by chemoradiation demonstrated a 44% R0 (margin negative) resection rate (Hosein PJ, 2013)(Peter J Hosein1*, 2012). Acknowledging the limits of a small retrospective trial and brief follow-up, this trial suggests that a neoadjuvant approach utilizing FOLFIRINOX is feasible. In a recent study performed at our institution (to be published and was presented at 2013 SSO meeting and GI ASCO 2013), of 25 patients with locally advanced pancreatic cancer, 13 (52%) unresectable and 12 (48%) with borderline resectable disease, were treated with FOLFIRINOX. Following treatment with FOLFIRINOX, 11 underwent surgical resection, of which 4 (31%) were initially unresectable. 36% of resected patients (4 of 11 patients) received additional chemotherapy and/or radiation therapy prior to surgery. The R0 resection rate for borderline resectable patients was 6/8 (75%). Of the 10 initially unresectable patients, 3 (33%) underwent surgical resection, with 2 (20%) R0 resections. The overall R0 resection rate was 38%. A total of 6 patients (55%) demonstrated a significant pathologic response (data to be published).

Definition of pCR has been well established and recently retrospective analysis has been done to evaluate pCR that have demonstrated varying results from 10-35% (Evans et al 1992, White et al, 2009).

Gemcitabine and *nab*-paclitaxel have been evaluated in the neoadjuvant resectable setting. Our institution participated in a multi-center feasibility trial of preoperative gemcitabine/*nab*-paclitaxel. Subjects meeting NCCN criteria for potentially-resectable pancreatic cancer received 3 cycles of gemcitabine and *nab*-paclitaxel (1000mg/m² & 125mg/m² – day 1, 8, and 15) followed by surgical resection. The primary endpoint was grade III/IV pathological response in $\geq 30\%$ of resected tumor specimens. Of 15 patients that completed all 3 cycles, 6 required dose reduction. 5 patients were unable to complete all 3 cycles of therapy due to serious adverse events (Grade 3 or 4 toxicities). To date, 10 patients have undergone surgical resection. All 10 achieved negative surgical margins (R0 100%) and a decrease in CA19-9 from baseline (mean 181.7 U/ml) to end of therapy (mean 44.2 U/ml) was also noted (response measured after three cycles). There were no unexpected postoperative complications. A $\geq 90\%$ tumor necrosis (Grade III/IV) was seen in 3 patients, with 4 Grade 2, 1 Grade 1, and 2 without effect. (Obtained from communication with the trial investigators). The available data suggests that gemcitabine/*nab*-paclitaxel is a safe and well-tolerated regimen in this population that is highly effective as demonstrated by the data above.

It would appear that both gemcitabine/*nab*-paclitaxel and FOLFIRINOX are effective in the metastatic setting where they each offer an OS advantage compared to therapy with gemcitabine alone. In our own institution, we have documented that a subset of patients who initially fail to respond to FOLFIRINOX, do demonstrate objective tumor responses when treated with gemcitabine/*nab*-paclitaxel and successfully underwent resection (data to be published, presented at GI ASCO). There are no direct comparisons of Gemcitabine/*nab*-paclitaxel vs. FOLFIRINOX in the setting of either the metastatic or LAD pancreatic adenocarcinoma. Given the non-overlapping responses seen in locally advanced patients treated with both FOLFIRINOX and gemcitabine/*nab*-paclitaxel, and the efficacy that both these regimens have in the metastatic setting, we believe that it will be critical to directly compare each regimen's efficacy in treating locally advanced pancreatic cancer for both efficacy and toxicity profile at this setting.

6.3. Tumor Markers in Pancreatic Cancer – Role of CA-19.9

The role of tumor biomarkers in monitoring and early diagnosis of cancer is an emerging field. However, pancreatic cancer lags behind other malignancies in the tumor markers available for monitoring. A variety of tumor markers have been investigated. Of these, Carbohydrate antigen 19-9 (CA19-9), which is an isolated

Lewis antigen of the MUC1 protein, has currently become the gold standard to diagnose and monitor treatment of pancreatic cancer (Herreros-Villanueva, 2013).

There is also evidence to suggest that response to CA19-9 can be used as a surrogate marker for tumor progression. In 2008, Wong *et al* (Wong D, 2008) compared CA19-9 to radiographic objective response as a surrogate for clinical outcomes in patients receiving chemotherapy for metastatic pancreatic cancer. Significant correlations were observed between maximum CA19-9 decline and both TTP ($P < 0.0001$) and OS ($P < 0.0001$). Median OS was 12.2 months for patients with more than a 75% decline in CA19-9, 7.5 months for those with 0% to 75% decline, and 3.5 months for those with no decline (Wong D, 2008).

Similarly, the response of CA19-9 to fixed dose gemcitabine has also been investigated. In a cohort of 76 patients with advanced pancreatic cancer receiving fixed-dose rate gemcitabine, it was shown that statistically significant correlations can be seen between CA19-9 decline, time to treatment failure and OS (Ko AH, 2005). Median survival time ranged from 12.0 months for patients with the greatest degree of biomarker decline (> 75%) compared with 4.3 months in those whose CA19-9 did not decline during therapy ($P < 0.001$). More recently, improved OS was demonstrated in patients with locally advanced pancreatic cancer in whom greater than 75% decrease in CA19-9 from baseline was seen in response to neo-adjuvant chemoradiation (gemcitabine, 5FU and radiation) (Singh, *et al* 2012). In this study, 88% of patients had LAD or borderline resectable disease. 34% of all patients had a greater than 75% reduction in CA19-9 from baseline with median survival in this group being 89.4 weeks compared to 41.3 weeks in patients who had less than 75% change in CA19-9. (Singh et al. 2012)

6.4. Role of Radiation Therapy in Pancreatic Cancer

6.4.1. Radiation Therapy Locally-advanced Pancreatic Adenocarcinoma

Studies by the Gastrointestinal Tumor Study Group (GITSG) established combined chemotherapy and external beam radiation therapy (EBRT) as the treatment of choice for locally-advanced pancreatic adenocarcinoma (Group, 1979)(Moertel CG, 1981)(Group., Radiation therapy combined with Adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. , 1985)(Group., Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone., 1988). Subsequent studies have confirmed a doubling in median survival time (from 3-6 months to 9 to 13 months) for combined chemoradiotherapy compared to observation, however improvements in 2-year survival have been minimal (Jr., 1979)(Gunderson LL, 1983)(Mohiuddin M, 1988). While combined 5-fluorouracil (5-FU) and EBRT is the most frequently used treatment in the United States, multiple other treatment options and combinations have been explored in an attempt to improve outcomes while maintaining acceptable levels of toxicity. Intraoperative radiation therapy (IORT) has shown promise as a technique for improving local control while limiting the dose to nearby normal tissue. Unfortunately, this improved local control has not translated into improved overall survival (Roldan GE, 1988).

Multiple chemotherapeutics have been tried in combination with or replacement of 5-FU to improve upon its radiosensitizing effects. The nucleoside analog gemcitabine (2',2'-difluoro-2'-deoxycytidine) has been proven to be a potent radiosensitizing agent in human pancreatic cancer cell lines (Lawrence TS, 1996). Furthermore, in a randomized trial comparing single agent gemcitabine with 5-FU for the treatment of advanced or metastatic pancreatic cancer, the 1-year survival for subjects treated with gemcitabine was 18% versus 2% for those treated with 5-FU(Burris HA III, 1997). Based upon these results it was believed that concurrent full dose gemcitabine and EBRT could provide maximal systemic effects while enhancing local control as pre-clinical trials demonstrated maximal radiosensitization at cytotoxic levels. While the combination has demonstrated promising results in maintaining local control, it has been associated with significant acute and late toxicities (Blackstock AW B. S., 1999)(Blackstock AW T. M., 2001)(McGinn CJ, 1998)(Wolf R). Investigators have tried to address this problem by either reducing the dose of gemcitabine

or EBRT or by increasing the number of fractions of EBRT (Poggi MM, 2006)(Wolff RA, 2001)(Symon Z, 2006).

6.4.2. Stereotactic Body Radiotherapy (SBRT)

SBRT is technique that combines highly conformal radiotherapy with real-time imaging to deliver high doses of radiation in a small number of fractions. Modeled after intracranial stereotactic radiosurgery, SBRT has now been studied in a variety of extra-cranial locations including the spine, lung, liver, pancreas, and head and neck cancers. Because of the precise targeting, SBRT has the potential to improve upon the local control achieved with conventional EBRT while minimizing the dose to normal tissue. Most prospective randomized trials of conventionally fractionated EBRT for the treatment of locally-advanced pancreatic cancer have reported local control rates of 35%-55% (Ben-Josef E. Shields AF, 2004)(Brade A, 2005). Koong, et al established the feasibility of using SBRT for locally-advanced pancreatic cancer in a phase I dose escalation study which achieved 100% local control with no treatment limiting toxicities at 25 Gy in a single fraction (Koong AC L. Q., 2004). A follow-up study combined conventionally fractionated 5-FU chemoradiotherapy with an SBRT boost resulting in 94% local control but no improvement in overall survival and an increase in toxicity compared to SBRT alone (Koong AC C. E., 2005). A recent study combining full dose gemcitabine with single fraction SBRT reported 81% local control and 100% 1-year freedom from local progression. While acute toxicities were minimal, a significant number of subjects (47%) experienced Grade 2 or greater late toxicities, primarily duodenal ulcers (Schellenberg D, 2008). It is possible that these late toxicities may be reduced by increasing the degree of conformance of the radiation dose cloud and increasing the number of fractions, as studies comparing conventionally fractionated RT with hypofractionated RT have found increase incidence of late GI toxicities in the hypofractionated group (Symon Z, 2006).

Another advantage to SBRT is the fractionation schedule. First, the entire course of treatment is often completed over 1 to 7 days versus the 5 to 8 weeks required for conventionally fractionated EBRT. Second, the accelerated fractionation schedule could improve overall survival by allowing earlier systemic doses of chemotherapy. Because locally-advanced pancreatic cancer is characterized by rapid progression to metastatic disease, early delivery of systemic chemotherapy is imperative to address potential sites of microscopic disease. In fact, some studies have evaluated the delivery of systemic chemotherapy followed by combined chemoradiotherapy for those subjects without evidence of disease progression. This strategy selects those subjects most likely to benefit from the local control provided by radiotherapy and in two separate studies has resulted in significant increases in TTP and OS for subjects treated with chemoradiotherapy compared to those receiving chemotherapy alone(Huguet F, 2007)(Krishnan S, 2007).

