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Title: A Phase IIa (Pilot) Study of Neoadjuvant Chemotherapy with Folinic Acid, 5-FU, Irinotecan and Oxaliplatin (FOLFIRINOX) with Digoxin in Patients with Resectable Pancreatic Cancer

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Abstract

Purpose: To determine the feasibility and safety of combining digoxin as a modulator of the hypoxia pathway in combination with FOLinic acid, 5-Fluorouracil, IRINotecan and OXaliplatin (FOLFIRINOX) in patients with resectable pancreatic cancer.

Methods: Patients with resectable pancreatic cancer will be treated with oxaliplatin 85 mg/m² IV over 2 hours, irinotecan 150 mg/m² given concurrently with folinic acid 400 mg/m² IV over 90 min, followed by a 46-hour infusion of 5-fluorouracil 2400 mg/m². Slow oral digitalization will be used starting with a daily dose of 0.125 (patients over age 65) or 0.25 mg (patients 65 or younger) PO daily. A steady-state will be achieved after five half-lives, which is about 7 to 10 days in the average subject. The initial blood level will be obtained one week after starting digoxin. Assuming the digoxin level is at steady-state and the renal function is stable, there is a linear relationship between digoxin dose and serum concentration. The target digoxin level is between 0.8 to 1.2 ng/mL. Patients will receive IV chemotherapy at 2 week intervals. Restaging imaging will be performed after 4 doses. If the patient has stable or responsive disease, an additional 4 doses will be given followed by restaging imaging. The patient will then undergo surgical exploration ~ 4 weeks after the last dose of chemotherapy.

Clinical Endpoints: Primary Endpoints: clinical toxicity. Other endpoints: status of pathologic margins, response rate, pathologic stage, progression-free survival, and overall survival.

Correlative Endpoints: Baseline exome sequencing of circulating cell free tumor DNA.

Measurement of quantity of circulating cell free tumor DNA at 4 week intervals while on chemotherapy and prior to surgery; resume at 3 month intervals after surgery. Blood will be collected for analysis of possible biomarkers of response to digoxin modulation.

SCHEMA

Starting dose Digoxin 0.125 mg (age > 65 years) or 0.25 mg (age 65 years or less) daily starting day 1

Protocol Therapy: FOLFIRINOX every two weeks x 4 cycles (each treatment is considered one cycle)

Restaging Imaging Studies: Stable or responsive disease?

No: Evaluate for surgical resection

Yes: Resume protocol therapy for 4 additional cycles. Repeat imaging studies. Evaluate for surgical resection

After recovery from surgery: patients will be offered standard adjuvant chemotherapy with gemcitabine days 1 & 8 every 21 days and capecitabine 1000 mg/m² twice daily on days 1-5 & 8-12 every 21 days or (or leucovorin 50 mg/m²/30 min and 5-FU 2700 mg/m²/24 hr on days 1 & 8 every 21 days.

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1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the feasibility and safety of neoadjuvant chemotherapy with FOLFIRINOX given with digoxin in patients with resectable pancreatic cancer. The regimen would be considered worthy of further investigation, if 14 (or more) of the 20 or more of patients are able to undergo resection.

1.2 Secondary Objectives

1.2.1 To evaluate the efficacy of neoadjuvant chemotherapy with FOLFIRINOX given with digoxin in patients with resectable pancreatic cancer

2.0 BACKGROUND

2.1 Current therapy for locally advanced pancreatic cancers

Pancreatic cancer accounts for about 3% of all cancers in the US and about 7% of cancer deaths. The American Cancer Society (ACS) estimates that about 53,070 people will be diagnosed with pancreatic cancer in 2016, and about 41,780 people will die of pancreatic cancer (1). Prognosis is directly related to the extent of tumor. The patients are usually classified into those with localized, locally advanced, or metastatic disease. The numbers below come from the National Cancer Data Base and are based on people diagnosed with exocrine pancreatic cancer between 1992 and 1998. In general, people who can be treated with surgery tend to live longer than those not treated with surgery. The 5-year survival rate for people with stage IA pancreatic cancer is about 14%. For stage IB cancer, the 5-year survival rate is about 12%. For stage IIA pancreatic cancer, the 5-year survival rate is about 7%. For stage IIB cancer, the 5-year survival rate is about 5%. The 5-year survival rate for stage III pancreatic cancer is about 3%. Stage IV pancreatic cancer has a 5-year survival rate of about 1%. Still, there are often treatment options available for people with this stage of cancer. Surgical resection offers the best chance for long-term survival. However, even in patients who undergo potentially curative surgery, median survival is about 20 months and 5-year overall survival has not exceeded 20%.

Because surgery alone rarely provides long-term cures, an alternative strategy is to treat pancreatic cancer before or after surgery with either systemic chemotherapy or combined chemo-radiation therapy. In the majority of studies, adjuvant therapy is administered following pancreatic resection. A US Intergroup study compared gemcitabine vs. infusional 5-FU chemotherapy for one month prior to and three months after chemoradiation (CRT) consisting of continuous infusional 5-FU as adjuvant therapy after pancreatic cancer resection; outcome in those with tumor located in the pancreatic head was the primary study endpoint (3,4). The gemcitabine plus CRT arm trended towards improved overall survival versus the 5-FU plus CRT arm with a median survival of 20.5 months vs 17.1 months ($p=0.08$); survival at 5-yr was 22% vs 18%. The gemcitabine arm had appreciable toxicity, with grade 3-4 hematologic and non-hematologic toxicities occurring in 58% and 58% of subjects, respectively. Oettle et al compared gemcitabine given at 1000 mg/m² weekly for 3 of 4 weeks x 6 cycles to no adjuvant therapy in 368 patients with resected pancreatic cancer (5). Adjuvant gemcitabine was associated with a significant improvement in disease-free survival (13.4 vs 6.9 months), and a trend towards improvement in overall survival (median 22.1 vs 20.2 months). Overall survival was higher in those receiving gemcitabine: 3-yr and 5-yr survival was 30.4% & 23.5% vs 20.5% & 11.5% with surgery alone. Grade 3-4 hematologic and non-hematologic toxicities

occurred in fewer than 5% of subjects receiving gemcitabine. Another randomized trial with 1088 patients compared 6 months of gemcitabine 1000 mg/m²/30 min weekly for 3 of 4 weeks to folinic acid 20 mg/m² + 5-FU 425 mg/m² IV push days 1-5 every 4 weeks. There was no difference in either median progression-free survival (PFS) Gem vs FU/LV: 14.3 vs 14.1 months, or median overall survival (OS): Gem vs FU/LV: 23.2 vs 23.0 months (6).

While these studies indicate improvement with adjuvant therapy compared to surgery alone, there is still a need to improve upon these results (7). A disadvantage of adjuvant therapy is that as many as 25% of patients never receive adjuvant therapy or have their treatment delayed due to post-operative complications (8-10). In an effort to increase the number of patients receiving adjuvant therapy, chemotherapy alone or with radiation therapy can be administered pre-operatively to potential surgical candidates. Additional potential benefits of pre-operative therapy include the delivery of therapy to well-oxygenated tissues, the potential to downstage tumors, and the opportunity to observe patients for the development of metastatic disease during therapy. After maximal tumor shrinkage and no interval development of metastatic disease, surgery can be considered.

Because pancreatic cancer is characterized by early dissemination of disease, use of systemic chemotherapy is reasonable (11-15). A meta-analysis suggested that gemcitabine plus fluoropyrimidine combinations are superior to gemcitabine alone in the treatment of patients with metastatic pancreatic cancer: hazard ratio 0.90, p = 0.03 (16). With the advent of combination chemotherapy regimens using FOLFIRINOX or protein-bound paclitaxel with gemcitabine, the response rates, PFS and OS have improved vs gemcitabine alone in pancreatic cancer patients with locally advanced unresectable and distant metastatic disease. (17-18). The superior outcomes have prompted the use of combination chemotherapy in the neo-adjuvant setting. A retrospective analysis of 575 patients with locally advanced pancreatic cancer was published in 2016 (19). Patients receiving Gem were older (P=0.005); the resection rate was highest in those who had received FOLFIRINOX:

Neoadjuvant Therapy	N	Median age	Resection
FOLFIRINOX	125	59.8 yr	61%
Gem + radiation	322	62.7 yr	47%
Other combinations	128	60.7 yr	52%

The following table shows the pathologic outcome in patients who underwent resection.

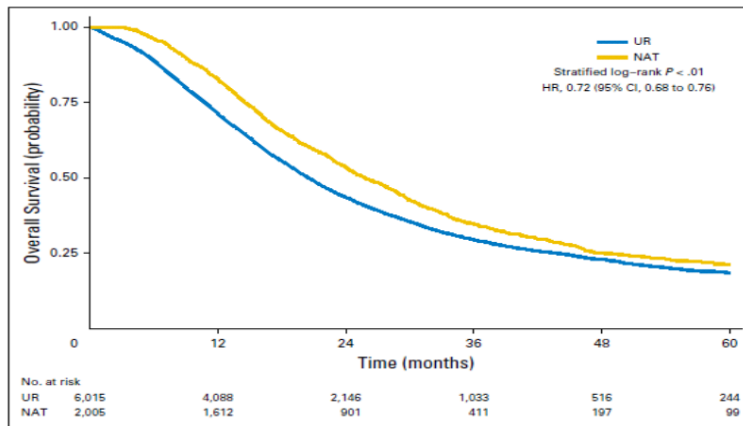
Category	Folfinrox [A]	Gem [B]	Other [C]	P
Resected cases [n]	76	150	66	A vs B+C
at presentation				
M0	61.8%	92.6%	83.3%	< 0.0001
M1	31.2%	7.4%	16.7%	
pT0-1	10.6%	8.0%	3.0%	0.048
pT2	3.9%	0%	3.0%	
pT3	81.6%	79.3%	81.8%	
pT4	3.9%	12.7%	21.2%	
pN0	50%	57.7%	28.8%	0.004
pN1	50%	42.3%	71.2%	
R0	40.8%	31.3%	27.3%	0.041
R1	59.2%	56.7%	65.2%	
R2	0	8.0%	6.5%	
Rx	0	4.0%	1.5%	

The value of neoadjuvant chemotherapy in patients with resectable pancreatic cancer is further supported by the following retrospective analysis. This analysis used the National Cancer Data Base with a propensity score matched analysis in pancreatic cancer patients that were clinical stage I or II. 2005 patients received neoadjuvant therapy prior to resection, while 6015 patients had initial resection (20).

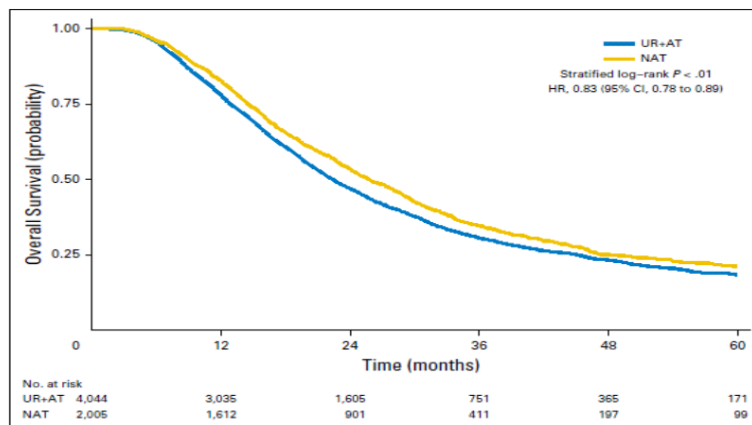
Comparison of pathology outcomes in the matched data set are shown in the following table:

Pathology	Initial Surgery (n=6105)	Chemotherapy (n=2005)	P
T0-1	3%	13%	< 0.01
T2	11%	15%	
T3	79%	60%	
T4	7%	13%	
Positive nodes	73%	48%	< 0.01
Positive margins	24%	17%	< 0.01
90-day mortality	8%	6%	

Kaplan-Meier curve evaluating OS between the upfront resection group and neoadjuvant therapy group showed a superior outcome in those receiving neoadjuvant chemotherapy:



The survival benefit persisted when comparing the neo-adjuvant chemotherapy group to the upfront resection group who received adjuvant chemotherapy:



In summary, the reasons to consider initial neoadjuvant therapy in resectable pancreatic cancer include the following: Post-op complications & early disease recurrence may limit planned adjuvant therapy. At large volume academic centers, 26% - 38% of patients did not receive post-op chemotherapy (21, 22). The median PFS after surgery alone is only about 7 months, which suggests that initial surgical resection benefits only a minority of patients. Pre-op chemotherapy will allow better patient selection for surgical resection, by excluding those with undetected distant or rapidly progressive disease, and avoiding the morbidity of surgery.

2.2 Rationale for the use of digoxin as a biologic modulator of Hif-1

An elevated rate of glycolysis occurs in cancer cells, even in the presence of atmospheric oxygen (the Warburg effect). Despite the inefficiency of ATP generation through glycolysis, the breakdown of glucose into lactate provides cancer cells with a number of advantages, including the ability to withstand fluctuations in oxygen levels, and the production of intermediates that serve as building blocks to support rapid proliferation. Recent evidence from many cancer types supports the notion that pervasive metabolic reprogramming in cancer and stromal cells is a crucial feature of neoplastic transformation (23-25). Under extended exposure to reduced oxygen levels, cells are able to survive

through the transcriptional activation of a series of genes that participate in angiogenesis, glucose metabolism, and cell proliferation. The oxygen-sensitive transcriptional activator HIF-1 (hypoxia-inducible factor-1) is a key transcriptional mediator of the response to hypoxic conditions. The HIF-1 pathway is a master regulator of angiogenesis. Whether the process is physiological or pathological, HIF-1 seems to participate in vasculature formation by synergistic interactions with other proangiogenic factors such as VEGF (vascular endothelial growth factor), PlGF (placental growth factor), or angiopoietins. Considering the important contributions of HIF-1 on angiogenesis and vasculogenesis, it should be considered a promising target for treating cancer. A number of studies have reported a correlation with increased tumor expression of HIF-1 with decreased survival in breast cancer, hepatocellular cancer, lung cancer, renal cell cancer and gastric cancer (26-30).

Studies from the laboratory of Dr. Pankaj Singh have demonstrated higher expression of HIF-1 alpha and the corresponding downstream glucose metabolism genes in pancreatic tumor cells as compared to the surrounding stroma. Data from his and other laboratories have indicated that inhibition of HIF-1 is an important strategy in the treatment of pancreatic cancer (31-36). A commercially available inhibitor of HIF-1 is digoxin. Data from Dr. Singh's laboratory indicated that treatment with digoxin significantly reduced tumor glucose uptake and increased survival in wild type mice. In a gemcitabine-resistant tumor model, the tumors had a higher expression of HIF-1, GLUT1, and Ki67. Treatment with digoxin alone in Gem-R-tumor-bearing mice produced a significant reduction in HIF-1, GLUT1 and Ki67 staining, and abrogated glucose metabolism and tumor growth in vivo.

Participants in this study will have no contraindications to receive digoxin, which is approved for the treatment of congestive heart failure and ventricular heart rate control in patients with supraventricular arrhythmias such as atrial fibrillation. Slow oral digitalization will be used starting with a daily dose of 0.125 (patients over age 65) or 0.25 mg (patients 65 or younger) PO daily. A steady-state will be achieved after five half-lives ($T_{1/2}$ -beta), which is about 7 to 10 days in the average subject. The initial blood level will be obtained one week after starting digoxin. Assuming the digoxin level is at steady-state and the renal function is stable, there is a linear relationship between digoxin dose and serum concentration. We will target a serum digoxin level between 0.8 to 1.2 ng/mL. Digoxin levels will be obtained weekly for four weeks; if the digoxin dose remains stable, it will be checked at 4-week intervals thereafter. The lowest dose that results in achieving the therapeutic range will be used. Digoxin will be given for 4-8 cycles (2 weeks/cycle). The lower dose of digoxin (such as 0.125 mg/day) will be chosen if serum level reaches 0.8 ng/mL. It is possible that some patients may need to receive 0.5 mg per day to reach this targeted drug level. No further titration will be allowed beyond this FDA approved digoxin dose.

Contraindications to digoxin therapy include AV block, sick sinus syndrome, bradycardia, and hypersensitivity to digoxin or digitalis preparations.

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

- 3.1.1 Pathologically confirmed adenocarcinoma of the pancreas. Patients must have resectable disease with no evidence of distant metastasis (defined in Appendix A).
- 3.1.2 Age: Patients must be 19 years of age or older. (This is the age of consent in Nebraska. Pancreatic cancer does not occur in the pediatric age group.)
- 3.1.3 ECOG PS of 0-1 (Appendix B)
- 3.1.4 Patients who received chemotherapy for malignancies other than pancreatic cancer are eligible, provided that chemotherapy was completed > 5 years ago and there is no evidence of the prior malignancy at the time of study entry.
- 3.1.5 All patients must have radiographically assessable disease
- 3.1.6 Patients must have an initial ANC greater than or equal to 1000/ μ L and platelet count greater than or equal to 100,000/ μ L
- 3.1.7 Patient must have normal serum potassium, magnesium and corrected calcium level
- 3.1.8 Patients must have a serum creatinine less than or equal to 2.0 mg/dL
- 3.1.9 Patients must have a total bilirubin $\leq$ 1.5 mg/dL (unless the patient has Gilbert disease with elevated non-conjugated (indirect) bilirubin; in such cases, the indirect bilirubin should be $\leq$ 1.0 mg/dL). If the patient has biliary obstruction, biliary decompression will be required. Either endoscopic placement of biliary stent or percutaneous transhepatic drainage are acceptable. Once biliary drainage has been established, institution of FOLFOX therapy may proceed when the total bilirubin falls to $\leq$ 5.0 mg/dL. The addition of irinotecan will be delayed until the total bilirubin is 1.5 mg/dL or lower.
- 3.1.10 The patient must be aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts.
- 3.1.11 No prior chemotherapy for pancreatic cancer

3.2 Exclusion criteria

- 3.2.1 Patients who cannot undergo staging laparoscopy. For example, this may include patients with a prior history of multiple abdominal operations in which laparoscopy may not be technically feasible or might be potentially harmful.
- 3.2.2 Patients with a contra-indication to receiving digoxin therapy, such as AV block, sick sinus syndrome, bradycardia, and hypersensitivity to digoxin or digitalis preparations.
- 3.2.3 Uncontrolled inter-current illness including, but not limited to ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, or serious, uncontrolled cardiac arrhythmia, that might jeopardize the ability of the patient to receive the therapy program outlined in this protocol with reasonable safety.
- 3.2.4 Pregnant and nursing women are excluded from this study because of the risk posed by the chemotherapy agents. Female patients of childbearing potential must have a negative urine pregnancy test before receiving the first dose of study drug

Note: All subjects of reproductive potential must agree to use two barrier methods of birth control during the course of the study and for 6 months after the last dose of study drug(s).

3.2.5 Patients with prior malignancy will be excluded except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas, or other cancers from which the patient has been disease-free for at least 5 years.

3.2.6 Patients with known HIV infection or active hepatitis B or C infection due to concern for increased toxicity

Note: Patients without a history of AIDS-defining opportunistic infections are eligible.

Patient with a history of AIDS-defining opportunistic infections are eligible if they have not had an opportunistic infection within the past 12 months.

3.2.7 Patients with an active autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus (SLE), ulcerative colitis, Crohn's Disease, multiple sclerosis (MS), ankylosing spondylitis).

3.2.8 Patients with a recognized acquired, hereditary, or congenital immunodeficiency disease including cellular immunodeficiency, hypogammaglobulinemia, or dysgammaglobulinemia.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

The date of enrollment is the date of consent. However, all eligibility criteria does not need to be met until the date of the first study related treatment.

All patients with pancreatic cancer or suspicious pancreatic masses referred to the Nebraska Medicine / UNMC are evaluated in a multidisciplinary team conference may be eligible for this trial.

Screening eligibility is based on standard clinical care performed by the medical oncologist. Patients with resectable pancreatic adenocarcinoma who meet the eligibility criteria will be offered participation in this trial. An informed consent will be signed by the subject after thorough review of the study is completed with the physician and his/her designee.

4.1 Eligibility Verification/Registration

Before patients are registered into the study, an eligibility checklist (Appendix C) must be completed to verify the subject meets the eligibility criteria. The eligibility checklist will be maintained in the study file as source documentation only if it has been reviewed, signed, and dated prior to registration by the treating physician.

Subjects will be registered by contacting the UNMC Investigator Initiated Trial (IIT) office Research Project Coordinator. Study personnel will contact the Project Coordinator if a potential subject appears to meet the eligibility criteria. They will email the following information:

- Registration request with Demographics cover sheet (located in the Study site Manual)

- Signed, completed eligibility checklist (Appendix C)
- Copy of the signed and dated consent form

Once the UNMC Research Project Coordinator confirms that the patient meets criteria, and target accrual has not been met, approval for the patient will be given and study subject number assigned. The UNMC Research Project Coordinator will send a confirmation of registration email to the site. The Project coordinator can assign a subject study number prior to final registration confirmation of a subject.

Each subject consented to the protocol is loaded into the UNMC Clinical Trial Management System (CTMS) within 7 days of consent. CTMS registration includes entering the required demographic information (included on the registration request form) as stated in the SRC policies and procedures.

4.2 Instructions for Subjects Who Do Not Start Assigned Protocol Treatment (Screen Failure)

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study because results of screening labs/tests for eligibility show the subject not to be eligible. All consented subjects are assigned a study subject number. If a subject does not receive any assigned protocol treatment after consenting, minimal baseline data will still be collected and included in the electronic data capture system. Data is for reporting to the regulatory authorities and publishing. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.0 TREATMENT PLAN

This is a Phase IIa study of digoxin during an up to 4-5 months time period in patients with resectable pancreatic cancer. Digoxin is taken at the time of neo-adjuvant chemotherapy treatment, prior to surgery. This is an open-labeled study.

5.1 Assessment Schedule

5.1.1 Screening assessments

On initial presentation, the following are performed

- history and physical examination and performance status is assessed
- laboratory data, including hematologic and chemistry panels, magnesium and T bilirubin
- electrocardiogram (ECG)
- Imaging studies obtained include a high-resolution computed tomography (CT) scan of the chest, abdomen and pelvis. A PET CT Scan will be performed at baseline to assess metabolic activity of the tumor and to exclude occult metastatic disease.
- Patients without evidence of metastatic disease on imaging studies will be evaluated for potential resectability (NCCN Guidelines- Appendix A).

Imaging studies available for use in defining resectability include multiphase CT scan using pancreas

protocol, (MRI scan will be done if CT scan is not sufficient for evaluating if the tumor is resectable), endoscopic ultrasound, and laparoscopic intraoperative ultrasound. The CT scan obtained is an imaging protocol specifically designed to evaluate the pancreas using a triple phase contrast scan with thin (< 3 mm) cross-sectional images with 3-dimensional reconstruction availability. CT mesenteric angiography will be obtained when clinically indicated. Endoscopic ultrasound and laparoscopic ultrasound will be utilized when additional information regarding tumor relationship with surrounding vascular structures, or when diagnostic tissue samples are required.

5.1.2 Staging laparoscopy is considered standard of care

Patients without evidence of metastatic disease on imaging studies will undergo laparoscopy to exclude the presence of occult metastatic disease, if this has not been performed. Routine inspection of the liver, peritoneal surfaces and serosa of abdominal viscera will be performed. Biopsy will be performed of suspicious lesions for histologic examination. The staging laparoscopy must be done within 28 days of treatment start.

The standard of care outside clinical trials setting for patients with localized or locally advanced pancreatic cancer with resectable disease has been surgery followed by adjuvant therapy with chemotherapy alone or chemotherapy and chemoradiation. This strategy has been rethought as mounting evidence indicates that pancreatic cancer in the vast majority of patients is a systemic disease at presentation, and the relatively poor long-term outcomes in patients who have initial surgery.

5.2 Chemotherapy with FOLFIRINOX (standard of care)

The protocol treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 8. Appropriate dose modifications are described in Section 5.8. No investigational or commercial agents or therapies other than those described in this protocol may be administered with the intent to treat the patient's malignancy.

Per ASCO guidelines, obese patients will be treated with their actual BSA (37).

Oxaliplatin 85 mg/m² will be given IV over 2 hours first followed by irinotecan 150 mg/m² IV over 90 min given concurrently with leucovorin 400 mg/m² via a Y-site connection followed by a continuous infusion of 5-fluorouracil 2400 mg/m² IV over 46 hours. Treatment will be repeated at 2-week intervals, for up to 4 doses.

A window of -2 up to +7 days will be allowed to start planned cycles of therapy provided all other criteria to restart the new cycle have been met.

5.3 Administration of Digoxin

At the time that participants start FOLFIRINOX, they will also begin digoxin. Participants in this study will have no contraindications to receive digoxin. Digoxin is approved for the treatment of congestive heart failure and ventricular heart rate control in patients with supraventricular arrhythmias such as atrial fibrillation. Slow oral digitalization will be used starting with a maintenance dose of 0.125 (participants over 65 year of age) or 0.25 mg PO daily. A steady-state will be achieved after

five half-lives ($T_{1/2}$ -beta), which is about 7 to 10 days in the average subject. The initial blood level will be obtained one week after starting digoxin. Assuming the digoxin level is at steady-state and the renal function is stable, there is a linear relationship between digoxin dose and serum concentration. We will target a digoxin level between 0.8 to 1.2 ng/mL. Digoxin dose is adjusted accordingly based on the participant's blood concentration levels. Digoxin levels will be obtained weekly for four weeks; if the digoxin dose remains stable, it will be checked at 4-week intervals thereafter. The lowest dose that results in achieving the therapeutic range will be used. Digoxin will be given for 4-8 cycles (2 weeks/cycle). The lower dose of digoxin (such as 0.125 mg/day) will be chosen if serum level reaches 0.8 ng/mL. It is possible that some patients may need to receive 0.50 mg per day to reach this targeted drug level. No further titration will be allowed beyond this FDA approved digoxin dose.