6.4.3. Experience with SBRT at the University of Pittsburgh Cancer Institute

A retrospective review from our institution evaluated the outcome in 71 subjects with pancreatic cancer treated with SBRT(Rwigema JC P. S., 2010). With a median follow-up of 12.7 months the freedom from local progression at 6 months and 1 year was 72% and 49%, respectively. Median overall survival for the entire group was 10.3 months. Treatment-related toxicity was minimal with only 3 patients experiencing acute grade 3 toxicity (4%). There was no recorded late toxicity. Another study from our institution examined outcomes in 24 patients treated post-operatively with SBRT(Rwigema JC H. D., 2010). Sixty-six percent of the patients had positive margins and the remainder had close margins of 1-2.5mm. The median follow-up was 1 year. The freedom from local progression at 6 months and 1 year was 95% and 66%. There was no acute or late grade 3-4 toxicity, and 2 patients (8%) had late grade 1-2 toxicity, again demonstrating that when done properly, SBRT has a low potential for toxicity.

The current study seeks to further investigate the impact of up-front systemic therapy in combination with fractionated SBRT for potentially resectable, locally-advanced pancreatic adenocarcinoma.

Combination chemoradiotherapy for locally advanced pancreatic cancer has been analyzed in a number of trials; however any survival benefit accrued has at best been modest. One recently presented study (ECOG 4201) of gemcitabine with or without RT, was terminated early due to poor accrual. This study showed a barely significant increase in OS, however at the cost of a significant increase in grade 4 toxicity (41 vs. 6 percent).

One recently utilized strategy to reduce the complication risk of chemoradiation has as its basis an attempt to limit chemoradiotherapy to those who would most likely benefit by offering an initial period of chemotherapy and limiting subsequent chemoradiation to those without evidence of disease progression. As part of phase II and III trials conducted by the European Groupe Cooperateur Multidisciplinary en Oncologie (GERCOR), a retrospective series evaluated 181 patients with locally advanced disease. Chemotherapy was given for three months upfront, and at the patients and physicians discretion, those who had not progressed were treated by chemoradiation therapy. Interestingly, of 128 patients eligible for chemoradiation, subsequent radiotherapy after initial chemotherapy was associated with an increase in median OS (15 vs. 11.7 months). A separate study from the MD Anderson (Krishan et al 2007) similarly showed a survival advantage of 11.9 vs. 8.5 months for those patients treated by an initial period of chemotherapy, and subsequently reserving radiation therapy for those who did not progress.

7.0. Rationale

As discussed above, gemcitabine in combination with nab-Paclitaxel and FOLFIRINOX appear to be feasible and effective treatment options in the metastatic setting. While FOLFIRINOX demonstrates a higher RR (31.6 vs. 23%) and OS (11.1 vs 8.5 months) compared to gemcitabine/nab-paclitaxel, it is somewhat difficult to compare directly. FOLFIRINOX was primarily studied in academic tertiary centers in France and there were a paucity of pancreatic head tumors in their study population. The generalizability and external validity with the MPACT study of gemcitabine/nab-paclitaxel is better as it was conducted in a community setting with well distributed cases, including patients with KPS >70 or ECOG PS 2. In addition, in the phase I/II trial of gemcitabine and nab-paclitaxel, the authors showed RR and OS of 48% and 12.2 months, respectively, in certain patient population (Von Hoff DD R. R.-S., 2010) when conducted in an academic tertiary setting. This certainly indicates that the true RR and OS may in fact be closer to the FOLFIRINOX trial. Recently, two retrospective studies of FOLFIRINOX have demonstrated increased R0 resection and pCR rates, both of which predict OS benefit and are consistent with historic controls. In our institution, we have seen responses, by CA19-9 and in terms of resectability in a subset of patients who received gemcitabine and nab-paclitaxel after failing FOLFIRINOX, suggesting there are non-overlapping populations in terms of responses. Plus, the toxicity profiles for these two regimens are different.

Additionally as discussed above, there is great variability in the pCR rates. Historically it has been in realm of 3% with some increase to 5-7% with recent advances in SBRT. Our recent feasibility data has shown pCR around 55%. With the introduction of both FOLFIRINOX and gemcitabine/nab-paclitaxel for treatment of pancreatic cancer as well as the additional use of SBRT, it is expected that we will see an improvement to 20% in the pCR after surgery. In addition, concerns have been raised regarding the toxicity of FOLFIRINOX regimen particularly with the addition of the 5FU bolus owing to significant component of the hematologic toxicities seen in patients. For these reasons, we now wish to formally study the pathological response and ability to obtain R0 resections in this group of patients using a modified FOLFIRINOX (mFOLFIRINOX) regimen where the 5-FU bolus is eliminated. As stated above, recent trials have demonstrated similar efficacy with mFOLFIRINOX compared to FOLFIRINOX itself. By using the modified regimen, we can eliminate the hematologic toxicities without compromising the efficacy. The current study seeks to further investigate the impact of up-front systemic therapy in combination with fractionated SBRT for potentially resectable, locally-advanced pancreatic adenocarcinoma.

8.0. Patient Selection and Eligibility

8.1. Selection of Subjects

Enrollment is defined as the first day of the randomization. Potential subjects will be identified from the Principal Investigator's and co-investigators' current clinic population, or will be referred to the Principal Investigator by their own physician. They will be approached and informed of the study by an individual who is involved in their care. No cold-calling will occur, and no advertising will be used. The consent process will be carried out as a joint effort among the subject's physician, the study coordinator, and/or co-investigators on the study.

8.2. Number of Subjects

The proportions of patients who attain R0 resection and pCR will be estimated for each arm. A significant difference in the efficacy endpoint between arms is not expected; the proportion of patients achieving R0 resection and pCR is expected to be between 0.10 and 0.15 in both arms. However, the proportion of patients encountering Grade 4 toxicity is expected to be much lower in the gemcitabine plus nab-paclitaxel arm than in the mFOLFIRINOX arm. If the true probability of Grade 4 toxicity is 0.01 with gemcitabine plus nab-paclitaxel and 0.20 with mFOLFIRINOX, a direct comparison on 40 participants randomized 1:1 using Fisher's exact test at $\alpha=0.1$ will have 62% power to reject the null hypothesis. The expected width of 95% confidence intervals around the probabilities of toxicity would be 0.17 (for $\pi=0.01$) and 0.38 (for $\pi=0.20$). While a direct comparison is underpowered, the results will be necessary to motivate and design a definitive Phase III trial. Patients will be replaced if they withdraw from the study.

8.3. Inclusion Criteria

All patients must meet the following criteria within 28 days of randomization (unless otherwise indicated) to be enrolled in the protocol:

- Patient must have the ability to give written informed consent
- Histologically or cytologically proven adenocarcinoma of the pancreas. If the patient has mixed tumor with predominant adenocarcinoma pathology, they can be enrolled.
- Subjects will be staged according to the 2010 AJCC staging system with pathologic stage T1-4, N0 being eligible; and have a primary tumor of the pancreas (either pancreatic head, neck, uncinate process, or body/tail)
- The tumor must be deemed as being borderline resectable. Final CT confirmation of surgical staging/ eligibility will be at the discretion of the pancreatic surgeon of the patient.
- Disease is confined to locoregional site as confirmed by the CT and / or diagnostic staging laparoscopy to avoid occult peritoneal deposits. Diagnostic laparoscopy will be only if absolutely required
- Measurable disease per RECIST (v1.1) on imaging studies CT
- Screening Endoscopic ultrasound if done prior to consent but within 6 weeks of expected randomization date it may be used.
- Karnofsky performance status greater than or equal to 70 or ECOG performance of 0-2.
- Age ≥ 18
- Estimated life expectancy ≥ 12 weeks
- If female patient is of child bearing potential, she must have a negative serum pregnancy test (β hCG) documented up to 72hrs prior to administration of first study drug
- Patient has screening blood work performed which includes the following (should be drawn ≤ 14 days prior to randomization)
 - ANC $\geq 1.5 \times 10^9/L$
 - Platelet count $\geq 100000/mm^3$
 - Hemoglobin (HgB) $\geq 9g/dL$
 - AST,ALT $\leq 2.5 \times$ upper limit of normal (ULN) Total Bilirubin \leq ULN
 - Serum Cr within normal limits (WNL) or calculated GFR $\geq 60ml/min$
 - Coagulation studies with PT/INR and PTT within normal limits ($\pm 15\%$). If the patient is on Coumadin – we would switch the patient to LMW heparin product such as fondaparinux (Arixtra) or enoxaparin (Lovenox). An anti-factor Xa test should be

available demonstrating adequate anti-coagulation on the LMWH (therapeutic range 0.4-0.8). However, if this is not possible then INR must be kept ≤ 3 .

- Patient has a urinalysis obtained (≤ 14 days prior to randomization) and the results are deemed not clinically significant by the investigator.
- Patient has no evidence of jaundice at the time of enrolment. If stent is required to alleviate jaundice, it should be metallic. If patient has a previously placed stent and this is plastic, this should be changed to metallic.
- Patient's pain symptoms have remained stable with no adjustment to analgesics within 7 days prior to randomization. Patient must be able to swallow entreat medications with no requirement for a feeding tube. Patient's must not have intractable nausea or vomiting which prohibits the patient from oral medications
- Diabetes must be controlled prior to enrollment
- Disease must be encompassed in a reasonable SBRT "portal" as defined by the treating radiation oncologist

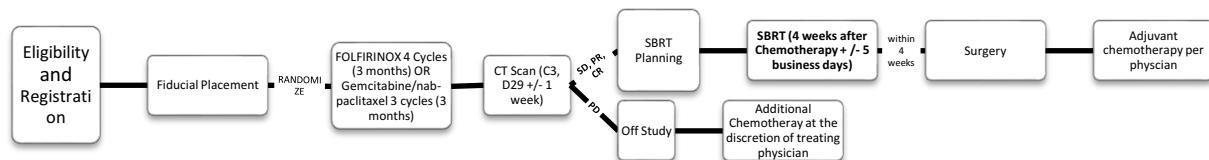
8.4. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

- Ineligible Histology including non-adenocarcinomas, adenosquamous carcinoma, islet cell carcinomas, cystadenomas, cystadenocarcinomas, carcinoid tumors, duodenal carcinomas, distal bile duct and ampullary carcinomas
- Evidence of distant metastasis on upright CXR, CT or other staging studies
- Subjects with recurrent disease
- Prior radiation therapy to the upper abdomen or liver at the discretion of the treating radiation oncologist could impair delivery of the prescribed radiation treatment
- Prior chemotherapy
- Subjects in their reproductive age who are breast feeding or have a positive pregnancy test
- Any co-morbid condition of sufficient severity to limit full compliance with the protocol per assessment by the individual treating physician
- Concurrent active infection
- Previous or current malignancies of other histologies within the last 3 yrs prior to randomization; with the exception of cervical cancer in situ, adequately treated basal cell or squamous cell carcinoma of skin or treated low risk prostate cancer
- Patient with known historical or active infection with HIV, Hepatitis B or Hepatitis C
- Patient who has undergone recent major surgery, other than diagnostic surgical procedure within 4 weeks prior to randomization.
- Patient who has a history of allergy or hypersensitivity to any of the study drugs.
- Patients with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, interstitial pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies
- Patients with greater than 2 screening peripheral neuropathy.