Throughout administration of digoxin standard labs including, complete metabolic panel and magnesium will be performed as noted on the study parameters (Section 7.0) to monitor electrolyte levels.

The patient will be given a medication information sheet at the beginning of their digoxin treatment. The patient will also be asked to maintain documentation of medication adherence by filling out a calendar of when and how many tablets of digoxin were taken. The patient will be asked to bring the calendar back along with any leftover medication at their convenience at the end of treatment.

5.4 Imaging during NeoAdjuvant Chemotherapy/Digoxin treatment

Restaging CT scan of the chest, abdomen & pelvis will be performed after each set of 4 doses of chemotherapy. An MRI scan may be performed if CT scan is not adequate to determine response and suitability for resection.

Only 8 cycles of neoadjuvant therapy/digoxin will be given. If surgical resection is not possible after 8 cycles and the clinician determines that continuation of the standard of care chemotherapy is appropriate (FOLFIRI), it will be resumed when the clinician determines the patient has sufficiently recovered. The patient would be treated until evidence of disease progression. If the decision is made by the treating physician to continue standard of care chemotherapy with no surgical resection possible, then the subject will be removed from the study.

5.5 Surgery

Patients without metastasis and with resectable disease will undergo definitive surgery. At the time of surgical resection, an extensive examination of the abdomen will be performed to exclude the presence of metastatic disease. All operations will be performed with curative intent with resection of all gross tumor (i.e. R0 [negative margins]). Resection of adjacent involved organs or vascular structures will be performed as clinically indicated. Standardized histopathologic analysis of resected specimens will be performed. Margins to be evaluated include: common bile duct, pancreatic, retroperitoneal (tissue between superior mesenteric artery and duodenum), as well as tissue along the superior mesenteric vein and artery. Examination of regional lymphatics will be performed according to standard pathology techniques.

As grading schemes for assessment of treatment effect in patients with pancreatic cancer receiving pre-operative chemotherapy alone are not well established (38), standard synoptic criteria will be

used in the pathology report using the American Joint Committee on Cancer (AJCC) 8th edition.

If a patient enrolled in this study has a surgical resection or other procedure and enrolled in the 440-16-EP IRB tissue banking protocol, a tissue specimen will be requested for analysis as part of this protocol.

5.6 Adjuvant chemotherapy after surgical resection

As part of standard treatment, participants can be offered 4 additional cycles of FOLFIRINOX after recovery from surgery if there persistent sensory neuropathy is grade 1-2 or 4 additional cycles of FOLFIRI if persistent sensory neuropathy is grade 3 or worse. Conroy et al reported the results of FOLFIRINOX versus gemcitabine as adjuvant therapy for pancreatic cancer (48). 493 patients with resected pancreatic ductal adenocarcinoma were randomized to receive 12 cycles of modified FOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 150 mg/m² (reduced from 180 mg/m² after a protocol-specified safety analysis), leucovorin 400 mg/m² & fluorouracil 2400 mg/m²/46 hr given every other week or gemcitabine 1000 mg/m² weekly for 3 of 4 weeks for 6 cycles. After a median follow-up of 33.6 months, the median overall survival was 55.4 months in the modified FOLFIRINOX group compared to 35.5 months in the gemcitabine group. The overall survival rate at 3 years was 63.4% in the FOLFIRINOX group versus 48.6% in the gemcitabine group (Hazard ratio 0.65 [95% CI 0.48 to 0.86], p = 0.003). This was at the expense of a higher incidence of toxic effects: grade 3-4 adverse events occurred in 75.9% in those treated with FOLFIRINOX versus 52.9% in the gemcitabine group.

If the participant prefers not to receive additional FOLFIRINOX or FOLFIRI, they can be offered 3 months of standard adjuvant chemotherapy with gemcitabine and capecitabine based on the results of the ESPAC-4 trial (39). In this trial, 732 patients enrolled, 730 were included in the final analysis. Of these, 366 were randomly assigned to receive gemcitabine 1000 mg/m² weekly for 3 of 4 weeks for 6 cycles and 364 to the same dose & schedule of gemcitabine given with capecitabine (830 mg/m² PO BID for 21 of 28 days). The Independent Data and Safety Monitoring Committee requested reporting of the results after there were 458 (95%) of a target of 480 deaths. The median overall survival for patients in the gemcitabine plus capecitabine group was 28.0 months (95% CI 23.5–31.5) compared with 25.5 months (22.7–27.9) in the gemcitabine group (hazard ratio 0.82 [95% CI 0.68–0.98], p=0.032). Grade 3-4 adverse effects occurred in 63% of the gemcitabine/capecitabine group compared to 53.6% in the gemcitabine group.

In clinical practice, the majority of patients cannot receive gemcitabine weekly for 3 of 4 weeks due to myelosuppression on day 15. Therefore, in this trial, gemcitabine will be given as 1000 mg/m²/100 min weekly for 2 of 3 weeks. Since it is recognized in clinical practice that patients in the United States do not tolerate the recommended doses of capecitabine employed in European studies, the dose of capecitabine will be 2000 mg/m² given in two divided doses on days 1–5, & 8–12 every 21 days.

Some patients would receive infusional 5-FU with leucovorin instead of capecitabine for several reasons: out of pocket expense for capecitabine; reluctance to take capecitabine, or intolerance to capecitabine (GI upset). In this case, the schedule will be gemcitabine 1000 mg/m²/100 min, leucovorin 50 mg/m² and 5-FU 2700 mg/m²/24 hours on days 1 & 8 of a 21 day cycle. If the

decision is made by the treating physician to treat with any other adjuvant therapy, then the subject will be removed from study.

At the end of the 2-3 months of chemotherapy, the following assessments will be done as part post adjuvant therapy surveillance. Additional follow-up is noted in Section 5.12.

- CBC with differential
- Basic metabolic panel (BMET)
- CA 19-9, if initially elevated
- Carcinoembryonic antigen (CEA), if initially elevated
- CT (Chest) and abdomen and pelvis (with IV and oral contrast)
- Research blood sample, cell free DNA

5.7 Adjuvant chemoradiation after surgical resection

The worth of adjuvant radiation therapy in addition to adjuvant chemotherapy is currently the subject of a randomized clinical study. If the decision is made by the treating physician in conjunction with the patient to pursue post-operative chemoradiation therapy after completion of adjuvant chemotherapy, then the patient will be removed from study.

5.8 Dose Modifications

The NCI Common Toxicity Criteria version 5.0 will be used, available at the CTET web-site. See Appendix E for the web-site link.

5.8.1 Chemotherapy

For all cycles, the planned treatment dosing may be either interrupted or omitted for significant treatment-related toxicities occurring on the day of or in the prior 24 hr of planned therapy: platelet count $< 75,000/\mu\text{L}$, ANC $< 1000/\mu\text{L}$, grade 2 or worse non-hematologic toxicity (excluding nausea & vomiting on sub-optimal anti-emetic therapy, alopecia, elevated transaminases).

At the start of each new cycle, dose adjustments may also be made based upon significant toxicities occurring at any time in the previous cycle.

5.8.2 Initiation of Next Cycle of FOLFIRINOX

The next treatment cycle will commence 14 days after the start of the prior cycle provided that the absolute granulocyte count is greater than or equal to $1000/\mu\text{L}$, the platelet count is greater than or equal to $75,000/\mu\text{L}$, and all clinically significant treatment-related non-hematologic toxicities have resolved to no more than grade 1 in severity. If multiple toxicities have been seen in the preceding cycle, the dose administered should be based on the most severe toxicity experienced. If the ANC is the only hematologic parameter that would delay starting the next cycle, the patient can be offered filgrastim administration so they can try to keep on schedule. If filgrastim is administered, the CBC/diff will be checked daily until the ANC is adequate. Otherwise, treatment can be delayed by one week.

5.8.3 Dose Reductions for Hematologic Toxicity Occurring During the Prior Cycle of

FOLFIRINOX (doses in mg/m²)

ANC /μL	Platelet x 1000/μL	Oxaliplatin	Irinotecan	Leucovorin	5-FU
> 1000	and > 75	100%	100%	100%	100%
500 - 999	or 59 - 74.9	100%	100%	100%	100%
< 500	< 50	75%	75%	100%	100%

5.8.4 Dose Modifications for Treatment-Related Non-Hematologic Toxicity Occurring the Prior Cycle of FOLFIRINOX

Diarrhea or Mucositis	Oxaliplatin	Irinotecan	Leucovorin	5-FU
gr 0-2	100%	100%	100%	100%
grade 3-4	75%	75%	100%	75%

Neuropathy	Oxaliplatin	Irinotecan	Leucovorin	5-FU
resolved	100%	100%	100%	100%
persistent	75%	100%	100%	100%

Other	Oxaliplatin	Irinotecan	Leucovorin	5-FU
gr 0-2	100%	100%	100%	100%
grade 3-4	75%	75%	100%	75%

5.8.5 Dose Modifications for Digoxin Toxicities

Since renal insufficiency can increase the risk of digoxin toxicity, particular attention will be paid to assuring the patient is well hydrated. The patient will receive supplemental hydration by diluting irinotecan in one liter of normal saline and calcium leucovorin in 250 mL of normal saline (given over 90 minutes). The subject will receive one liter of normal saline when the 5-FU infusion is disconnected. The patient will be encouraged to push oral hydration. If the subject is unable to maintain adequate oral intake due to nausea, diarrhea or reduced desire to drink liquids, arrangements should be made for the patient to receive supplemental IV hydration from one to three times weekly as needed.

Since electrolyte abnormalities can increase the risk of digoxin toxicity, low potassium (3.4 mmol/L or less), low magnesium (1.7 mg/dL or less), or high calcium (10.5 mg/dL or higher) should be corrected regardless of patient's symptoms.

If subject present with clinical symptoms of digoxin toxicities, such as confusion, changes in vision (seeing the color yellow more than normal, blurriness, increased sensitivity to light, flashing lights), or cardiac toxicity (heart block, bradycardia or tachyarrhythmias), then a digoxin level, ECG and electrolyte labs would be obtained. Electrolyte abnormalities will be corrected. Digoxin will be held until symptoms have resolved.

If the digoxin level is found to be supra-therapeutic, the dose will be reduced by 50%. If the digoxin level is in the therapeutic range, the dose would be reduced by 25%.

If the patient experiences a second instance of toxicity requiring withholding of digoxin, then no further digoxin would be given to that patient.

However, if the patient needs to be hospitalized for management of symptomatic digoxin-associated cardiac toxicity, then no further administration of digoxin will be given to the affected individual, regardless of the digoxin level.

5.9 Supportive Care Guidelines

5.9.1 Prophylactic Anti-Emetic Premedication

Patients must be pre-medicated for nausea & vomiting with the following antiemetic regimen as outlined below. These recommendations follow the ASCO guidelines for the use of anti-emetic therapy (40) Dexamethasone may be omitted in patients with diabetes.

fosprepitant 150 mg IV
ondansetron 8 mg IV with dexamethasone 12 mg IV
OR palonosetron 0.25 mg IV with dexamethasone 12 mg IV
Lorazepam 1 mg PO or sublingual once PRN

5.9.2 Diarrhea

Patients will be instructed to begin taking loperamide after the first poorly formed or loose stool or first episode of 2 or more bowel movements in one day. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg with each subsequent diarrheal stool until diarrhea-free for at least 12 hours. Patients must notify the research team as to when they initiated loperamide therapy. If diarrhea persists despite loperamide therapy, then the patient should be evaluated for the need for IV fluid & electrolyte replacement.

Alternative anti-diarrhea agents:

Somatostatin analog (Octreotide[®]) 100 - 500 mcg SC/IV tid; maximum daily dose = 1500 mcg/day; alternatively, somatostatin analog may be given at 25-50 mcg/hour as a continuous IV infusion.

Atropine/diphenoxylate which is available as either a 0.025/2.5 tab, or 0.025/2.5 per 5 mL liquid.

Patients should take 1-2 tabs PO tid or qid or 5-10 mL PO tid/qid.

Atropine/difenoxin (Motofen) 0.025/1 tab; 2 tabs PO x 1, then 1 tab PO q 2-4 hr (max 8 tabs per day)

Paregoric: (an antidiarrheal opiate): 5 - 10 mL PO 1-4 times daily: maximum 40 mL/day

Codeine 30 mg PO Q 6 hours

OTC meds: bismuth subsalicylate 262 mg tabs: 2 tabs PO q 1 hr prn; maximum 4200 mg/24 hr

5.9.3 Stomatitis

Mild symptoms will be treated with topical antiseptic & analgesic agents. Various versions of "magic mouthwash" exist, and represent a combination product for the topical treatment of mild oropharyngeal pain. Such mouthwashes usually consist of viscous lidocaine, diphenhydramine, aluminum and magnesium hydroxide, 70% sorbitol, and orange flavoring. Both viscous lidocaine and diphenhydramine have local anesthetic properties, while the aluminum hydroxide component of Maalox has a beneficial drying property. Patients with severe pain require systemic narcotic analgesics. Topical anti-fungal agents will be added as clinically indicated. More severe symptoms will require all of the above as well as stronger analgesic agents & admission to hospital for IV fluid & electrolyte replacement if dehydrated. Patients will be advised to take L-lysine PO 500 mg tid if they develop mouth sores.

5.9.4 Requirement for Venous Access

Central venous access is required for protocol participation. A previously placed central venous access device that is functioning properly (free infusion of saline, unimpeded blood return, good condition of external appliance, no recent history of device infection or thrombosis) can be used. Should the patient require a central venous access, an implanted port central venous access device will be placed (e.g. a Medi-Port, Port-a-Cath, Power Port) after appropriate informed consent has been obtained. Other aspects of catheter/port management will be in accordance with standard nursing clinic central venous port procedures and ASCO guidelines (41).

5.9.5 Treatment of Fever & Neutropenia

ASCO guidelines will be followed (42). Subjects developing a fever of 100.5° C or higher will have a CBC with WBC differential obtained along with a history & physical examination to look for signs of infection. If the ANC is < 500/ μ L, the patient will be treated with empiric antibiotic therapy as an inpatient & undergo appropriate radiographic & laboratory investigation for sources of infection, & development of a specific treatment plan. Fever & neutropenia occurring during a treatment cycle will require interruption of chemotherapy. The patient may resume chemotherapy at the start of the next scheduled cycle if therapy for infection has been completed & the patient meets other criteria for starting a new cycle. If the ANC is between 500-1000/ μ L, antibiotic therapy will be instituted if there is clinical suspicion of an infection. Daily CBCs with differentials will be obtained if the patient remains febrile.

If the ANC is > 1000/ μ L, & there is no clinical evidence of an infection, then therapy may resume.

5.9.6 Use of Leukocyte Colony-Stimulating Factors and Erythropoetin

Colony stimulating factors (CSFs) will be used as clinically indicated according to ASCO guidelines (43). If a low ANC is the only parameter that would delay resumption of chemotherapy, the patient can be offered filgrastim. In this case, the CBC/diff would be checked daily until the ANC is adequate for resumption of therapy. Use of any CSFs must be discontinued at least 24 hours prior to initiation of the next cycle of chemotherapy & must be documented in the patient record. If filgrastim is used, consideration can be given to using pegfilgrastim following subsequent doses of chemotherapy (6 mg subcut given on day 3 after the 5-FU infusion is disconnected).

Erythrocyte stimulating hormones will be used as clinically indicated according to ASCO guidelines (44).

5.9.7 Pancreatic Enzyme Replacement

Patients with signs & symptoms of pancreatic insufficiency should receive pancreatic enzyme supplement.

5.9.8 Nutritional Supplementation

Patients will be evaluated by a nutritionist to review their caloric needs and daily caloric intake. Patients will be encouraged to supplement their nutrition with a high-protein, low fat nutritional drink during the neoadjuvant therapy phase of the trial.

Strong consideration should be given for early, elective placement of an enteral feeding tube if the patient has lost 10% or more of their body weight.

5.9.9 Acute cholinergic reaction to irinotecan

An early cholinergic syndrome can occur during or shortly following irinotecan administration and usually manifests with symptoms of lacrimation, diaphoresis, flushing, nasal congestion, or abdominal cramping and occasional hyperperistalsis that can lead to diarrhea. This syndrome may be treated with 0.5 -1 mg atropine IV or SQ (unless there is a relative or absolute contraindication to its use such as but not limited to closed-angle glaucoma, urinary retention, or previous untoward reactions to the administration of atropine). For patients with recurrent problems with cholinergic symptoms, up to 1 mg of IV or S.C. atropine may be considered for prophylaxis in subsequent cycles. Additional anti-diarrheal measures may be used at the discretion of the treating physician.

5.9.10 Hypersensitivity

Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, antihistamines and epinephrine; bronchodilators and vasopressors may be required. Platinum hypersensitivity is an extremely rare event (approximately 0.5% of patients) and should be treated promptly. Depending on the severity of the reaction, the patient can be offered a rechallenge with the following premedication regimen: dexamethasone 20 mg PO the night before & morning of chemotherapy; prior to chemotherapy: solumedrol 125 mg IV, diphenhydramine 50 mg IV, ranitidine 50 mg IV.

5.9.11 Pharyngo-laryngeal Dysesthesias

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

cold avoidance. If grade 1 (mild) pharyngo-laryngeal dysesthesias occurs while treatment is being administered, increase the duration of infusion to 6 hours. If grade 2 (moderate) or grade 3 (severe) pharyngo-laryngeal dysesthesias occurs during treatment administration, stop oxaliplatin infusion, administer benzodiazepine, reassure the patient and monitor. At the discretion of the investigator, the infusion may be re-started at 1/3 original infusion rate. Increased duration of infusions is not required for subsequent treatment administration.

5.10 Duration of Study

We estimate that there will be about 20 patients enrolled into this protocol over a 2-3 year period. The sample size was determined based on the feasible number of patients that can be recruited to the trial.

5.11 Duration of Follow up

If the patient undergoes surgical resection, and has completed protocol chemotherapy, the patient will then be seen every 3 months for the 1st year and every 4 months for 2nd year, then every six months thereafter for up to 5 years. Restaging radiographic scans, CBC with differential, chemistry panel and tumor markers will be performed at each of these visits as part of standard of care.

5.12 Post-trial Assessments

Patients who go off study treatment at any time during the trial will be followed for 30 days after the last day of digoxin treatment or until other disease-related treatment begins. For all patients, drug-related SAEs and AEs will be followed until baseline or grade 1 or less levels. Patients may refuse to participate in the post-trial assessments. The following standard of care labs will be repeated, CBC with differential, complete metabolic panel and any tumor markers that are found to be initially elevated.

5.13 Criteria for Removal from Study

5.13.1 Progression of Disease

5.13.2 If at any time the constraints of this protocol are detrimental to the patient's well being, or if the patient is unable to comply with the requirements of the protocol, the patient will be removed from protocol therapy. In this event, the reason(s) for withdrawal will be documented.

5.13.3 If the patient experiences an adverse reaction that, in the opinion of the investigator, necessitates the removal of the patient from the study, including any unresolved serious adverse event.

5.13.4 Any patient who suffers a serious systemic allergic response or severe degree of intolerance to the study medication will be withdrawn from further study treatment but will be followed up for a period of three years following treatment.

5.13.5 Development of intercurrent medical problems that would make continued protocol therapy detrimental to the patient's safety.

5.13.6 There is concurrent illness or other reasons that would, in the opinion of the investigator, affect assessment of clinical status or conduct of the study to a significant degree.

5.13.7 The patient completes study treatment as per study schedule.

5.13.8 The patient chooses to discontinue treatment or follow-up. In this event, the reason(s) for withdrawal will be documented.

The reason(s) for withdrawing the patient from the treatment portion of the study will be documented in the case report form. If available, the following information will be recorded in the case report form: date of disease relapse, date of death, cause of death, and autopsy report.

6.0 MEASUREMENT OF EFFECT

6.1 Tumor Response

Measurable Disease Response: CTEP's. Criteria for Radiographic Response Evaluation (RECIST) version 1.1 guidelines will be followed: The RECIST guidelines can be downloaded at the following URL: https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf

Patients enrolled in this study must have a measurable pancreatic cancer which is defined as lesions that can be accurately measured in at least one dimension: [longest diameter to be recorded] on the CT scan or MRI scan. When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline

The same method of assessment & the same technique should be used to characterize each identified & reported lesion at baseline & during follow up.

Parameters to Measure

Response Outcome:

- 1 Clinical examination
- 2 Chest radiograph
- 3 CT & MRI scans
- 4 Tumor markers
- 5 Cytology & histology

6.2 Response criteria: RECIST 1.1

Taking into account the measurement of the longest diameter only for those lesions with size response, response criteria are defined as:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): at least a 30% decrease in the longest diameter of a lesion, taking as reference the baseline sum diameters.

Progressive Disease (PD): at least a 20% increase in the longest diameter of a lesion, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the longest diameter since the treatment started.

6.3 Time to Treatment Failure

The time to treatment failure will be defined as from the first date of therapy until the date the patient is removed from study for any reason.

6.4 Time to Disease Progression

The time to disease progression will be defined as from the first date of therapy until the date that disease progression has occurred based on radiographic or clinical grounds

6.5 Survival

Survival will be defined as from the first date of therapy until the date the patient dies.

6.6 Toxicity criteria

The NCI Common Toxicity Criteria Adverse Events version 5.0 will be used to grade toxicity; it is available at the CTEP internet web-site indicated in Appendix E.

7.0 Study Parameters

		Neoadjuvant Chemotherapy (2 week cycles)									Post-Trial Assessments (30 days after last dose of digoxin or until other disease-related treatment begins) ($\pm$ 7 days)
Test/Assessments	Screening (Day -28 to 0)	Baseline (Day 1)	2 weeks (-2 to +7 days)	4 weeks (-2 to +7 days)	6 weeks (-2 to +7 days)	8 weeks (-2 to +7 days)	10 weeks (-2 to +7 days)	12 weeks (-2 to +7 days)	14 weeks (-2 to +7 days)	16 weeks	
Informed consent	X										
Physical Exam and history Vital Signs and performance status (PS) (ECOG)	X	X	X	X	X	(X)	(X)	(X)	(X)		
ECG	X										
CBC/diff ³	X		X	X	X	(X)	(X)	(X)	(X)	X	X
CMET ³	X		X	X	X	(X)	(X)	(X)	(X)	X	X
Magnesium	X		X	X	X	(X)	(X)	(X)	(X)	X	
T Bilirubin ³	X		X	X	X	(X)	(X)	(X)	(X)	X	
CA 19-9, CEA		X		X ¹		X ¹		X ¹		X	X ¹
HIV, Hep B surface antigen and Hep C antibody ⁷	X										
Urine Pregnancy test	X										

Staging laparoscopy, as clinically indicated ⁹	X										
CT Chest ⁴	X									X	
CT Abdomen & Pelvis with IV & oral contrast (pancreas protocol) ⁴	X					X				X	
MRI Abdomen w/out contrast ⁴	X ²					X ²				X ²	
PET CT Scan ⁴	X									X	
Evaluate for Surgery ¹⁰						X				(X)	
Adverse Event assessment ¹¹		----- X -----									
Concomitant medication assessment ¹²		----- X -----									
Blood for sequencing		X									
Blood for cell free DNA		X		X		X		X		X	
Blood for nucleoside metabolites studies ⁶		X		X		(X)		(X)			
FOLFIRINIX administration ⁸		X	X	X	X	(X)	(X)	(X)	(X)		
Digoxin administration (daily)		-----X-----				----- (X) -----					
Digoxin Levels ⁵		X (weekly to week 4)		X ⁵		(X ⁵)		(X ⁵)			

¹ tumor markers will be obtained at baseline and will be obtained at 4 week intervals in the pre-operative period if initially elevated.

² A MRI abdomen w/ contrast will be obtained if CT Scan using pancreas protocol is not adequate for defining extent of disease; this will be obtained at ~ 8 week intervals

³ Baseline Lab studies must be obtained within 7 days of initiating protocol therapy. Follow-up labs once protocol therapy has been initiated that are to be obtained prior to each dose of chemotherapy may be obtained within a window of + / - 3 days. If therapy is delayed due to myelosuppression, a CBC/diff will be obtained prior to administration of chemotherapy. The CMET & T. Bilirubin do not have to be repeated if unremarkable.

⁴ Baseline imaging studies must be obtained within 28 days of initiating protocol therapy. Repeat imaging studies (CT abdomen / pelvis or MRI abdomen w/ contrast) will be obtained ~ 2 weeks after the 4th and 8th doses of chemotherapy. A window of 7 days is permitted

A follow-up PET CT Scan will be obtained ~ 2 weeks after the 8th dose of chemotherapy. A window of 7 days is permitted

⁵ Digoxin levels will be obtained weekly for four weeks; if the digoxin dose remains stable, it will be checked at 4-week intervals thereafter while on digoxin. Subjects presenting with signs or symptoms of digoxin toxicity may have additional unscheduled digoxin levels obtained for safety.

⁶ Blood collection is every 4 week while participants are on digoxin.

⁷ Testing for HIV, Hepatitis B, and C completed prior by standard clinical testing is acceptable for study eligibility. No additional testing is required. If no prior testing was completed, must be completed for eligibility.