9.0. Investigational Plan and Study Evaluations

9.1 Overall Design



9.2. Pretreatment Evaluation

The following tests/procedures will need to be performed up to 28 days prior registration in order to ascertain eligibility unless otherwise specified or at the discretion of the treating physician

- Signed informed consent by the patient (not a surrogate)
- Complete physical examination, body weight and height taken within 21 days prior to randomization. This will then be used to calculate the BSA which will be used to dose chemotherapy drugs (mFOLFIRINOX or gemcitabine/*nab*-paclitaxel)
- Medical history (including documented Past medical history, Social history, use of other tobacco products), concomitant medications, medical conditions (AEs)
- Diagnostic endoscopic ultrasound (EUS)
- Placement of metallic biliary stent if indicated
- Placement of infusaport for chemotherapy
- Pathology review or biopsy for diagnosis and correlative studies
- Blood work (within 14 days of randomization) will include:
 - CBC, differential and platelets
 - CMP (Na, K, CL, CO₂, Glucose, BUN, Creatinine, Calcium, Protein Total, Albumin, AST, ALT, ALK Phos, Bili T), Magnesium, LDH, and Phosphorus
 - Coagulation studies including INR, PT, PTT
 - CA19-9 CEA
 - Anti-factor Xa only if on fondaparinux (Arixtra) or enoxaparin (Lovenox)
 - Research blood for correlative studies
- CT scan or Spectral CT Scan and tumor measurement
- Urinalysis
- QoL questionnaire (FACT-HB)
- Women of child bearing potential will have a serum pregnancy test within 72 hours of randomization
- EKG/ECG
- Evaluation by the pancreatic surgeon to confirm surgical status.
- Evaluation by a radiation oncologist to confirm SBRT candidate.

9.3. Day 0

- Randomization will be performed in a 1:1 fashion utilizing a computerized block randomization technique.
- Placement of gold fiducials via EUS.

9.4. During Study Evaluation

During each active treatment visit, the patient's evaluation will consist of:

- Complete physical examination including performance status
- History, concomitant medication and adverse event evaluation
- Blood work (days 1, 8, 15 for gemcitabine/*nab*-paclitaxel arm or Day 1 of mFOLFIRINOX Arm):

- CBC with differential, platelets
- CMP (Na, K, Cl, CO₂, Glucose, BUN, Creatinine, Calcium, Protein Total, Albumin, AST, ALT, ALK Phos, Bili T), Magnesium, LDH, and Phosphorus
- Tumor markers CA 19-9 and CEA will be drawn day 1 of every cycle
- If on anti-coagulation therapy Anti- Xa level will be tested at least once during chemotherapy at the physician's discretion
- Research blood for correlative studies
- QoL questionnaire (FACT-HB)
- Administration of chemotherapy based on the randomization . Patients randomized to the gemcitabine/nab-paclitaxel arm will receive up to 3 cycles of chemotherapy (3 weeks on/ 1 week off every 28 days). Patients randomized to the mFOLFIRINOX arm will receive Oxaliplatin, Irinotecan and 5FU 46 hour infusion every 14 days for up to 6 cycles. Patients will be assessed during every cycle of chemotherapy with appropriate dose modifications as required. Chemotherapy will be divided such that 3 or 6 cycles of therapy will be administered prior to restaging depending upon arm.

9.5. Disease Response Evaluation (MDC Evaluation)

At the completion of the assigned cycles of therapy the patient will have:

- CT Scan or Spectral CT Scan of the chest, abdomen and pelvis (CT Scan) to re-evaluate response to neoadjuvant chemotherapy.

NOTE: Patients who are deemed as having SD but remains unresectable or PD after 3 months of treatment will be deemed off treatment. They may then receive additional off study chemotherapy based on the discretion of the treating physician. These subjects will be followed for TTP and survival.

9.6 SBRT within 4 weeks of completion of chemotherapy (+/- 5 business days)

Patients who are deemed as having SD, PR or CR by imaging will be seen by the pancreatic surgeon and radiation oncologist to confirm resectability and SBRT planning.

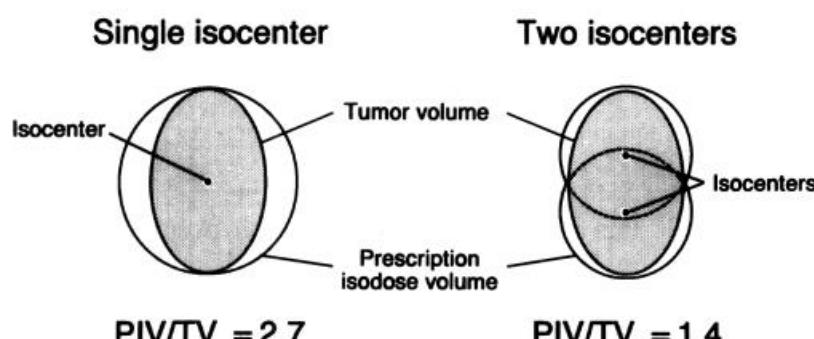
An SBRT plan will be created based on the disease contoured on the CT. The plan will be to deliver fractionated SBRT to the isodose line best encompassing the PTV:

12 Gy x 3 fractions (36 Gy total).

Careful evaluation of the each plan will be conducted by the radio-surgical team to ensure that normal tissues and critical structures tolerances are maintained.

The maximum dose (in Gy) within the treatment volume (MD), prescriptions dose (PD), and the ratio of MD/PD (as a measure of heterogeneity within the target volume), prescription isodose volume (PIV in mm³), tumor volume (TV in mm³), and the ratio of PIV/TV (as a measure of dose conformity of the treatment relative to the target) will be recorded in the patient's medical record. This concept is illustrated in

Figure 2: Example illustrating the concept of PIV/TV



During the SBRT the patient will have:

- Physical exam including PS performed by the Radiation Oncologist
- Medical history, Con meds, AE evaluation
- CT Scan or Spectral CT Scan of the chest, abdomen and pelvis for radiation planning will be done by the treating radiation oncologist. This CT scan is planning for measurements
- Blood work: research blood for correlative studies
- The time from the end of last cycle of chemotherapy regardless of arm to SBRT start should within 4 weeks (+/- 5 business days)

9.7. Pre-Op Visit - will be done within 2 (+/- 3 business days) weeks of completing SBRT

- Physical Exam including PS
- Medical history, Con meds, AE evaluation
- Blood work: CMP, CBC diff and platelets, magnesium, coagulation studies if on anticoagulation therapy, CA19-9 CEA, anti-factor Xa, and research blood for correlative studies.

9.8. Surgery within 4 weeks (+/- 5 business days) of Completing SBRT

Surgical specimen will have SPARC and SMAD4 testing performed by pathology as standard of care. Margin status will be recorded in the patient's medical record and research data base. If the subject agrees a tissue specimen will be collected from surgery for correlative studies.

9.9. Post treatment Assessment/Follow Up

Patients will be taken off treatment if they remain surgically unresectable at the restaging scan point. At this stage patients can come off study therapy and additional chemotherapy may be administered at the discretion of the treating oncologist. These patients will be followed for TTP and survival.

Follow-up after surgery is recommended at Q3 (+/- 4 weeks) months for 6 months, then every 6 (+/- 4 weeks) months for 24 months but this will be at the discretion of treating physician. During follow up the patient will have CT scan or Spectral CT Scan (chest abdomen/pelvis).

9.10. Treatment

9.10.1. Study Drug and Doses

Patients will be treated on an outpatient basis with mFOLFIRINOX or Gemcitabine/nab-Paclitaxel.

Gemcitabine/nab-Paclitaxel:

Patients will receive nab-paclitaxel plus gemcitabine with 125 mg/m² nab-paclitaxel as a 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) followed by 1000 mg/m² gemcitabine as a 30- to 40-minute infusion (maximum 40 minutes) for 3 weeks followed by a week of rest.

Supportive care and antiemetics per the treating institution standard can be provided at the Investigator's discretion

mFOLFIRINOX:

Patients will receive FOLFIRINOX consisting of oxaliplatin at a dose of 85 mg/m², given as a 2-hour intravenous infusion, immediately followed by irinotecan at a dose of 180 mg/m², given as a 90-minute intravenous infusion. This treatment will be immediately followed by fluorouracil as a continuous intravenous infusion of 2400 mg /m² over a 46-hour (+/- 30 minutes) period every 2 weeks. As noted in the rationale previously, elimination of bolus 5-FU appears to offer similar response rates in locally advanced pancreatic cancer without the added hematologic side effects. As such, we will eliminate the 5-FU bolus and leucovorin throughout this study.

Supportive care and antiemetics per treating institution standard will be administered for both chemotherapy combinations. Suggested anti-emetics for mFOLFIRINOX including serotonin 5HT3 receptor blocker (eg: ondansetron), steroids pre chemotherapy and for 5days post chemotherapy at a dose of 4 mg dexamethasone PO BID x 2 days, 2 mg PO BID x 2 days 2mg x 1 day 5 unless there is a contraindication due to severe diabetes. If patient has severe diabetes it is suggested this be controlled as best as possible prior starting chemotherapy. Following the chemotherapy administration, it is suggested that patients be on round-the-clock anti-serotonergic as antiemetics for 3 days. The addition, of a second antiemetic can be added at the investigator's discretion. The antiemetic regimen for the gemcitabine/nab-paclitaxel arm will be at the discretion of the investigator

Please see Section 13 for full details of supportive care.

10.0. Treatment Plan

10.1. Gemcitabine / nab-Paclitaxel

Parameter	Screening ¹	Day 0	Cycle 1			Cycle 2			Cycle 3 ³			MDC evaluation	SBRT ⁴ #>	Pre - Op ¹³	Follow-up (+/-4 weeks) ⁵	
			Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15					
Physical Exam ⁶ PS, HT ² and Wt, BSA	X [^]		X			X			X					X	X	X
Randomization		X														
History, Con Meds and AE Evaluation	X		X			X			X					X	X	
Diagnostic endoscopic ultrasound (EUS)(If not already completed)>	X															
Placement of Biliary stent ¹¹	X															
Port placement ¹²	X															
Pathology review or Biopsy for diagnosis and correlative studies(if not already completed)	X															
CBC with diff, plt	X [%]		X	X	X	X	X	X	X	X	X			X		
CMP (Na, K, CL, CO2, Glucose, BUN, Creatinine, Calcium, Protein Total, Albumin, AST, ALT, ALK Phos, Bili T), Magnesium, LDH, and Phosphorus	X [%]		X	X	X	X	X	X	X	X	X			X		
Coagulation studies including INR, PT, PTT ⁶	X [%]														X	
Anti Xa level ⁷	X [%]														X	
Ca 19-9 and CEA	X [%]		X			X			X						X	
CT Scan or Spectral CT Scan (chest/abdomen/pelvis) and tumor measurement	X											X ⁸	X ⁹		X	
Urinalysis	X															
Placement of Gold Fiducials via EUS>		X														
Quality of Life questionnaire (FACT-HB)	X		X			X			X				X ¹⁰			
Serum Pregnancy Test (can be up to 72 hrs prior) if pt is < 60ys age	X [^]															
Gemcitabine/nab-paclitaxel			X	X	X	X	X	X	X	X	X					
Correlative studies Blood work ¹⁴	X		X			X			X					X		

EKG/ECG	X										
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¹ Screening tests will be done within 28 days of randomization.

² Height needs to be documented once at screening

³ Only patients who are deemed to have had a response (SD, PR or CR) will proceed to SBRT and surgery

⁴ Only patients who have a response after cycle 3 of chemotherapy will proceed to SBRT (completed at UPMC Shadyside Hospital) within four weeks after completion of chemotherapy (+/- 5 business days).

⁵ Follow-up after surgery is recommended at Q3 months for 6 months, then every 6 months for 24 months but this will be at the discretion of treating physician. Additional imaging and tumor markers will be at the discretion of the oncologist.

⁶ Patients who are on Coumadin will require their INR to be checked every cycle or according to the treating oncologist

⁷ If patient is on anticoagulation with either enoxaparin or fondaparinux, Anti Xa level should be tested at least once during chemotherapy. Additional levels can be done at the discretion of treating oncologist

⁸ Disease measurements are based on CT after 3 cycles of chemotherapy. This CT should be performed on the patient's off week prior to MDC clinic. At the MDC clinic it will be reviewed by the medical oncologist, surgeon and radiation oncologist to make decision as to whether patient proceeds to SBRT and surgery.

⁹ Planning CT scan for measurement only

¹⁰ QOL questionnaires will be done at the end of SBRT.

¹¹ If patient has biliary obstruction and a stent is required, it must be a metallic stent. If a pre-existing plastic stent is present, this will need to be changed to a metallic stent prior to starting chemotherapy.

¹² If patient is randomized to gemcitabine/nab-paclitaxel, port placement is at the discretion of the treating physician.

¹³ If patient proceeds to surgery - surgery will be done within 2 (+/- 3 business days) weeks after completion of SBRT. Pre-op visit will be organized accordingly

¹⁴ Blood will be drawn for HMGB1, sRAGE, IL-6. This will be done at the start of every cycle, at the end of SBRT and pre-op (morning of surgery). Blood will be drawn in 2 green top tubes (heparin), two citrate, and two red top tubes. Dr. Lotze research lab will provide lab supplies and process all research samples.

¹⁵ If patient has an extensive cardiac history

MD visit during chemotherapy will be with oncologist on day 1 of every cycle. If patient proceeds to SBRT, they will be seen by radiation oncologist. Follow-up with radiation oncologist is as needed.

% tests need completed within 14 days of randomization

[^]Completed within 7 days of randomization

> Must be completed at UPMC Shadyside Hospital

10.2.mFOLFIRINOX

Parameter	Screening ¹	Day 0	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 ³	Cycle 6 ³				
Physical Exam# PS, HT ² and Wt, BSA	X [^]		X	X	X	X	X	X		X	X	
Randomization		X										
History, Con Meds and AE Evaluation	X		X	X	X	X	X	X		X	X	
Diagnostic endoscopic ultrasound (EUS)(If not already completed) >	X											
Placement of Biliary stent ¹¹	X											
Port placement ¹²	X											
Pathology review or Biopsy for diagnosis and correlative studies(if not already completed)	X											
CBC with diff, plt	X%		X	X	X	X	X	X		X		
CMP (Na, K, CL, CO2, Glucose, BUN, Creatinine, Calcium, Protein Total, Albumin, AST, ALT, ALK Phos, Bili T), Magnesium, LDH, and Phosphorus	X%		X	X	X	X	X	X		X		
Coagulation studies including INR, PT, PTT ⁶	X%										X	
Anti Xa level ⁷	X%										X	
Ca 19-9 and CEA	X%		X	X	X	X	X	X		X		
CT Scan or Spectral CT Scan (chest/abdomen/pelvis) and tumor measurement	X								X ⁸	X ⁹		X
Urinalysis	X											
Placement of Gold Fiducials via EUS>		X										
Quality of Life questionnaire (FACT-HB)	X		X	X	X	X	X	X		X ¹⁰		
Serum Pregnancy Test (can be up to 72 hrs prior) if pt is < 60ys age	X [^]											
mFOLFIRINOX			X	X	X	X	X	X				
Correlative studies Blood work ¹⁴	X		X	X	X	X	X	X		X	X	
EKG/ECG	X											

¹ Screening tests will be done within 28 days of randomization.

² Height needs to be documented once at screening

³ Only patients who are deemed to have had a response (SD, PR or CR) will proceed to SBRT and surgery

⁴ Only patients who have a response after cycle 3 of chemotherapy will proceed to SBRT (completed at UPMC Shadyside Hospital) within four weeks after completion of chemotherapy (+/- 5 business days).

⁵ Follow-up after surgery is recommended at Q3 months for 6 months, then every 6 months for 24 months but this will be at the discretion of treating physician. Additional imaging and tumor markers will be at the discretion of the oncologist.

⁶ Patients who are on Coumadin will require their INR to be checked every cycle or according to the treating oncologist

⁷ if patient is on anticoagulation with either enoxaparin or fondaparinux, AntiXa level should be tested at least once during chemotherapy. Additional levels can be done at the discretion of treating oncologist

⁸ Disease measurements are based on CT after 3 cycles of chemotherapy. This CT should be performed on the patient's off week prior to MDC clinic. At the MDC clinic it will be reviewed by the medical oncologist, surgeon and radiation oncologist to make decision as to whether patient proceeds to SBRT and surgery.

⁹ Planning CT scan for measurement only¹⁰ QOL questionnaires will be done at the end of SBRT.

¹¹ If patient has biliary obstruction and a stent is required, it must be a metallic stent. If a pre-existing plastic stent is present, this will need to be changed to a metallic stent prior to starting chemotherapy.

¹² If patient is randomized to mFOLFIRINOX arm, port placement should be done prior to starting therapy.

¹³ If patient proceeds to surgery - surgery will be done within 2 (+/- 3 business days) weeks after completion of SBRT. Pre-op visit will be organized accordingly

¹⁴ Blood will be drawn for HMGB1, sRAGE, IL-6. This will be done at the start of every cycle, at the end of SBRT and pre-op (morning of surgery). Blood will be drawn in 2 green top tubes (heparin), two citrate, and two red top tubes. Dr. Lotze research lab will provide lab supplies and process all research samples.

[#] MD visit during chemotherapy will be with oncologist on day 1 of every cycle. If patient proceeds to SBRT, they will be seen by radiation oncologist. Follow-up with radiation oncologist is as needed.

[%] tests need completed within 14 days of randomization

[^]Completed within 7 days of randomization

[>] Must be completed at UPMC Shadyside Hospital

11.0. Chemotherapeutic Agents

11.1. Gemcitabine Hydrochloride (Gemzar®)

Please refer to the package insert for complete information.

11.1.1. Description

2'-Deoxy-2', 2'-difluorocytidine monohydrochloride (Gemcitabine hydrochloride or Gemcitabine®) is a white to off-white or translucent solid with a molecular weight of 299.66.

Mechanism of Action: Gemcitabine, like ara-C, is an analog of deoxycytidine. This antimetabolite, a pyrimidine analog inhibiting both DNA and RNA viruses, is cell-cycle-specific in blocking the cells at the G1/S and is retained in human tumor cells for long periods. Studies suggest that gemcitabine is activated by deoxycytidine kinase. Deoxycytidine has been shown to reverse the growth inhibitory activity of gemcitabine.

11.1.2. Toxicology

Human Toxicology: Dose limiting toxicity is bone marrow suppression with mild to moderate granulocytopenia, anemia and thrombocytopenia. There has been no evidence of cumulative WBC or platelet toxicity. Gastrointestinal toxicities include nausea, vomiting, and diarrhea. Gemcitabine should be used with caution in patients with impaired liver function since abnormalities of liver transaminase enzymes have been reported. Mild proteinuria and hematuria have been reported but were not clinically significant and usually not associated with any change in serum creatinine or BUN. A few cases of renal failure of uncertain etiology have been reported. While on study, one patient who received prior mitomycin developed hemolytic uremic syndrome requiring dialysis. The relationship of this event to gemcitabine is not known. Gemcitabine should be used with caution in patients with impaired renal function. Toxicities associated with allergic reaction include rash, pruritus, desquamation, vesication, ulceration, and dyspnea. Bronchospasm has been reported in less than 1% of patients. Twenty percent (20%) of patients have also experienced flu-like symptoms such as fever, headache, back pain, chills, myalgia, asthenia, anorexia, cough, rhinitis, malaise and sweating. Other toxicities include edema in 30% of patients, alopecia, somnolence, diarrhea, constipation, and oral toxicity (soreness and erythema). Pulmonary edema has been a rare occurrence (less than 1%). A few cases of hypotension have been reported, as well as myocardial infarction, congestive heart failure and arrhythmia. However, there is no clear evidence that gemcitabine causes cardiac toxicity.

Pregnancy and Lactation: Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of $< 2 \text{ mg/m}^2$. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

11.1.3. Pharmacology

Kinetics: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. Additional metabolites have not been identified in either plasma or urine. The gemcitabine di- and tri-phosphates does not appear to circulate in plasma in measurable amounts. The compound is metabolized principally by the liver to form an inactive uridine derivative (dFdU or 2'-deoxy- 2',2'-difluorouridine). The plasma protein binding of gemcitabine is negligible. Following a single 1,000 mg/m²/30 min [14C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of parent and dFdU accounted for 99% of the excreted dose, and less than 1% of the dose was

excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

Half-life ranged from 11 to 26 minutes for patients receiving single dose infusions (1,000 mg/m² to 2,500 mg/m²) of 1.1 hours or less. Following longer duration infusions (3.6 to 4.3 hours), the half-life ranged between 18.5 and 57.1 minutes for single gemcitabine doses between 2,500 mg/m² and 3,600 mg/m². The increase in half-life may relate to the appearance of a possible third exponential phase (representing a deep compartment) that is not observed following the shorter infusions.