⁸ FOLFIRINOX treatment is given for 4 cycles. A window of -2 up to +7 days will be allowed to start planned cycles of therapy provided all other criteria to restart the new cycle have been met. Restage to see if responding. If subject is responding then up to 4 more cycles may be given (all procedures on table in) to indicate occurrence. If not, then evaluate for surgery.

⁹ Staging laparoscopy must be done within 28 days of treatment start.

¹⁰ If a patient enrolled in this study has a surgical resection or other procedure and enrolled in the 440-16-EP IRB tissue banking protocol, a tissue specimen will be requested for analysis as part of this protocol.

¹¹ Adverse events are closely followed for toxicity from the time of first dose of digoxin until 30 days after last administration of the final digoxin dose. The reporting is only for study medication until 30 days after last administration of the final digoxin dose.

¹² Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

	Adjuvant Therapy ⁴ after Surgery	Surveillance after adjuvant therapy		
Test/Assessments	Day 1 (-3 days) of cycles for 2-3 months	Every 3 months/ Year 1 (+/- 1 month)	Every 4 months/ Year 2 (+/- 1 month)	Every 6 months/ Year 3(+/- 1 month)
Physical Exam	X	X	X	X
CBC/diff ⁵	Weekly	X	X	X
BMET ³	Weekly	X	X	X
Hepatic function panel	X			
CA 19-9 ¹		X	X	X
CEA ¹		X	X	X
CT Chest with contrast	X ²	X	X	X
CT Abdomen & pelvis with IV & oral contrast (pancreas protocol)	X ²	X	X	X
Blood for cell free DNA		X	X	X

¹Assessment is done only if initially elevated.

²A follow-up CT Scan will be obtained prior to initiating standard of care adjuvant chemotherapy.

³During adjuvant chemotherapy, weekly CBC/diff and BMET will be obtained during the 3 weeks of chemotherapy. Dose modifications will follow standard of care guidelines.

⁴See section 5.6 Adjuvant chemotherapy after surgical resection for option of standard treatments allowed for adjuvant therapy in this study.

7.1 Research Blood and Excess Tissue for Correlative Studies

Nucleoside Metabolites (Pankaj Singh laboratory)

Nucleoside metabolites, including cytidine, will be measured to determine if circulating nucleotide pools correlate with overall therapy response. Process blood as directed in the study lab manual.

Excess tissue will be collected if a patient enrolled in this study has a surgical resection or other procedure and enrolled in the 440-16-EP IRB tissue banking protocol, a tissue specimen will be requested for analysis as part of this protocol to determine the digoxin levels in tumors and determine the effect of digoxin on nucleotide metabolism that regulates responsiveness to therapy.

Blood Collection for cell free DNA and sequencing (Hollingsworth lab)

Four BD K2 EDTA 10 mL tubes will be obtained & processed within four hours as described in the study lab manual.

Analysis for cell free DNA, WGS, and WES (Hollingsworth Lab)

Next generation sequencing allows one to detect new, unknown mutations and examine tumor evolution over time. Cell free DNA from tumor cells is a small fraction of the DNA in circulation. Multiple approaches exist for the analysis of cell free DNA in patient samples. Digital droplet PCR (ddPCR) allows for targeted mutational analysis. The major drawback to ddPCR is that only known tumor-specific mutations can be identified. Whole exome sequencing (WES) or whole genome sequencing (WGS) allows for a more broad analysis of mutational patterns in the DNA.

Any blood specimens remaining after completing the correlative studies for this protocol will be banked for future research, if subjects grant consent for banking.

8.0 DRUG FORMULATION and PROCUREMENT

8.1 Fluorouracil (5-FU)

8.1.1 Chemistry

Chemical Name: 5-fluoropyrimidine- 2,4(1H,3H)-dione.

Chemical formula: C₄H₃FN₂O₂

Molecular weight: 130.1

Physical form: A white to almost white, practically odourless, crystalline powder

Solubility: Sparingly soluble in water; slightly soluble in ethanol

8.1.2 Mechanism of Action

5-FU is an analog of uracil, & can be metabolized intracellularly to both ribonucleotides & deoxyribonucleotides. Fluorouridine triphosphate can be incorporated into RNA by RNA polymerase, & consequently interferes with RNA processing & function. Fluorodeoxyuridine monophosphate (FdUMP) is a potent inhibitor of thymidylate synthase, the enzyme in the de novo pathway of pyrimidine biosynthesis that converts dUMP to dTMP. Depletion of dTTP interferes with DNA synthesis & repair. FdUTP can also be incorporated into DNA.

8.1.3 Clinical Formulation

5-FU is available in 10 ml ampules as a colorless aqueous solution containing 500 mg/10 ml. The

pH of the solution is adjusted to approximately 9.2 with sodium hydroxide. This undiluted preparation is suitable for direct intravenous injection.

Storage: Unused vials may be stored at room temperature & should be protected from light. If a precipitate forms due to exposure to low temperatures, resolubilize by heating to 140°F & shaking vigorously. Allow the solution to cool to body temperature before administering.

Stability: The vials bear an expiration date. 5-FU solutions may discolor slightly during storage, but the potency & safety are not adversely affected. 5-FU prepared for protracted continuous infusion is stable for 14 - 28 days (Handbook on Injectable drugs: Lawrence A. Trissel, 9th Edition. American Society of Health-System Pharmacists= Product Development Office. 1996).

8.1.4 Clinical Pharmacology

5-FU is cleared predominantly by enzymatic means. Catabolism of 5-FU to dihydrofluorouracil by dihydropyrimidine dehydrogenase is the rate-limiting step in 5-FU clearance. The half-life of 5-FU in plasma averages 8-12 minutes. Less than 10% of the administered dose is excreted as parent drug in the urine.

8.1.5 Clinical toxicity

GI: nausea, vomiting, diarrhea, anorexia, enteritis, stomatitis, esophagopharyngitis, GI bleeding
Cutaneous: alopecia, dermatitis, pigmentation abnormalities, palmar plantar erythrodysesthesia, erythema, photosensitivity, ulceration.

Systemic: lethargy, malaise

Ocular toxicity: conjunctivitis, lacrimation, lacrimal duct stenosis, photophobia

Myelosuppression: leukopenia, thrombocytopenia, anemia

Cardiac: chest pain and rhythm abnormalities

CNS toxicity: acute cerebellar syndrome, confusion, headache

8.1.6 Drug Interactions

Calcium leucovorin, warfarin. Possible: zidovudine, allopurinol. Several investigational drugs are inhibitors of dihydropyrimidine dehydrogenase; these include the antiviral drugs brivudine and soruvudine.

8.1.7 Route of Administration

5-FU will be given as a 46 hr continuous IV infusion starting immediately after completion of oxaliplatin, irinotecan & leucovorin using an ambulatory infusion pump

8.2 Calcium Leucovorin (LV)

8.2.1 Chemistry

Chemical name: The calcium salt of racemic folinic acid (1:1).

Other names: folinic acid, 5-formyl-tetrahydrofolate, citrovorum factor

Molecular formula: $C_{20}H_{21}CaN_7O_7$

Molecular weight: 511.5

Physical form: A yellowish-white or yellow, odorless, powder.

Solubility: Very soluble in water; practically insoluble in alcohol; Protect from light.

8.2.2 Mechanism of action

LV is a water soluble vitamin in the folate group. LV is the formyl derivative and active form of folic acid used to counter the hematologic and other toxicities associated with methotrexate and other antifolates. Upon intracellular conversion to 5,10-methylenetetrahydrofolate, it serves as the reduced folate cofactor involved in the de novo production of dTMP from dUMP. Pharmacologic concentrations of reduced folates enhance the stability of the covalent complex formed with FdUMP and thymidylate synthase.

8.2.3 Clinical Formulation

LV is commercially available as scored oral tablets in dosages of 5 mg, 10 mg, 15 mg, and 25 mg, and also as a sterile, lyophilized powder in vials containing 25 mg, 50 mg, and 100 mg.

Reconstitution with 10 ml of Sterile Water for Injection, USP, yields a 2.5 mg/ml, 5 mg/ml or 10 mg/mL solution of LV as the calcium salt, respectively. The final administration solution may be prepared by adding the proper LV dose to 100 ml of 5% Dextrose Injection, USP.

8.2.4 Storage: Tablets and intact vials may be stored at room temperature, protected from light. Constituted and further diluted solutions should be stored in the refrigerator. If Bacteriostatic Water for Injection, USP (benzyl alcohol preserved) is used for reconstitution, the resulting solution is stable for seven days. If reconstituted with Sterile Water for Injection, USP, the manufacturer recommends using the solution immediately.

8.2.5 Clinical Pharmacology

Calcium folinate is well absorbed after oral and intramuscular administration and, unlike folic acid, is rapidly converted to biologically active folates. Folate is concentrated in the liver and CSF although distribution occurs to all body tissues. Folates are mainly excreted in the urine, with small amounts in the feces. After a single oral dose of 15 mg (7.5 mg/m²), the time to peak serum folate concentration is 1.7 ± 0.1 hr, and the peak serum folate concentration is 268 ± 18 ng/ml (0.57 ± 0.04 μ M). The serum folate half-life was 3.5 hr. Bioavailability was 100% compared to the same dose given i.v., but absorption is saturable with higher doses.

8.2.6 Clinical Toxicity

Allergic sensitization (urticaria and anaphylactoid reactions) has been reported following both oral & parenteral administration of LV. The administration of LV with 5-FU augments the severity of toxicity typically associated with 5-FU, particularly GI tract toxicities. Pyrexia has occurred rarely after injections. Seizures and syncope have rarely been reported.

8.2.7 Route of Administration

Calcium leucovorin will be given IV injection over 90 minutes immediately prior to 5-FU when given as a 24-hr infusion.

8.2.8 Drug Interactions

Calcium leucovorin may augment the toxicity associated with 5-FU and capecitabine. Calcium leucovorin is used to protect against the toxicity associated with high-dose methotrexate.

8.3 Irinotecan

For complete prescribing information, please refer to the approved package insert.

8.3.1 Other Names

Camptothecin-11, CPT-11, Camptosar®

8.3.2 Classification

Topoisomerase I inhibitor

8.3.3 Mode of Action

Topoisomerase I is intimately involved in DNA replication and RNA transcription as it relieves the torsional strain introduced ahead of the moving replication fork. The cytotoxicity of irinotecan results from single and double strand DNA breaks that are produced by the inhibited topoisomerase during the course of DNA and RNA synthesis. Irinotecan is an inactive prodrug and must be metabolized in vivo by carboxyesterases to the active compound SN-38.

8.3.4 Storage and Stability

Undiluted vials are stored at room temperature (15-30 degrees C), and protected from light. Irinotecan diluted in 5% dextrose is stable at refrigerated temperatures for 48 hours when protected from light.

8.3.5 Dose Specifics

150 mg/m². If patient does not experience any toxicity > grade 1 during the first 2 treatment courses, irinotecan may be escalated to 180 mg/m². (See Section 5.4.1)

8.3.6 Preparation

Irinotecan must be diluted before infusion. The recommended diluent for short intravenous administration of irinotecan is 500 mL of dextrose 5% or a concentration range between 0.12 to 2.8mg/mL. Stability is less in normal saline. The diluted solution should be inspected visually for particulate matter.

8.3.7 Administration

Irinotecan is administered IV over 90 minutes (after oxaliplatin)

8.3.8 Incompatibilities

Solutions other than dextrose 5% or normal saline should not be used for dilution. Other compatibility information is not available.

8.3.9 Drug Interactions

Dexamethasone when administered concurrently with irinotecan causes increased lymphopenia and hyperglycemia.

Laxative use should be curtailed during irinotecan administration and in the immediate days following irinotecan administration.

Simultaneous administration of prochlorperazine and irinotecan has increased the incidence of akathisia.

Diuretic use with irinotecan may exacerbate dehydration induced by diarrhea and chemotherapy-induced nausea and vomiting.

St. John's wort decreases the AUC of SN-38 presumably by induction of CYP3A4 activity.

Ketoconazole via inhibition of CYP3A4 significantly increase exposure of the active metabolite SN-38, which could result in exaggerated toxicity. Consideration of dose reduction in patients on ketoconazole and other agents known to inhibit CYP3A4 should be considered for irinotecan.

8.3.10 Availability

Commercially available in 20mg/mL concentration in 2 and 5mL vials.

8.3.11 Side Effects

Hematologic: Leukopenia, neutropenia, anemia, thrombocytopenia, neutropenic fever, hemorrhage

Gastrointestinal: Diarrhea (early and late – see administration above), nausea and vomiting, anorexia, abdominal pain, flatulence, stomatitis, dyspepsia, dehydration

Hepatic: Elevated transaminases.

Cardiovascular: Vasodilation, hypotension, myocardial infarction, stroke, edema CNS: Dizziness, confusion, somnolence, insomnia, back pain

Respiratory: Pulmonary embolism, Dermatologic: Alopecia, rash

Other: Asthenia, thrombophlebitis, sweating, weight loss, chills,

8.3.12 Nursing/Patient Implications

Premedicate with antiemetics in anticipation of mild to moderate nausea and vomiting. When used in combination with 5-fluorouracil and leucovorin the nausea and vomiting will likely be worse.

Fatalities have been reported with thromboembolic events and neutropenic sepsis in patients receiving 5-fluorouracil, leucovorin and irinotecan.

Monitor for diarrhea. Diarrhea occurring within one hour of irinotecan has been treated with atropine 0.25 to 1mg IV or SC. Loperamide has been effective in treating later diarrhea and the patient should be instructed on its immediate use at the first loose stool following the irinotecan (see Administration).

Monitor CBC, platelets, and liver function tests.

Dose modifications per the protocol should be followed for hematologic and gastrointestinal toxicity.

Advise patient of likely post-treatment neutropenia and instruct in appropriate neutropenic precautions.

Administration of an oral quinolone antibiotic may decrease the risk of neutropenic sepsis in patients receiving 5-fluorouracil/leucovorin and irinotecan.

8.4 Oxaliplatin

For complete prescribing information, please refer to the approved package insert.

8.4.1 Other Names

Eloxatin®, trans-1-diaminocyclohexane oxalatoplatinum, cis-[oxalato(trans-1,1,2-diaminocyclohexane)platinum(II)].

8.4.2 Classification

Alkylating agent.

8.4.3 Mode of Action

The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

8.4.4 Storage and Stability

Oxaliplatin vials are stored at room temperature between 20° and 25°C protected from light. After further dilution in 5% dextrose, the solution is stable for 24 hours at room temperature.

8.4.5 Dose Specifics

85 mg/m² IV in 500 mL D5W

8.4.6 Preparation

Dilution is needed in 250 - 500 mL of 5% dextrose prior to administration.

8.4.7 Route of Administration Intravenous

8.4.8 Incompatibilities

Oxaliplatin may degrade in the presence of aluminum-containing needles or IV infusion sets or alkaline medications (such as fluorouracil). Oxaliplatin is incompatible with sodium chloride solutions.

8.4.9 Availability

Oxaliplatin is commercially available in 50 or 100 mg vials.

8.4.10 Reported Adverse Events and Potential Risks

Allergy/Immunology: Rhinitis, Allergic/Hypersensitivity reactions (including drug fever). Can be fatal and occur with any cycle of therapy. Manifested by: urticaria, pruritus, flushing of the face, diarrhea (during infusion), shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation, and syncope.

Auditory: Middle ear/hearing (ototoxicity, mild), inner ear/hearing (mild hearing loss).

Blood/Bone Marrow: decreased hemoglobin, hemolysis (e.g. immune hemolytic anemia, drug-related hemolysis), decreased leukocytes, decreased platelets, neutropenia. Single-agent oxaliplatin produces only mild myelosuppression with minimal to severe neutropenia, anemia or thrombocytopenia. In combination, more grade 3/4 neutropenia or thrombocytopenia may be noted.

Cardiovascular (Arrhythmia): Sinus tachycardia, supraventricular arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmias (PVCs/ bigeminy/ trigeminy/ventricular tachycardia).

Cardiovascular (General): Edema, hypertension, hypotension

Coagulation: DIC (disseminated intravascular coagulation), thrombosis/embolism (including pulmonary embolism), prolonged prothrombin time, increased INR, thrombotic microangiopathy (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome). The hemolytic uremic syndrome should be suspected in individuals who experience the following: unexplained severe hemolysis, hemoglobinemia and renal failure as demonstrated by an increase in serum creatinine. Patients suspected of experiencing HUS should have the following laboratory analyses conducted: Creatinine, BUN; Urinalysis with microscopic evaluation; CBC with differential and platelets; PT/PTT; Fibrinogen, Fibrinogen Degradation Products (FDP); Anti-thrombin III (ATIII); Von Willebrand Factor (VWF); Anti-nuclear antibodies (ANA); Rheumatoid Factor (RhF); C3, C4, CH50; Anti-platelet antibodies; Platelet associated IgG; Circulating immune complexes.

Oxaliplatin should be discontinued for any suspected occurrence of hemolytic uremic syndrome.

Constitutional Symptoms: Fever (in the absence of neutropenia, where neutropenia is defined as ANC < 1000 / μ L), fatigue (lethargy, malaise, asthenia), rigors/chills, insomnia, sweating, weight gain, weight loss.

Dermatology/Skin: Erythema or skin eruptions, alopecia, hand-foot skin reaction, injection site reaction, rash/desquamation, urticaria, pruritus/itching, dry skin, nail changes, pigmentation changes.

Endocrine: Hot flashes/flushes.

Gastrointestinal: Anorexia, ascites (non-malignant), colitis, constipation, dehydration, diarrhea, dysphagia, enteritis, esophagitis, flatulence, gastritis, gastrointestinal reflux (heartburn, dyspepsia), ileus (or neuroconstipation), intestinal obstruction, nausea, odynophagia (painful swallowing), stomatitis/pharyngitis (oral/pharyngeal mucositis), taste disturbance (dysgeusia), typhilitis, ulcer, vomiting, xerostomia (dry mouth).

Hemorrhage: CNS hemorrhage/bleeding, hemoptysis, hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, melena, GI bleeding, rectal bleeding/hematochesia, pulmonary hemorrhage, vaginal hemorrhage, other (hemorrhage NOS).

Hepatobiliary/Pancreas: increased alkaline phosphatase, increased bilirubin, increased GGT (gamma glutamyl transpeptidase), hepatic enlargement, increased SGOT (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase), pancreatitis, hepatic veno- occlusive disease (manifested by hepatomegaly, ascites, and jaundice).

Infection/Febrile Neutropenia: Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented fever (ANC <1000 per μ L fever >38.5°C), infection (documented clinically or micro biologically with grade 3 or 4 neutropenia (ANC <1000 per μ L), infection with unknown ANC, infection without neutropenia.

Metabolic/Laboratory: Acidosis (metabolic or respiratory), hypoalbuminemia, hypocalcemia, hyperuricemia, hyperglycemia, hypoglycemia, hypokalemia, hypophosphatemia, hyponatremia, hypomagnesemia

Musculoskeletal: Involuntary muscle contractions, trismus.

Neurology: Ataxia (incoordination, including abnormal gait), cerebrovascular ischemia, confusion, dizziness, extrapyramidal movements/restlessness, insomnia, mood alteration (depression, anxiety), neuropathy cranial (ptosis), vertigo, acute sensory neuropathy induced or exacerbated by cold (including acute laryngo-pharyngeal dysesthesias, Lhermitte's sign, upper extremity paresthesia), chronic peripheral neuropathy (paresthesias, dysesthesias, hypoesthesias), seizure, somnolence, speech impairment, syncope.

Ocular/Visual: Conjunctivitis, vision abnormalities including blindness, optic neuritis, papilledema, hemianopsia, visual field defect, transient blindness.

Pain: abdominal pain or cramping, athralgia (joint pain), bone pain, chest pain (non-cardiac and non-pleuritic), headache (including migraine), myalgia (muscle pain including cramps and leg cramps).

Pulmonary/Upper Respiratory: Bronchospasm/wheezing, Pulmonary fibrosis, cough, dyspnea (shortness of breath), hiccoughs (hiccups, singultus), pneumonitis/pulmonary infiltrates (including eosinophilic pneumonia, interstitial pneumonitis, and interstitial lung disease), laryngospasm, nasal cavity/paranasal sinus reactions, voice changes (hoarseness, loss or alteration in voice, laryngitis).

Renal/Genitourinary: Increased creatinine, renal failure, urinary retention, urinary urgency, dysuria. Hemolytic Uremic Syndrome (HUS) – see coagulation.

Vascular: Phlebitis, thrombosis

Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined: tongue paralysis, anemia, aphasia, abnormal hepatic function, hyporeflexia, anxiety, depression, dysarthria,

insomnia, increased sweating, rhinitis, epistaxis, gout, pancreatitis, idiopathic thrombocytopenia (5 cases), thrombocytopenia associated with hemolytic anemia (2 cases).

NOTE: Oxaliplatin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

8.5 Digoxin (Nebraska Medicine)

8.5.1 REVERSAL AGENT/TOXICITY

Digoxin immune Fab (Digibind) is recommended for acute and chronic toxicity. In addition, discontinuation of digoxin plus advanced supportive measures should be instituted. Treatment of serum potassium levels greater than 5.5 mEq/L should include sodium bicarbonate plus glucose with insulin or Kayexalate. Treat bradycardias with atropine or a pacemaker and other arrhythmias with anti-arrhythmic drugs.

8.5.1.1 Indications and Usage for Digibind

Digibind, Digoxin Immune Fab (Ovine), is indicated for treatment of potentially life-threatening digoxin intoxication. Although designed specifically to treat life-threatening digoxin overdose, it has also been used successfully to treat life-threatening digitoxin overdose. Since human experience is limited and the consequences of repeated exposures are unknown, Digibind is not indicated for milder cases of digitalis toxicity.

Manifestations of life-threatening toxicity include severe ventricular arrhythmias such as ventricular tachycardia or ventricular fibrillation, or progressive bradyarrhythmias such as severe sinus bradycardia or second or third degree heart block not responsive to atropine.

Ingestion of more than 10 mg of digoxin in previously healthy adults or 4 mg of digoxin in previously healthy children, or ingestion causing steady-state serum concentrations greater than 10 ng/mL, often results in cardiac arrest. Digitalis-induced progressive elevation of the serum potassium concentration also suggests imminent cardiac arrest. If the potassium concentration exceeds 5 mEq/L in the setting of severe digitalis intoxication, therapy with Digibind is indicated.

8.5.1.2 Digibind Description

Digibind, Digoxin Immune Fab (Ovine), is a sterile lyophilized powder of antigen binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep. Production of antibodies specific for digoxin involves conjugation of digoxin as a hapten to human albumin. Sheep are immunized with this material to produce antibodies specific for the antigenic determinants of the digoxin molecule. The antibody is then papain-digested and digoxin-specific Fab fragments of the antibody are isolated and purified by affinity chromatography. These antibody fragments have a molecular weight of approximately 46,200.

Each vial, which will bind approximately 0.5 mg of digoxin (or digitoxin), contains 38 mg of digoxin-specific Fab fragments derived from sheep plus 75 mg of sorbitol as a stabilizer and 28 mg of sodium chloride. The vial contains no preservatives.

Digibind is administered by intravenous injection after reconstitution with Sterile Water for Injection (4 mL per vial).

8.5.2 Dosage Forms - Nebraska Medicine

Excipient information presented when available (limited, particularly for generics); consult specific product labeling. Solution, Oral: Generic: 0.05 mg/mL (60 Ml). Tablet, Oral: Generic: 0.125 mg, 0.25 mg

8.5.3 Brand Names: U.S. Digitek; Digox; Lanoxin; Lanoxin Pediatric
Index Terms Digitalis; Lanoxicaps

8.5.4 Pharmacologic Category Antiarrhythmic Agent, Miscellaneous; Cardiac Glycoside

8.5.5 Medication Safety Issues

Sound-alike/look-alike issues:

Digoxin may be confused with Desoxyn, doxepin; Lanoxin may be confused with Lasix, levothyroxine, Levoxyl, Levsinex, Lomotil, Mefoxin, naloxone, Xanax

8.5.6 High alert medication:

The Institute for Safe Medication Practices (ISMP) includes this medication among its list of drugs which have a heightened risk of causing significant patient harm when used in error.

Geriatric Patients: High-Risk Medication:

Beers Criteria: Digoxin is identified in the Beers Criteria as a potentially inappropriate medication to be avoided in patients 65 years and older as first-line therapy for atrial fibrillation (due to more effective alternatives and potential for increased mortality) or as first-line therapy for heart failure (due to potential for increased mortality, questionable effects on risk of hospitalization, and lack of additional benefit when higher doses are used despite the increased risk of toxicity). If used, avoid doses greater than 0.125 mg/day due to decreased renal clearance of digoxin which may result in increased risk of toxic effects; further dose reductions may be warranted in patients with Stage 4 or 5 chronic kidney disease (Beers Criteria).

Pharmacy Quality Alliance (PQA): Digoxin (at doses greater than 0.125 mg/day) is identified as a high-risk medication in patients 65 years and older on the PQAs, Use of High-Risk Medications in the Elderly (HRM) performance measure, a safety measure used by the Centers for Medicare and Medicaid Services (CMS) for Medicare plans.

Daily maintenance dose (Note: Loading dose not recommended): Oral: 0.125 to 0.25 mg once daily; higher daily doses (eg, 0.375 to 0.5 mg daily) are rarely necessary. If patient is >70 years of age, has impaired renal function, or has a low lean body mass, low doses (eg, 0.125 mg daily or every other day) should be used initially.