The population pharmacokinetic analyses of the effect of patient specific characteristics showed that clearance normalized for BSA was affected by gender. The clearance obtained for the female patient for all studies was 46.2 L/hr/m² and the male's was 66.8 L/hr/m². These moderate to high gemcitabine values suggest that gemcitabine may be metabolized by various tissues, including the liver. The renal clearance for gemcitabine is less than 10% of the systemic clearance. The maximum dFdU plasma concentrations were achieved from 0 to 30 minutes after the discontinuation of the gemcitabine infusions, ranging from 0.4 to 4.75 hours. The apparent formation of dFdU (determined from the fraction of the gemcitabine dose excreted as dFdU) ranged from 91.2% to 98.2% of gemcitabine clearance in a single-dose study. Based on the imputed formation rate of dFdU, the mean dFdU volume of distribution at steady-state was 150.4 L/m², indicating that dFdU was extensively distributed into tissues. The metabolite was excreted in urine without undergoing further biotransformation. The mean apparent clearance of dFdU was 2.5 L/hr/m².

Formulation: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1,000 mg (1 gram) of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate.

Storage and Stability: The lyophilized compound should be stored at controlled room temperature, 59° to 86°F (15° to 30°C). Reconstituted solution should be stored at controlled room temperature and used within 24 hours; any unused portion should be discarded.

Reconstitution: Normal saline without preservatives is the only diluent approved. Do not use other diluents.

Administration: Intravenous over 30 minutes

Handling Precautions: Gemcitabine is a toxic material which could cause skin and eye irritation. Ingestion or inhalation exposure of sufficient quantities could result in decreased white and red blood cells, hypospermatogenesis, gastrointestinal disturbances, and other signs of toxicity. The compound was positive in one of three tests for mutagenicity. Laboratory animal studies indicate that compounds in this therapeutic class may be reproductive toxins and may induce fetal malformations. Contact or inhalation should be avoided.

11.2. nab-Paclitaxel (AbraxaneTM)

11.2.1. nab-paclitaxel Packaging, Labeling, and Storage

nab-paclitaxel (Abraxane) - each single-use 50-mL vial will contain 100 mg paclitaxel and human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products. Unreconstituted nab-paclitaxel (Abraxane) should be stored at controlled room temperature (20 to 25C or 68F to 77F) and reconstituted nab-paclitaxel (Abraxane) must be refrigerated at 2 to 8C (36 to 46F) and used within 8 hours. Both forms of Nab-paclitaxel (Abraxane) should be stored in an area free of environmental extremes and must be accessible only to study personnel.

11.2.2. nab-paclitaxel (AbraxaneTM) Administration

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of Nab-paclitaxel (Abraxane). In any event, filters of pore size less than 15 microns (15 μ m) must not be used.

The Investigator or designee will calculate the body surface area (BSA) of the patient in order to determine the total amount of Nab-paclitaxel (Abraxane) to be administered.

11.2.3. Reconstitution and Use of Nab-paclitaxel (AbraxaneTM)

Calculate the patient's BSA according to standard institutional methods. BSA will be calculated on Cycle 1 Day 1 and recalculated per the site's standard of care, or if body weight changes by more than 10%. Actual heights and weights should be used to calculate surface areas (no downward adjustment to "ideal" weight). This principle applies to individuals whose calculated surface area is 2.2 m² or less. In those rare cases where a patient's surface area is greater than 2.2 m², the actual surface area or 2.2 may be used. Dosing BSA may be capped if the treating physician believes it is in the best interest of an obese patient.

Calculate the total dose (in mg) to be administered by:

$$\text{Total Dose (mg)} = \text{BSA (study dose mg/m}^2\text{)}$$

Calculate the total number of vials required by:

$$\text{Total Number of Vials} = \text{Total dose (mg)} / 100 \text{ (mg/vial)}$$

Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

Using sterile technique, prepare the vials for reconstitution.

Swab the rubber stoppers with alcohol.

Reconstitute each Nab-paclitaxel (Abraxane) vial by using a 50-cc or 60-cc sterile syringe. (Note: Change the syringes after reconstituting every 3 vials).

Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the inside wall of the vial.

DO NOT INJECT the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.

Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.

Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam. Each mL of reconstituted product will contain 5 mg of Abraxane.

Calculate the exact total dosing volume (to the nearest mL) of 5 mg/mL suspension required for the patient:

$$\text{Dosing volume (mL)} = \text{Total dose (mg)} / 5 \text{ (mg/mL)}$$

The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to use. Use immediately following reconstitution. If not used immediately, replace the reconstituted vial in the carton and store reconstituted Abraxane in a refrigerator for not more than 8 hours.

Using a new, sterile 50-cc or 60-cc syringe, withdraw the reconstituted Abraxane solution. Do not remove the rubber stopper from the Abraxane vials as this can compromise the sterility of the drug preparation.

Inject the calculated dosing volume of reconstituted Abraxane suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid

dislodging plastic material into the IV bag. Repeat until the patient's entire required dose is injected into the IV bag.

Remove the injection port.

Once the exact volume of reconstituted Abraxane has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures for cytotoxic drugs.

Administer the calculated dosing volume of reconstituted Abraxane suspension by IV infusion over 30 minutes.

11.3. modified FOLFIRINOX

(pronounced full-fear-o-knocks) is made up of the following drugs:

- **FOL** – Folinic acid (Leucovorin), a vitamin B derivative that helps fluorouracil function better within the cell; - eliminated from this protocol
- **F** – Fluorouracil (5-FU), gets into the DNA cancer molecule and stops synthesis;
- **IRIN** – Irinotecan (Camptosar), prevents DNA cancer cell from uncoiling and duplicating, and;
- **OX** – Oxaliplatin, inhibits DNA synthesis in cancer cells.

11.3.1. Rounding Drug Doses [1]

- Rounding the doses of 5-FU, oxaliplatin, and irinotecan is optional.
- If the treating physician decides to round the dose(s), follow these rules.

(These rules also apply for dose modifications.)

- 5-FU (2400 mg/m² continuous infusion) 5-FU should be rounded to the nearest 50 mg.
- Irinotecan (180 mg/m²) Irinotecan should be rounded to the nearest 5 mg.
Oxaliplatin (85 mg/m²) Oxaliplatin should be rounded to the nearest 5 mg.

11.3.2. Fluorouracil (5-FU)

An antineoplastic antimetabolite, is a colorless to faint yellow aqueous, sterile, nonpyrogenic injectable solution available in a 50 mL and 100 mL Pharmacy Bulk Package for intravenous administration. Each mL contains 50 mg fluorouracil in water for injection, USP, pH is adjusted to 8.6 to 9.4 with sodium hydroxide.

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4 (1H,3H)-pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water.

Molecular formula: C₄H₃FN₂O₂

Molecular weight 130.08

A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion.

11.3.2.1. Clinical Pharmacology

There is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner, fluorouracil interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells which grow more rapidly and which take up fluorouracil at a more rapid rate.

Following intravenous injection, fluorouracil distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. In spite of its limited lipid solubility, fluorouracil diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

Seven to twenty percent of the parent drug is excreted unchanged in the urine in six hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catabolic metabolism of fluorouracil results in degradation products (e.g., CO₂, urea and α-fluoro-β-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours. When fluorouracil is labeled in the six carbon position, thus preventing the ¹⁴C metabolism to CO₂, approximately 90% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position approximately 90% of the total radioactivity is excreted in expired CO₂. Ninety percent of the dose is accounted for during the first 24 hours following intravenous administration.

Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an intravenous injection.

11.3.2.2. Precautions: General

Fluorouracil is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised, since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of fluorouracil despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

- Stomatitis or esophagopharyngitis, at the first visible sign.
- Leukopenia (WBC under 3500) or a rapidly falling white blood count.
- Vomiting, intractable.
- Diarrhea, frequent bowel movements or watery stools.
- Gastrointestinal ulceration and bleeding.
- Thrombocytopenia (platelets under 100,000).
- Hemorrhage from any site.

The administration of 5-fluorouracil has been associated with the occurrence of palmar-planter erythrodysesthesia syndrome, also known as hand-foot syndrome. This syndrome has been characterized as a tingling sensation of hands and feet which may progress over the next few days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Although pyroxine has been reported to ameliorate the palmar-planter erythrodysesthesia syndrome, its safety and effectiveness have not been established.

11.3.2.3. Dosage and Administration

All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

It is recommended that prior to treatment each patient be carefully evaluated in order to estimate as accurately as possible the optimum initial dosage of Adrucil.

The administration of 5-fluorouracil is given as 1200 mg/m²/day continuous infusion for 2 days (over 46 hours) every 14 days in combination with irinotecan and oxaliplatin.

11.3.2.4. Handling and Disposal

Procedures for proper handling and disposal of anticancer 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.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If a precipitate occurs due to exposure to low temperatures, resolubilize by heating to 140°F and shaking vigorously; allow cooling to body temperature before using.

Directions for proper use of pharmacy bulk package(Not for Direct Infusion): The 50 mL and 100 mL Pharmacy Bulk Packages are for use in a Pharmacy Admixture Service only. They should be inserted into a plastic hanging device and suspended as a unit in a laminar flow hood. Use only if clear and seal is intact and undamaged.

Use of this product is restricted to a suitable work area, such as a laminar flow hood. Use only if clear and seal is intact and undamaged. Prior to entering the vial, remove the flip-off seal and cleanse the rubber closure with a suitable antiseptic agent. The container closure may be penetrated only one time, utilizing a suitable sterile transfer device or dispensing set which allows measured distribution of the contents. The date and time the vial was initially opened should be recorded in the space provided on the vial label. Transfer individual dose(s) to appropriate intravenous infusion solutions. Use of a syringe with a needle is not recommended. Multiple entries increase the potential of microbial and particulate contamination.

The withdrawal of container contents should be accomplished without delay using aseptic technique. However, should this not be possible, a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operations. It is recommended that the transferred fluids be used promptly.

Recommended Storage Conditions after Opening: Keep under laminar flow hood at room temperature. The 50 mL and 100 mL pharmacy bulk packages are packaged 5 vials per shelf pack.

Store at room temperature 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from light. Retain in carton until time of use. NOTE: Although fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected.

11.3.3. Irinotecan

Irinotecan hydrochloride injection is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11.

Irinotecan hydrochloride injection is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials containing 40 mg Irinotecan hydrochloride, and 5 mL-fill vials containing 100 mg Irinotecan hydrochloride. Each milliliter of solution contains 20 mg of Irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan

hydrochloride injection is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semi-synthetic derivative of camptothecin, an alkaloid extract from plants such as Mappiafoetida and Camptothecaacuminata. The chemical name is (S) - 4,11 - diethyl - 3,4,12,14 - tetrahydro - 4 - hydroxy - 3,14 - dioxo - 1H - pyrano[3',4':6,7] - indolizino[1,2 - b]quinolin - 9 - yl - [1,4'bipiperidine] - 1' - carboxylate, monohydrochloride, trihydrate.

Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the molecular formula C33H38N4O6•HCl•3H2O and a molecular weight of 677.19. It is slightly soluble in water and organic solvents.