Dosing: Geriatric Dose is based on assessment of lean body mass and renal function. Elderly patients with low lean body mass may experience higher digoxin concentrations due to reduced volume of distribution. Decrease dose in patients with decreased renal function (see Dosing in Renal

Impairment).

Atrial fibrillation: Avoid as first-line therapy; if used, do not exceed 0.125 mg/day in patients ≥ 65 years (Beers Criteria).

Heart failure: If patient is >70 years of age, low doses (eg, 0.125 mg daily or every other day) should be used (ACCF/AHA [Yancy, 2013]). Avoid as first-line therapy; if used, do not exceed 0.125 mg/day in patients ≥ 65 years (Beers Criteria).

8.5.7 Use: Labeled Indications

Atrial fibrillation: Control of ventricular response rate in adults with chronic atrial fibrillation.
Heart failure: Treatment of mild-to-moderate (or stage C as recommended by the ACCF/AHA) heart failure (HF) in adults; to increase myocardial contractility in pediatric patients with heart failure. Note: In treatment of atrial fibrillation (AF), use is not considered first-line in patients with AF; digoxin may be considered for rate control in patients with heart failure with reduced ejection fraction (HFrEF) without pre-excitation or in sedentary patients (AHA/ACC/HRS [January 2014]). In the treatment of heart failure, digoxin should be considered for use only in HF with reduced ejection fraction (HFrEF) when symptoms remain despite guideline-directed medical therapy or as initial therapy in patients with severe symptoms yet to respond to guideline-directed medical therapy.

8.5.8 Contraindications

Hypersensitivity to digoxin, other forms of digitalis, or any component of the formulation;
ventricular fibrillation

8.5.9 Warnings/Precautions

Concerns related to adverse effects:

Digoxin toxicity: Signs and symptoms of digoxin toxicity include anorexia, nausea, vomiting, visual changes, and cardiac arrhythmias; toxicity is usually associated with digoxin levels >2 ng/mL, although symptoms may occur at lower levels. Patients at increased risk for digoxin toxicity include those with low body weight, advanced age, renal impairment, hypokalemia, hypercalcemia, or hypomagnesemia.

Proarrhythmic effects: Monitor for proarrhythmic effects (especially with digoxin toxicity)

Disease-related concerns:

Beri beri heart disease: Patients with beri beri heart disease may fail to adequately respond to digoxin therapy; treat underlying thiamine deficiency concomitantly.

Electrolyte imbalance: Correct electrolyte disturbances, especially hypokalemia or hypomagnesemia, prior to use and throughout therapy; toxicity may occur despite therapeutic digoxin concentrations (eg, <2 ng/mL). Hypercalcemia may increase the risk of digoxin toxicity and hypocalcemia can nullify the effects of digoxin; maintain normocalcemia.

Heart failure: Digoxin should be considered for use only in heart failure (HF) with reduced ejection

fraction (HFrEF) when symptoms remain despite guideline-directed medical therapy. It may also be considered in patients with both HF and atrial fibrillation; however, beta blockers may offer better ventricular rate control than digoxin. Withdrawal of digoxin in clinically stable patients with HF may lead to recurrence of HF symptoms. Monitor serum concentrations closely; may be associated with an increased risk of mortality especially when serum concentrations are not properly controlled.

Hypermetabolic states: Atrial arrhythmias associated with hypermetabolic (eg, hyperthyroidism) or hyperdynamic (hypoxia, arteriovenous shunt) states are very difficult to treat; treat underlying condition first. If digoxin is used, ensure digoxin toxicity does not occur.

Hypertrophic cardiomyopathy (HCM) with outflow tract obstruction: Outflow obstruction may worsen due to the positive inotropic effects of digoxin; avoid use unless used to control ventricular response with atrial fibrillation. Digoxin is potentially harmful in the treatment of dyspnea in patients with HCM in the absence of atrial fibrillation.

Myocarditis: In a murine model of viral myocarditis, digoxin in high doses was shown to be detrimental. If used in humans, therefore, digoxin should be used with caution and only at low doses. The manufacturer recommends avoiding the use of digoxin in patients with myocarditis. Preserved left ventricular function: Decreased cardiac output may occur in patients with preserved left ventricular systolic function, including restrictive or hypertrophic cardiomyopathy, constrictive pericarditis, amyloid heart disease, and acute cor pulmonale; in general, the manufacturer recommends to avoid use unless used to control ventricular response with atrial fibrillation.

Renal impairment: Use with caution in patients with renal impairment; dosage adjustment needed.

Sinus node disease and atrioventricular (AV) block: Because digoxin slows sinoatrial and AV conduction, the drug commonly prolongs the PR interval. Digoxin may cause severe sinus bradycardia or sinoatrial block particularly in patients with preexisting sinus node disease. Avoid use in patients with second- or third-degree heart block (except in patients with a functioning artificial pacemaker); incomplete AV block (eg, Stokes-Adams attacks) may progress to complete block with digoxin administration. In such patients, if treatment with digoxin is necessary, consider the insertion of a pacemaker before treatment.

Thyroid disease: Use with caution in patients with hypothyroidism, higher digoxin concentrations may result due to significant reduction in digoxin clearance. In patients with hyperthyroidism, lower digoxin concentrations may result due to an increase in renal clearance of digoxin. No significant differences in absorption were seen in either thyroid condition compared with those with normal thyroid function. Note: New-onset atrial fibrillation or exacerbation of ventricular arrhythmias should prompt evaluation of thyroid status.

8.5.10 Concurrent drug therapy issues:

Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

8.5.11 Special populations:

Low body weight: Patients with decreased body weight are at an increased risk of drug-related toxicity.

Other warnings/precautions:

Elective electrical cardioversion: It is not necessary to routinely reduce or hold digoxin therapy prior to elective electrical cardioversion for atrial fibrillation; however, exclusion of digoxin toxicity (eg, clinical and ECG signs) is necessary prior to cardioversion. If signs of digoxin excess exist, withhold digoxin and delay cardioversion until toxicity subsides (AHA/ACC/HRS [January 2014]).

Adverse Reactions Incidence not always reported.

Cardiovascular: Accelerated junctional rhythm, asystole, atrial tachycardia with or without block, AV dissociation, first-, second- (Wenckebach), or third-degree heart block, facial edema, PR prolongation, PVCs (especially bigeminy or trigeminy), ST segment depression, ventricular tachycardia or ventricular fibrillation

Central nervous system: Dizziness (6%), mental disturbances (5%), headache (4%), apathy, anxiety, confusion, delirium, depression, fever, hallucinations

Dermatologic: Rash (erythematous, maculopapular [most common], papular, scarlatiniform, vesicular or bullous), pruritus, urticaria, angioneurotic edema

Gastrointestinal: Nausea (4%), vomiting (2%), diarrhea (4%), abdominal pain, anorexia

Neuromuscular & skeletal: Weakness

Ocular: Visual disturbances (blurred or yellow vision) Respiratory: Laryngeal edema <1%, postmarketing, and/or case reports (limited to important or life-threatening): Asymmetric chorea, gynecomastia, thrombocytopenia, palpitation, intestinal ischemia, hemorrhagic necrosis of the intestines, vaginal cornification, eosinophilia, sexual dysfunction, diaphoresis

Reference Range

Digoxin therapeutic serum concentrations:

Heart failure: 0.5 to 0.9 ng/mL (ACCF/AHA [Yancy, 2013])

Adults: <0.5 ng/mL; probably indicates under-digitalization unless there are special circumstances

Toxic: >2 ng/mL

Digoxin-like immunoreactive substance (DLIS) may cross-react with digoxin immunoassay. DLIS has been found in patients with renal and liver disease, heart failure, neonates, and pregnant women (3rd trimester).

Dietary considerations maintain adequate amounts of potassium in diet to decrease risk of hypokalemia (hypokalemia may increase the risk of digoxin toxicity).

9.0 TOXICITY AND ADVERSE EVENT REPORTING GUIDELINES

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC/Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All subjects will be closely followed for toxicity from the time of first dose of digoxin until 30 days after last administration of the final digoxin dose. The reporting is only for study medication until 30 days after last administration of the final digoxin dose. Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

Adverse event will be assessed by reports from subjects to their physician/Investigator and by physical examinations. Per NCI guidelines, serious adverse events (SAEs) and adverse events (AEs) will be graded and toxicity assessed using the revised NCI CTCAE version 5.0 (Appendix E). Adverse events and SAEs will be followed until resolution or baseline. All ongoing AEs considered to be related to the study drug will be followed until resolution, the patient is lost to follow-up, patient death or until the EOT visit, whichever is earliest.

Serious adverse events should be followed until resolution, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC DSMC.

9.1 Definitions

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 5.0, Treatment Plan) and/or if the investigator considers them to be adverse

events.

Unexpected Adverse Event

An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event

A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

- Results in death
- Is a serious threat to life, health, safety or welfare-fare of subject ¹
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Required intervention to prevent permanent impairment or damage
- Persistent or significant disability or incapacity²
- Is a congenital anomaly or birth defect
- Another serious important medical event³
- Any medical event in an investigational drug study that requires treatment to prevent one of the outcomes listed above
- The rights, safety, or welfare of subjects is seriously jeopardized

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.2 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC)

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTC-AE) version 5.0 (Appendix E)

9.2.1 IRB REPORTING

The sponsor-investigator must notify the Ethics Review Committee/Institutional Review Board (EC/IRB) of adverse events in writing in accordance with international and local laws and regulations.

All internal adverse events (AE) must be reported to the IRB promptly per institutional human research protection program policy.

9.2.2 Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) Reporting

Reporting of the following will be done in accordance with DSMC guidelines:

- All Serious adverse events (SAEs) and toxicity will be reported to the DSMC
- All adverse events grade 3 or higher (expected or unexpected, regardless of attribution) will be reported to the DSMC. In certain investigator-initiated institutional trials where virtually 100% of subjects are guaranteed to experience very specific known grade 3 or higher toxicities (e.g., hematologic toxicity in stem cell transplant studies), the requirement for reporting of those toxicities may be waived at the discretion of the DSMC based on initial protocol review and in conjunction with investigator input if required.

Attribution of AEs: The likelihood of relationship of the AE to the study drug(s) will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

Definitely related: There occurrence and timing of the AE are clearly attributable to the study treatment.

All SAEs and AE reporting will be completed using DSMC approved forms. Detailed policy and procedures for this section may be reviewed at:

<http://www.unmc.edu/cancercenter/clinical/prms.html>

9.3 Adverse Event Recording for Data Capture forms

All AEs will be assessed by the Investigator and recorded, including but not limited to, the following: the event term, the date of onset, seriousness, severity, and relationship to study drug(s).

During the neoadjuvant/Digoxin treatment, AEs will be captured starting immediately after the patient has been administered the first dose of study drug(s) until 30 days following the last digoxin administration.

Surgery complications will be captured for 30 postoperative days and will be recorded on the post-surgery data capture form, but not captured as AEs.

During the adjuvant treatment period, AEs will be captured starting immediately after the patient has been administered the first dose of chemotherapy and until 30 days following the last chemotherapy administration. The worst grade of an AE which occurred during the adjuvant treatment period will be recorded in the data capture forms. Since the patient's adjuvant treatment will be standard of care and not include any of the study drug (digoxin), AEs during adjuvant treatment will not be considered reportable to the DSMC.

9.4 Monitoring

Various methods will be implemented to exchange information with study personnel:

- Site Initiation/Orientation
- Investigator meetings as feasible
- Email distributions/reports as needed

9.4.1 Data Monitoring

For this study, data monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirement(s). Monitoring is a Quality Control, continuous process during the entire trial.

9.5 Auditing

Auditing is a systematic and independent examination of trial-related activities and documents to determine:

- whether the evaluated trial-related activities were conducted
- the data were recorded, analyzed, and accurately reported, according to the protocol, to the sponsor's SOPs, GCP, and applicable regulatory requirement(s).

Auditing is a Quality Assurance, one point process during the trial.

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo audit on at least a semi-annual basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

Detailed policy and procedures for this section may be reviewed at:
<https://www.unmc.edu/cancercenter/clinical/prms.html> .

10.0 STATISTICAL CONSIDERATIONS

This is a single-center Phase IIa study evaluating the safety and tolerability of neoadjuvant chemotherapy with FOLFIRINOX given with digoxin as well as the response and event free survival of this regimen in patients with resectable pancreatic cancer. We estimate that there will be about up to 20 subjects enrolled into this protocol over a 2-3 year period. We assume that the maximum surgical resection rate of a poor drug is 0.5, and the minimum surgical resection rate is 0.8 for a good drug. A study with 20 patients will be used to test whether the surgical resection rate is less than or equal to 0.5 or greater than or equal to 0.8. If 14 or more patients out of 20 patients are able to undergo surgical resection, the hypothesis that the surgical resection rate is lower than 0.5 is rejected with an error rate of no more than 0.1. Otherwise, the hypothesis that the surgical resection rate is more than 0.8 is rejected with an error rate of no more than 0.1. Following this, if 14 patients or more out of the 20 patients is able to undergo surgical resection, we consider this regimen worthy of further investigation.