11.3.3.1. Pharmacology

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent resealing of these single-strand breaks. Current research suggests that the cytotoxicity of Irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either Irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from Irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as Irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to Irinotecan varies from 2- to 2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of Irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for Irinotecan. The precise contribution of SN-38 to the activity of Irinotecan is thus unknown. Both Irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of Irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

11.3.3.2. Pharmacokinetics

After intravenous infusion of Irinotecan in humans, Irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of Irinotecan and SN-38 are similar to those of total Irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m², the AUC of Irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of Irinotecan.

Pharmacokinetic parameters for Irinotecan and SN-38 following a 90-minute infusion of Irinotecan at dose levels of 125 and 340 mg/m² determined in two clinical studies in patients with solid tumors.

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which Irinotecan and SN-38 predominantly binds is albumin.

11.3.3.3. Metabolism and Excretion

The metabolic conversion of Irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. In vitro studies indicate that Irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyltransferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which Irinotecan was administered as a single-agent (350 mg/m²) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype). SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The disposition of Irinotecan has not been fully elucidated in humans. The urinary excretion of Irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of Irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of Irinotecan in two patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

11.3.3.4. Administration

Irinotecan is administered at a dose of 180mg/m² intravenous, diluted in 500 mL D5W and administer over 90 minutes. Premedication with dexamethasone and a 5-HT₃ blocker is recommended 30 minutes prior to administration; prochlorperazine may be considered for subsequent use (if needed). Consider atropine 0.25-1 mg I.V. or Sub Q as premedication for or treatment of cholinergic symptoms (eg, increased salivation, rhinitis, miosis, diaphoresis, abdominal cramping) or early onset diarrhea.

11.3.4. Oxaliplatin

11.3.4.1. Dosage and Administration

Oxaliplatin for Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

11.3.4.2. Dosage

Administer Oxaliplatin for Injection in combination with 5-fluorouracil every 2 weeks. Oxaliplatin for Injection 85 mg/m² intravenous infusion in 250-500 mL 5% Dextrose Injection, given over 120 minutes followed by 5-fluorouracil 1200 mg/m²/day continuous infusion for 2 days (over 46 hours).

The administration of Oxaliplatin for Injection does not require pre-hydration. Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone, is recommended.

11.3.4.2.1. Preparation of Infusion Solution

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.

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.

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)].

Oxaliplatin for Injection is not light sensitive.

Oxaliplatin for Injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present.

Needles or intravenous administration sets containing aluminum parts that may come in contact with Oxaliplatin for Injection should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

Dosage Forms and Strengths: Oxaliplatin for Injection is supplied in single-use vials containing 50 mg or 100 mg of Oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution.

Contraindications: Oxaliplatin for Injection should not be administered to patients with a history of known allergy to Oxaliplatin for Injection or other platinum compounds.

11.3.3.4. Warnings and Precautions

Allergic Reactions: Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to Oxaliplatin for Injection has been observed in 2 to 3% of colon cancer patients. These allergic reactions which can be fatal, can occur within minutes of administration and at any cycle, and were similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with Oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and may require discontinuation of therapy. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.

Neuropathy: Oxaliplatin for Injection is associated with two types of neuropathy:

(1) An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received Oxaliplatin for Injection with 5-fluorouracil/leucovorin. In any individual cycle acute neurotoxicity was

observed in approximately 30% of patients. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 cycles in the previously treated patients the median number of cycles administered on the Oxaliplatin for Injection with 5-fluorouracil/leucovorin combination arm was 6.

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1 to 2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplatin for Injection because cold temperature can exacerbate acute neurological symptoms.

(2) A persistent (> 14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesia, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving Oxaliplatin for Injection with 5-fluorouracil/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of Oxaliplatin for injection.

11.3.5. Gemcitabine

11.3.5. 1. Premedication for Gemcitabine

Antiemetic therapy should be administered at the physician's discretion. A combination [redacted] of a 5-HT3 antagonist and dexamethasone is strongly recommended. Additionally, for delayed nausea, a combination of dexamethasone 4mg and ondansetron 8mg twice a day orally for three days, and prochlorperazine 10 mg orally four times daily on as needed basis for nausea are recommended. Examples of standard antiemetics include ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®), compazine, and dexamethasone. The dosage and route of administration will be determined by the treating oncologist based upon the given clinical scenario.

11.3.5.2. Toxicity and Dose Modifications for Gemcitabine

Gemcitabine dose modifications are presented in Appendix C.

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting (see Section 9.0). A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). **All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.**

Toxicities:

- **Hematologic** - In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with gemcitabine, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during gemcitabine therapy and dosage modified or suspended according to the degree of hematologic toxicity
- **Gastrointestinal** - Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (World Health Organization [WHO] Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

- **Hepatic** - In clinical trials, Gemcitabine was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to gemcitabine or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving gemcitabine. Elevated transaminases are rarely of clinical significance.
- **Renal** - In clinical trials, mild proteinuria and hematuria were commonly reported. Hemolytic Uremic Syndrome (HUS) has been reported rarely (0.25%) with the use of gemcitabine. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.
- **Fever** - The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that gemcitabine 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.
- **Rash** - Rash was reported in 30% of patients. 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 for 13% of patients.
- **Pulmonary** - In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with gemcitabine therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of gemcitabine. The etiology of these effects is unknown. If such effects develop, gemcitabine should be discontinued and the patient at this stage will be taken off trial. Early use of supportive care measures may help ameliorate these conditions.
- **Edema** - Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.
- **Flu-like Symptoms** - “Flu syndrome” was reported for 19% of patients. 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 patients discontinued due to flu-like symptoms.
- **Infection** - Infections were reported for 16% of patients. Sepsis was rarely reported.
- **Alopecia** - Hair loss, usually minimal, was reported by 15% of patients.
- **Neurotoxicity** - There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

11.3.6. nab-Paclitaxel

11.3.6.1. Toxicity for nab-Paclitaxel (AbraxaneTM)

Dose modifications for *nab*-paclitaxel are presented in Appendix C. This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting (see Section 9.0). A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). **All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.**

nab-Paclitaxel Toxicities

- **Myelosuppression, predominantly neutropenia** - Grade 4 neutropenia was reported and typically resolved in <7 days and did not require colony stimulating factor support.
- **Peripheral neuropathy, predominantly sensory** - Grade 3 peripheral neuropathy was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the ABI-007 dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart ABI-007 dosing at a lower dose level.

- **Nausea and vomiting** - Nausea and vomiting were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens.
- **Myalgias and arthralgias** - Myalgias and arthralgias were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication.
- **Mucositis** - Mucositis was reported typically Grade 1 or 2. It was not dose-limiting.
- **Alopecia** - Alopecia was reported by most patients and was similar to that seen with Taxol.
- **Sepsis**
- **Pulmonary interstitial pneumonitis.**

12. Dose Modifications for Chemotherapy

12.1. mFOLFIRINOX

Neutrophils ($\times 10^9/L$)	Delay of treatment	Occurrence	Dose Modifications		
			Fluorouracil	Irinotecan	Oxaliplatin
1.5 or greater	None		100%	100%	100%
Less than 1.5 on day 1 or at any time since the previous cycle	Hold treatment for 1 week (2 weeks if necessary) and continue at same doses	1st	100%	150mg/m ²	100%
		2nd	75%	150mg/m ²	60mg/m ²
		3rd	stop treatment	stop treatment	stop treatment

*Add Pegfilgrastim (Neulasta) or filgrastim at 1st incidence of ANC < 1.5 x 10⁹/L if not already receiving it.

If counts have not recovered after a delay of two weeks, despite appropriate supportive measures, it is recommended that treatment is stopped.

Platelets ($\times 10^9/L$)	Occurrence	Dose Modifications		
		Fluorouracil	Irinotecan	Oxaliplatin
75 or greater	N/A	100%	100%	100%
Platelets > 75 (<u>hold</u> the treatment until recovery) less than 75 on day 1 or a NCI-CTC grade 3/4 thrombocytopenia since the previous cycle	1st	75%	100%	60mg/m ²
		50%	150mg/m ²	60mg/m ²
		stop treatment	stop treatment	stop treatment

Adverse Event	Occurrence	Dose Modifications
Febrile Neutropenia	1st	Decrease Irinotecan to 150mg/m ²
Grade 3 or 4 Neutropenia lasting > 7 days	2nd	Decrease Oxaliplatin to 60mg/m ² in addition to Irinotecan dose reduction
Infection with Grade 3 or 4 neutropenia	3rd	Stop treatment
Grade 3 -4 thrombocytopenia	1st	reduce the oxaliplatin dose to 60 mg/m ² and the continuous 5-FU dose to 75 % of the original dose
	2nd	reduce also the dose of irinotecan to 150mg/m ² And the dose of continuous 5FU by an additional 25 % (to 50%)
	3rd	Stop treatment

<i>Hepatic Impairment</i>		
Drug	Bilirubin mg/dl	Dose (% of original)
5FU	>1.5 x ULN -	hold treatment for investigation
Irinotecan	> 1.5 x ULN	hold treatment for investigation
Oxaliplatin	> 1.5 x ULN	hold treatment for investigation

<i>Renal Impairment</i>	CrCl	Dose (% of original)
5FU	N/A	N/A
Irinotecan	N/A	limited data but not thought necessary
Oxaliplatin	<20	contraindicated

Diarrhea:

NCI-CTC grade 1 or 2 diarrhea occurring between cycles does not generally necessitate dose modification, unless accompanied by fever or neutropenia. However, diarrhea should resolve to < grade 2 before re-treatment, especially with irinotecan. If the diarrhea has not resolved delay treatment by seven days and reassess.

The Following dose modifications below should be applied to subsequent cycles where appropriate:

At any time since the previous cycle:

NCI-CTC grade 3/4 - accompanied by fever and / or NCI-CTC grade 3/4 neutropenia

<u>Occurrence</u>	<u>5FU</u>	<u>Irinotecan</u>	<u>Oxaliplatin</u>
1	Reduce by 25%	150mg/m2	100%
2	Reduce by 50%	150mg/m2	60 mg/m2
3	stop	stop	stop

Fluorouracil

- Where a NCI-CTC Grade 3 or 4 stomatitis occurs dose reduction of infusion will be to 75% of the original dose.
- For a NCI-CTC Grade 3 or 4 palmer-plantar erythrodysesthesia reduce the infusion dose to 75% of the original dose.
- Fluorouracil MUST be stopped in any case of angina pectoris or of myocardial infarction.

Oxaliplatin

- If the neurosensory toxicity is NCI-CTC Grade 1 or 2 and lasts less than seven days administer the full dose of oxaliplatin. If the toxicity is NCI-CTC Grade 2 and persists for more than seven days reduce the oxaliplatin dose to 60mg/m2.
- Oxaliplatin should be discontinued for neurosensory toxicities NCI-CTC grade 3 or above.
- For transient cold related dysesthesia or paresthesia without pain there is no need to delay or reduce oxaliplatin.
- For acute laryngopharyngeal dysesthesia increase the infusion time to 6 hours.
- There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptoms occur stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

12.2. nab-Paclitaxel (AbraxaneTM) and Gemcitabine (Gemzar[®])

12.2.1. Dose Modifications for Gemcitabine and/or Nab-paclitaxel

E.1.1

Doses will be reduced for hematologic and other toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.0.

E.1.2

Two levels of dose modifications are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either study drug, further treatment should be discontinued.

Modifications

Dose Level ^{a)}	Nab-paclitaxel Dose (mg/m ²) ^{b)}	Gemcitabine (mg/m ²) ^{b)}
Study Dose	125	1000
-1	100	800
-2	75	600

^{a)} A maximum of 2 dose level reductions are allowed.

^{b)} Dose reductions may or may not be concomitant. Please refer to [Table1](#) and [Table2](#) for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity, respectively. Please refer to [Table 3](#) and [Table 4](#) for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.

E.1.3

Patients experiencing study drug-related toxicities that require a delay in scheduled nab-paclitaxel or gemcitabine dosing for ≥ 21 days will be discontinued from further treatment in this study (except for peripheral neuropathy;). When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment (with the exception mentioned in

Table 3, namely: on Day 15, re-escalation with granulocyte-colony stimulating factor (G-CSF) support is permitted, after a previous dose reduction on Day 8 of the same cycle).

E.1.4 Dose Modifications at Day 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of nab-paclitaxel and gemcitabine may be adjusted as detailed in [Table1](#) and [Table2](#) as presented below:

Table1: Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

Treatment day counts and toxicity			
ANC	Platelets	Timing	
$\geq 1.5 \times 10^9/L$	And	$\geq 100 \times 10^9/L$	Treat on time
$< 1.5 \times 10^9/L$	Or	$< 100 \times 10^9/L$	Delay by 1 week intervals until recovery

Key: ANC = Absolute neutrophil count.

Table2: Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	Gemcitabine+nab-paclitaxel dose this cycle
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and nab-paclitaxel should both be reduced to next lower dose level; please refer to Section F 1.5)
Grade 3 toxicity ^{a)}	Decrease gemcitabine and nab-paclitaxel to next lower dose level
Grade 4 toxicity ^{b)}	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

Key: CTCAE = Common terminology criteria for adverse events.

- a) If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced.
- b) Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or a symptomatic, will be exempt from this requirement.

E.1.5 Dose Adjustments within a Treatment Cycle

In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in

Table3: Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Counts	Day 8 Nab-paclitaxel	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 Nab-paclitaxel	Day 15 Gemcitabine	Any Day Nab-paclitaxel	Any Day Gemcitabine
ANC >1000 and Platelets \geq 75,000	100%	100%	ANC >1000 and Platelets \geq 75,000	100%	100%		
			ANC 500-1000 or Platelets 50,000- 74,999	Full Dose (treat on time) + G-CSF ^a	Full Dose (treat on time) + G-CSF ^a		
			ANC <500 or Platelets <50,000	Hold + G-CSF ^a	Hold + G-CSF ^a		
ANC 500- 1000 ^b or Platelets 50,000- 74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	ANC >1000 and Platelets \geq 75,000	Return to Previous Dose level (treat on time) + G-CSF ^a	Return to Previous Dose Level (treat on time) + G-CSF ^a		
			ANC 500-1000 or Platelets 50,000- 74,999	Same Dose (as Day 8, treat on time) + G-CSF ^a	Same Dose (as Day 8, treat on time) + G-CSF ^a		
			ANC <500 or Platelets <50,000	Hold + G-CSF ^a	Hold + G-CSF ^a		
ANC <500 ^a or Platelets <50,000	Hold	Hold	ANC >1000 and Platelets \geq 75,000	Decrease Day 8 dose by 1 level (treat on time) + G-CSF ^a	Decrease Day 8 dose by 1 level (treat on time) + G-CSF ^a		

Table3: Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Counts	Day 8 Nab-paclitaxel	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 Nab-paclitaxel	Day 15 Gemcitabine	Any Day Nab-paclitaxel	Any Day Gemcitabine
			ANC 500-1000 or Platelets 50,000- 74,999	Decrease Day 8 dose by 1 level (treat on time) + G-CSF ^a	Decrease Day 8 dose by 1 level (treat on time) + G-CSF ^a		
			ANC <500 or Platelets <50,000	Hold + G-CSFa	Hold + G-CSFa		
Febrile Neutropenia (Grade 3 or 4) ^c						Hold. Upon resuming dosing, decrease to next lower level and do not reescalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower dose level and do not reescalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4) ^b						Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease 2 dose levels (to 600 mg/m ²) and do not re-escalate throughout the rest of treatment.

Abbreviations: ANC = Absolute neutrophil count; G-CSF = Granulocyte colony stimulating factor.

- G-CSF is optional if descent only affects platelets.
- If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.
- Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to screening levels before resuming chemotherapy treatment.

E.1.6

Dose modifications may also be made for non-hematological toxicity within a cycle as specified in [Table 4](#)

Table 4: Dose Modifications for Non-Hematological Toxicity within a Cycle

CTCAE Grade	Percent of Day 1 Nab-paclitaxel+Gemcitabine Dose
0-2 (and Grade 3 nausea/vomiting and alopecia)	100% ^a
3 (except nausea/vomiting and alopecia)	Hold either one or both drugs until resolution to \leq Grade 1. Then resume treatment at the next lower dose level.
4	Hold

E.1.7 Peripheral Neuropathy

Nab-paclitaxel treatment should be withheld in patients who experience \geq Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to \leq Grade 1. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-paclitaxel dosing for \geq 21 days will discontinue study treatment. The time to resolution to Grade \leq 1 should be the adverse event duration used for adverse event reporting.

E.1.8 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level for both drugs. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

E.1.9 Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, study drug should be withheld until resolution to \leq Grade 1, then reinstated at the next lower dose level of both drugs. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

E.1.10 Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

E.1.11 Interstitial Pneumonitis

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (ie, episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Study drug administration should be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

E.1.12 Colony Stimulating Factor Administration

Colony stimulating factors may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC <500 cells/ μ L (as per Table 3)

Patients who do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

E.1.13 Prophylaxis Against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever $\geq 38.5^{\circ}\text{C}$ (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily)—or amoxicillin/clavulanate (Augmentin®, 500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones—should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of $\geq 38.5^{\circ}\text{C}$ (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation.

E.1.14 Hypersensitivity Reactions

Hypersensitivity reactions are not expected with either nab-paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy.

Patients who develop a severe hypersensitivity reaction should not be re-challenged.

13.0. Supportive care

13.1. Both Chemotherapy Regimens

- All standard of care anti-emetics, anti-diarrheals, antibiotics are permitted.
- Use of growth factor support as primary prophylaxis to prevent neutropenia is not prohibited. An ANC < 1500 on day 1 of any cycle will require the use of growth factor for all remaining cycles unless otherwise not indicated. Choice of growth factor is at the investigator's discretion
- Use of an erythropoiesis-stimulating agent is NOT permitted. However it is suggested that anemia with a Hgb < 8.0 g/dl be treated by pRBC transfusion at the investigator's discretion.
- Because of the risk of sepsis with gemcitabine plus nab-paclitaxel, especially in those patients who have biliary stents due to biliary obstruction, patients must be instructed to begin taking either ciprofloxacin 500mg orally (or amoxicillin /clavulanate 875 orally if allergic to ciprofloxacin or similar drugs) for any fever $> 100.5^{\circ}\text{F}$ (38.3°C). They should then call their treating physician and be evaluated as soon as clinically indicated.
- Concomitant medications should be avoided with the exception of analgesics (only acetaminophen or narcotics may be given for pain), chronic treatments for concomitant medical conditions, or agents required for life threatening medical problems.
- No additional chemotherapy, immunotherapy, or other anti-tumor therapy is permitted during the study.

13.2. mFOLFIRINOX

13.2.1. Antidiarrheal Medications

Patients should be instructed to begin taking loperamide (2mg) at the earliest sign of poorly-formed or loose stools (\leq grade 1). Oral loperamide 2mg every two hours should continue until 12 hours after the last liquid stool.

Aggressive supportive care should be provided for patients with grade 4 ANC and \geq grade 3 diarrhea until neutropenia and diarrhea resolve. Hospitalization for evaluation and management of complicated diarrhea is strongly recommended.

13.2.2. Irinotecan-related Cholinergic Syndrome

Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine,

0.25-1.0 mg IV or SC should be used to treat these symptoms and should be used prophylactically. Additional antidiarrheal measures may be used at the discretion of the investigator.

Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

Diarrhea developing more than 24 hours after the irinotecan dose should be managed with loperamide as described above.

13.2.3. Antiemetic Therapy

Antiemetic therapy should be administered at the physician's discretion. A combination ~~of~~ of a 5-HT3 antagonist and dexamethasone is strongly recommended. Additionally, for delayed nausea, a combination of dexamethasone 4mg and ondansetron 8mg twice a day orally for three days, and prochlorperazine 10 mg orally four times daily on as needed basis for nausea are recommended. Examples of standard antiemetics include ondansetron (Zofran®), granisetron (Kytril®), dolasetron (Anzemet®), compazine, and dexamethasone. The dosage and route of administration will be determined by the treating oncologist based upon the given clinical scenario.

13.2.4. Growth Factor Support

We suggest that all patients should receive filgrastim or pegfilgrastim with all treatment cycles to prevent febrile neutropenic episodes. An ANC < 1500 on day 1 of any cycle will require the use of growth factor for all remaining cycles unless otherwise not indicated..

Use of an erythropoiesis-stimulating agent is NOT permitted. However it is suggested that anemia with an Hgb<8.0 g/dl be treated by pRBC transfusion at the investigator's discretion.

13.2.5. Fever

Because of the risk of sepsis with mFOLFIRINOX, especially in those patients who have biliary stents due to biliary obstruction, patients must be instructed to begin taking either ciprofloxacin 500mg orally (or amoxicillin /clavulanate 875 orally if allergic to ciprofloxacin or similar drugs) for any fever > 100. 5 deg F (38.3 C). They should then call their treating physician and be evaluated as soon as clinically indicated.

13.2.6. Management of Laryngopharyngeal Dysesthesias

Oxaliplatin may cause discomfort in the larynx or pharynx associated with the sensation of dyspnea, anxiety, and swallowing difficulty. Exposure to cold can exacerbate these symptoms.

Do NOT use ice chips or other forms of oral cryotherapy to decrease stomatitis in conjunction with oxaliplatin.

Anxiolytics may be used at the physician's discretion at any time during the study.

13.3. SBRT guidelines

13.3.1. Tissue constraints

Appropriate beam "nodes" or angles shall be selected to treat the primary site and areas at risk for occult disease spread. Careful target definition of these areas at risk is essential for optimal outcome. Beam shaping for treatment delivery shall be via conical or multi-leaf collimation (MLC). Treatment shall be via linear accelerator (LINAC) commissioned and equipped to deliver SBRT. Normal tissues and sensitive critical structures (e.g. duodenum, spinal cord, stomach, bowel, kidneys, liver, spleen, etc) shall be countered and the dose to these organs limited. See table below.

Normal Tissue Constraints

Organ	Maximum Dose in 3 fractions
Liver (700 cm3)	15 Gy
1/3 of total kidney volume (left and right)	15 Gy
Spinal Cord	18 Gy
Stomach	30 Gy
Duodenum/small bowel	18 Gy

The initial clinical target volume (CTV) will include all areas of measurable disease and adjacent high risk areas. A 1 mm margin will be added to the CTV create the initial planning target volume (PTV).

13.3.2. Dose Specification, Homogeneity Considerations & Plan Evaluation

The treatment plan used shall be based on the assessment of the dose-volume histogram (DVH) with attention to coverage of the planning tumor volume (PTV) and critical normal structures.

The prescription dose is the isodose cloud that encompasses at least 95% of the PTV.

- No more than 20% of any PTV shall receive doses >110% its prescribed dose
- No more than 2% of any PTV shall receive <93% of its prescribed dose
- No more than 5% of any normal tissue shall receive doses in excess of 110% of the primary PTV dose.

13.4. On-Treatment Assessment and Post-treatment Toxicity Evaluation

All subjects will be seen prior to each cycle of chemotherapy and completion of SBRT with toxicity evaluated by physical examination. Following this, follow-up will be at the discretion of the treating radiation oncologist.

13.4.1. Stereotactic Body Radiotherapy Risks

Short-term side effects include but not limited to skin reaction, local hair loss, fatigue, abdominal pain, nausea, vomiting, diarrhea, increasing liver function abnormality, GI bleeding or perforation which may require surgical intervention. Long term side effects are less likely to occur but if they do occur are more likely to be permanent. They include local hair loss, liver function abnormality, diarrhea, small bowel obstruction which may require surgical intervention, spinal cord injury which could result in paralysis, and kidney function abnormality.

13.4.2 Fiducial Placement Risks

In addition, all patients will have fiducial markers placed for localization at time of SBRT. Three to five soft-tissue fiducials (markers) will be placed in and/or around the tumor, at least 1cm apart. Oftentimes, these are placed at the time of endoscopic ultrasound and biopsy for diagnosis. If that is not the case, patients will be scheduled for a repeat EUS and have the markers placed prior to CT or FDG-PET/CT simulation. Alternatively, fiducials may be placed at the time of staging laparoscopy. The side effects of fiducial implantation will be similar to the biopsy of the tumor and stent placement. These include but are not limited to tumor seeding, infection, bleeding, pain at local area, and dislocation of the markers.

13.4.3. CT Risks

The subject will be exposed to radiation associated with the CT scans performed to assess response to therapy. CT scans are routinely performed as standard-of-care for tumor staging and to monitor response to therapy, and the radiation dose associated with these diagnostic scans are felt to represent minimal risk.

Adverse reactions to the administration of the FDG being used for the CT scans are not expected. However, as with the administration of any drug, the possibility of an adverse event cannot be totally excluded. The subject will be monitored for adverse events, and a physician and emergency drugs and equipment will be available in the scanning area should a reaction occur.

Claustrophobia: Possible anxiety, claustrophobia, and/or temporary discomfort may occur as a result of being placed in the scanning devices. Subjects will be monitored and removed from the scanner if required.

14.0. Statistics

(a) *Definition of primary endpoints:*

- Efficacy: pathological complete response (pCR) *and* R0 resection. Safety: Grade 4 toxicity.

(b) *Definition of secondary endpoint(s):*

- R0 resection rate in locally advanced pancreatic cancer after receiving chemotherapy (gemcitabine/*nab*-paclitaxel or mFOLFIRINOX) and SBRT
- Safety and toxicity profile will be evaluated utilizing number of grade 3 and 4 toxicities according to the National Cancer Institute Common toxicity Criteria for Adverse Events (NCI CTAE, v4.0) for the 2 chemotherapy regimens that occur after Cycle 1 Day 1.
- Radiological improvements will be evaluated by determining changes in density of measurable disease on CT at screening and post chemotherapy when scans are performed.
- TTP and overall survival of patients. Time to progression will be defined as disease progression after surgical resection.
- Ca19-9 response to neoadjuvant chemotherapy will be measured during every cycle
- To determine correlative factors including SPARC, RM1 and SMAD4

(c) *Analytic plan for primary objectives:*

- At enrolment, patients will be randomized to one of two regimens: (1) gemcitabine+*nab*-paclitaxel or (2) mFOLFIRINOX. All patients who receive at least one dose of their assigned regimen will be considered evaluable for response. Any patient who achieves an R0 resection and the surgical specimen is consistent with a pCR will be considered to have experienced R0 resection with pCR. Toxicity will be defined as an NCI CTCAE Grade 4 or worse adverse event probably or definitely related to treatment.
- The proportions of patients in each arm experiencing pathologic complete response and R0 resection will be estimated, and 95% exact binomial confidence intervals will be calculated. The proportions in the two arms will be compared by means of Fisher's exact test at $\alpha=0.1$, but no significant difference between arms is anticipated. The proportions of patients experiencing Grade 4 adverse events at least probably related to treatment will be analysed in the same fashion (although the difference between arms is anticipated to be larger).

(d) *Analytic plan for secondary objectives:*

- R0 resection rate will be assessed in all patients considered evaluable for the primary outcome measure. Any patient in who an R0 resection is obtained will be considered to have experienced an R0 resection success; all other patients will be considered to have experienced an R0 resection failure. The rate of R0 resection in each group will be calculated as the number of patients who have an R0 resection success divided by the number of patients who are evaluable for this endpoint. The R0 resection rate will be compared across randomized treatment arms in the same manner as the primary outcome measure.
- Each patient-cycle in which a grade 3 or 4 CTC AE ('relevant toxicity') was observed or a patient-cycle in which no such toxicity was observed but all protocol therapy was received will be considered evaluable for toxicity. The rate of each relevant toxicity will be calculated as the number of patient-cycles in which that toxicity was observed divided by the number of patient cycles considered for evaluation. These rates will be displayed according to cycle number and randomized regimen. Formal statistical testing of the toxicity rate will not be done.

- All patients who are considered evaluable for the primary endpoint and have surgery after the third cycle will be considered evaluable for the assessment of changes in density. ANCOVA will be used to characterize the change in density, where post-treatment density is the analysis variable and pre-treatment density is the covariate.
- Time to progression (TTP) is defined as the time from enrolment until disease progression, death or last patient contact, whichever comes first. A patient who dies or has disease progression will be considered to have experienced an event; otherwise the patient will be considered censored at last patient contact. Product-limit (Kaplan-Meier) estimates of the TTP function will be calculated, along with 95% confidence intervals. The log-rank test will be used to evaluate the significance of the difference in TTP between arms.
- Overall survival (OS) is defined as the time from enrolment until death or last patient contact, whichever comes first. A patient who dies will be considered to have experienced an event; otherwise the patient will be considered censored at last patient contact. The analysis plan is identical to that of TTP.
- CA-19-9 will be assessed at the start of each chemotherapy cycle. Patients will be segregated into groups according to their randomized regimen. The mean CA-19-9 level in U/ml will be calculated as well as the standard deviation. CA-19-9 time profiles will be compared using mixed effects linear (or, non-linear) models, as appropriate.
- IHC staining of SPARC, RM1 and SMAD4 (high, medium or low) will be compared between arms by means of cumulative logit models (appropriate specifically for ordinal outcomes).

(e) *Sample size justification:*

The proportions of patients who attain R0 resection and pCR will be estimated for each arm. A significant difference in the efficacy endpoint between arms is not expected; the proportion of patients achieving R0 resection and pCR is expected to be between 0.10 and 0.15 in both arms. However, the proportion of patients encountering Grade 4 toxicity is expected to be much lower in the gemcitabine plus nab-paclitaxel arm than in the mFOLFIRINOX arm. If the true probability of Grade 4 toxicity is 0.01 with gemcitabine plus nab-paclitaxel and 0.20 with mFOLFIRINOX, a direct comparison on 40 participants randomized 1:1 using Fisher's exact test at $\alpha=0.1$ will have 62% power to reject the null hypothesis. The expected width of 95% confidence intervals around the probabilities of toxicity would be 0.17 (for $\pi=0.01$) and 0.38 (for $\pi=0.20$). While a direct comparison is underpowered, the results will be necessary to motivate and design a definitive Phase III trial.

15.0. Reporting of Adverse Events

15.1. Adverse Event Definitions

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Adverse reaction means any adverse event caused by a drug.

Serious Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Specifically, results in death, is life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Any

subject death within 30 days of the last dose of study drug, regardless of the causality or a secondary malignancy should also be recorded as a serious adverse event.

Life-threatening, suspected adverse reaction. A suspected adverse reaction is considered “life-threatening” if, in the view of either the Investigator (i.e., the study site principal investigator), its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.

Unexpected, suspected adverse reaction. A suspected adverse reaction is considered “unexpected” if it is not listed in the general investigational plan or clinical protocol; or is not listed at the specificity or severity that has been previously observed and/or specified. If an investigator brochure is not required or available, suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. “Unexpected,” as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation. Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure can also be considered unexpected. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Suspected adverse reaction. Any adverse event for which there is a reasonable possibility that the drug caused the adverse event (considered “possibly related”). For the purposes of safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects’ case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the causal relationship between the adverse event and the study drug(s). All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0.

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Principal Investigator.

In the event of an adverse event the first concern will be for the safety of the subject.

Review of safety information. The principal investigator / sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

15.2. Reporting of suspected Adverse reactions

In the event of a serious adverse event, the PI, the institutional review board (per institutional reporting requirements), will be notified using the FDA Form 3500 MedWatch report.

All events meeting the definition of a serious adverse event should be recorded on a MedWatch 3500 Form (<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf>) and submitted to

1. [PI]: Nathan Bahary, MD
 - a. Phone: 412-864-7764
 - b. Email: baharyn@upmc.edu
2. Local Institutional Review Board per institutional reporting requirements

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Event Description (section 5) of the MedWatch 3500 form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports: Additional information may be added to a previously submitted report by adding to the original MedWatch 3500 report and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form.

16.0. Data Safety Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

16.1. Subject Removal Criteria

1. Development of a serious intercurrent medical illness according to the judgment of treating physician
2. Evidence of dose-limiting toxicity if no additional dose reductions can be made
3. Voluntary withdrawal
4. Discretion of the clinical investigator
5. Development of grade ≥ 4 toxicity related to experimental therapeutic

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