Progression-free survival (PFS) will be defined as the first date of therapy to the date of disease progression based on radiographic imaging, clinical grounds, or death. Overall survival will be measured from the date of therapy to the date of death. Patients who are lost to follow-up will be censored at the date they were last known to be alive.

Descriptive statistics will be employed to analyze the data. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum, maximum). Categorical variables will be presented as frequency counts and percentages and time-to-event variables will be summarized by Kaplan-Meier plots, medians and ranges.

All confidence intervals will be constructed at the 90% confidence level. All statistical analyses will be performed using SAS Version 9.4 or later.

10.1 Primary End Points

The safety of neoadjuvant chemotherapy with FOLFIRINOX given with digoxin in patients with resectable pancreatic cancer

10.2 Secondary End Points

Surgical complete resection (negative margin) rate
T & N status on the pathology specimen
Tumor response rate on CT/MRI (see 6.2.2 for definition of response)
Declines in tumor markers
PFS and overall survival.

10.3 Toxicity Endpoint

We will assess the safety of the neoadjuvant chemotherapy with FOLFIRINOX given with digoxin in patients with resectable pancreatic cancer, and also obtain a preliminary assessment of the efficacy. The toxicity endpoints for this trial include grade 4 thrombocytopenia and grade 3-4

diarrhea.

Conroy et al (17) reported a grade 3-4 toxicity rate of 9.1% for thrombocytopenia, and 12.7% for diarrhea in FOLFIRINOX treated pancreatic cancer patients with metastatic disease. In addition, the previous randomized trials (46, 47) showed that among the digoxin treated patients, 3.3% patients showed any grade of diarrhea. We also expect the digoxin associated cardiac toxicity rate is around 3%.

Therefore, we will anticipate potentially higher toxicity rates of 18.2% for grade 3-4 thrombocytopenia and 28.2% for grade 3-4 diarrhea in patients with resectable pancreatic cancer. We plan to accrue 20 patients into the study. Continuous monitoring (45) will be performed to monitor toxicity using Pocock stopping boundary that yields the probability of crossing the boundary at most 0.05 when the toxicity rate is equal to 0.182 or 0.28 separately. The table below displays the corresponding boundaries. If there are excessive numbers of toxicities, as indicated by b_{n1} or more number of grade 4 thrombocytopenia or b_{n2} or more number of grade 3-4 diarrhea out of n treated patients, then the accrual will be terminated. We will also stop the trial if 3 or more patients experienced digoxin only associated cardiac toxicity requiring inpatient management.

Table. Pocock boundary for $K=20$ when the true toxicity rate is 0.182 for thrombocytopenia and 0.282 for diarrhea.

Number of patients, n	1	2	3	4	5	6	7	8	9	10	11	12
Thrombocytopenia boundary, b_{n1}	-	-	3	4	4	4	5	5	5	6	6	6
Diarrhea boundary, b_{n2}	-	-		4	5	5	6	6	6	7	7	8

Number of patients, n	13	14	15	16	17	18	19	20
Thrombocytopenia boundary, b_{n1}	6	7	7	7	8	8	8	8
Diarrhea boundary, b_{n2}	8	8	9	9	10	10	10	11

10.4 Correlative End Points

The correlative endpoints under evaluation include (1) Measurement of circulating tumor DNA at 4 week intervals while on chemotherapy and prior to surgery, then at 3 month intervals after recovery from surgery; (2) Analysis of possible biomarkers for digoxin effect. The change in the ctDNA will be calculated and used to classify patients into group with or without ctDNA alteration (with ctDNA change more than 20%).

The clinical response will be compared between patients with ctDNA alteration versus others using chi-square or fisher exact test. The survival will be summarized using Kaplan-Meier curves and

compared between patients with and without ctDNA alternation using log-rank test. In addition, the genotype of the pre-therapy genomic DNA will be correlated with the presence of clinical toxicity among patients. Specifically, the toxicity incidence will be summarized using proportions and compared using chi-square test or fisher exact test when appropriate between rare variant carriers and others. Last, the biomarker change after treatment will be summarized using mean and standard deviation for continuous data and proportions for categorical data.

10.5 Analysis populations

All patients who complete at least one post-baseline assessment or discontinue study medication early due to disease progression will be considered evaluable for efficacy.

All patients who received study medication will be considered evaluable for the safety analysis regardless of the duration of treatment.

10.6 Efficacy analysis

Progressive disease (PD) is defined as at least a 20% increase in the longest diameter of a lesion, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression. The number and proportion of patients experiencing PD will be reported. An exact one-sided 90% confidence interval will be constructed round the progressive disease rate.

Secondary endpoints of tumor response rate on CT/MRI will be analyzed as described in section 6.1 (assessment of tumor response). The percent decline in tumor marker will be determined. Descriptive statistics will be used for the percentage of patients with positive lymph nodes. Progression-free survival and overall survival will be analyzed using Kaplan-Meier plots, medians and ranges.

10.7 Safety analysis

Safety variables to be analyzed are adverse events. Adverse events will be tallied for overall frequency (number and percentage of subjects), worst reported severity, and relationship to study drugs. Serious adverse events will be summarized similarly. Listings of deaths, SAEs and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

11.0 RECORDS TO BE KEPT

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology will be recorded on appropriate forms in the Forte electronic data capture system detailed below. Additionally, serious adverse events, when noted, will be recorded on site via the standard serious adverse event reporting as noted in Section 9 of this protocol.. Data obtained from the analysis of the correlative study samples will be maintain in a secure manner by the collaborating laboratories.

11.1 Quality assurance: Complete records must be maintained in a research chart on each patient treated on the protocol. Research chart can be maintained either as an electronic record, paper chart or a combination of both. These records should include primary documentation (e.g., lab. report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements & clinical assessment, as appropriate).

11.2 Forte Electronic Data Capturing (EDC) System

Data will be stored electronically for this study in the Forte EDC system on the Forte secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Forte logo.

Forte EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Forte through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

12.0 PATIENT CONSENT

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Patients are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Excess tissue will be collected if a patient enrolled in this study has a surgical resection or other procedure and enrolled in the 440-16-EP IRB tissue banking protocol, a tissue specimen will be requested for analysis as part of this protocol.

12.4 Recruitment and Informed Consent

Patients with an initial diagnosis of locally advanced pancreatic carcinoma seen and evaluated at Nebraska Medicine will be available for recruitment. These patients will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care

providers and prospective subjects as listed on the title page of this protocol.

12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent

If the patient chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects

It is anticipated that the use of neoadjuvant therapy in this patient population would result in greater tumor response and possibly prolong survival.

12.10 Potential Benefits to Society

Information obtained from this study may help other patients by contributing to the knowledge of the biology of pancreatic cancer, and whether this treatment offers potential advantages over other treatments currently available.

12.11 Potential Risks

The use of cytotoxic chemotherapy and surgical resection are associated with numerous potential risks. Combined chemotherapy is now considered a valid treatment option for patients with pancreatic cancer patients with resectable or borderline resectable disease. Adjuvant therapy following surgical resection for pancreatic cancer is considered a valid treatment option. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment.

12.12 Therapeutic Alternatives

If patients choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include immediate surgery, chemotherapy, or radiation, or a

combination of these approaches.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy in combination with surgical resection, we anticipate that patients who receive the treatment phase of the protocol will do no worse than expected with standard therapy, and may experience an improved outcome. The risk is considered to be acceptable in the setting of cancer.

12.14 Consent Form Documents

No information will be purposely withheld from the patients. The consent document used in this study will include the adult consent document.

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APPENDIX A

Criteria Defining Resectability Status

NCCN Clinical Practice Guidelines in Oncology™ Version 2.2011

RESECTABLE

HEAD/BODY/TAIL

- 1) No distant metastases
- 2) No radiographic evidence of superior mesenteric arteries (SMA) and portal vein abutment, distortion, tumor thrombus, or venous encasement
- 3) Clear fat plane around celiac axis, hepatic artery, and SMA.

BORDERLINE RESECTABLE

- 1) No distant metastases
- 2) Venous involvement of SMV/portal vein demonstrating tumor abutment with impingement and narrowing of lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- 3) Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- 4) Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.

UNRESECTABLE

HEAD

- 1) Distant metastases
- 2) Greater than 180 degrees SMA encasement, any celiac abutment
- 3) Unreconstructable SMV/portal occlusion
- 4) Aortic invasion or encasement

BODY

- 1) Distant metastases
- 2) SMA or celiac encasement greater than 180 degrees
- 3) Unreconstructable SMV/portal occlusion
- 4) Aortic invasion

TAIL

- 1) Distant metastases
- 2) SMA or celiac encasement greater than 180 degrees

NODAL STATUS

- 1) Metastases to lymph nodes beyond the field of resection should be considered unresectable.

APPENDIX B

ECOG Performance Status Scale

Grade ECOG PERFORMANCE STATUS

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

APPENDIX C: Eligibility Checklist

Date Completed:	Institution: Fred & Pamela Buffet Cancer Center	Subject ID #:	
IRB# 668-19 Title: A Phase IIa (Pilot) Study of Neoadjuvant Chemotherapy with <u>F</u> olinic Acid, 5- <u>F</u> U, <u>I</u> rinotecan and <u>O</u> xaliplatin (FOLFIRINOX) with Digoxin in Patients with Resectable Pancreatic Cancer		Waiver #:	
Inclusion Criteria: Response should be Yes		YES [†]	No
			N/A
1. Is a cancer patient with pathologically confirmed adenocarcinoma of the pancreas with resectable or borderline resectable disease with no evidence of distant metastases (See appendix A for criteria for resectability)		☐	☐
		☐	☐
2. Is the patient 19 years of age or older? Enter Age: _____		☐	☐
		☐	☐
3. Is the ECOG Performance Grade 0 or 1? Enter PS: ____		☐	☐
		☐	☐
4. Is the patient who received chemotherapy > 5 years ago for malignancies other than pancreatic cancer eligible, provided that chemotherapy was completed > 5 years ago and that there is no evidence of the second malignancy at the time of study entry?		☐	☐
		☐	☐
5. Is the patient disease radiographically assessable?		☐	☐
		☐	☐
6. Is the absolute neutrophil count 1,500 per mcL or higher and the platelet count is 100,000 per mcL or higher? Enter ANC: _____ Enter Platelet count: _____		☐	☐
		☐	☐
7. Patient must have normal serum potassium, magnesium and corrected calcium level. Enter K: _____ Mg _____ corrected Ca _____		☐	☐
		☐	☐
8. Is the serum creatinine at or below 2 mg/dL? Enter creatinine: _____		☐	☐
		☐	☐
[†] for criteria 9, one of these should be Yes		☐	☐
a. If there is no biliary obstruction, is the total bilirubin at or below 1.5 mg per dL? Enter bilirubin: _____		☐	☐
		☐	☐
b. If there is no biliary obstruction, & the patient has Gilbert syndrome is the indirect bilirubin at or below 1.0 mg/dL? Enter indirect bilirubin: _____		☐	☐
		☐	☐
c. If there is biliary obstruction, is the total bilirubin at or below 5.0 mg/dL? Enter bilirubin: _____		☐	☐
		☐	☐

10. The patient is aware of the neoplastic nature of his/her disease and willingly provide written, informed consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, & discomforts.	☐	☐	☐
11. No prior chemotherapy for pancreatic cancer	☐	☐	☐
Exclusion Criteria: Response should be NO			
1. Patient cannot undergo staging laparoscopy. For example, this may include patients with a prior history of multiple abdominal operations in which laparoscopy may not be technically feasible or potentially harmful.	☐	☐	☐
2. Does the patient have a contra-indication to receiving digoxin therapy, such as AV block, sick sinus syndrome, bradycardia, and hypersensitivity to digoxin or digitalis preparations?	☐	☐	☐
3. Does the patient have a history of uncontrolled inter-current illness including, but not limited to ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, or serious, uncontrolled cardiac arrhythmia, that might jeopardize the ability of the patient to receive the chemotherapy program outlined in this protocol with reasonable safety?	☐	☐	☐
4. Is the patient pregnant or breast feeding? Result of urine pregnancy test for females of childbearing potential. _____	☐	☐	☐
5. Does the patient have a history of prior malignancy except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas, or other cancers from which the patient has been disease-free for at least 5 years?	☐	☐	☐
6. Is the patient known to have HIV infection with HIV-AIDS? Note: Patients without a history of AIDS-defining opportunistic infections are eligible. Patient with a history of AIDS-defining opportunistic infections are eligible if they have not had an opportunistic infection within the past 12 months.	☐	☐	☐
7. Does the patient have an active autoimmune disease (e.g., rheumatoid arthritis, systemic lupus erythematosus (SLE), ulcerative colitis, Crohn's Disease, multiple sclerosis (MS),	☐	☐	☐

ankylosing spondylitis)?	
8. Does the patient have a recognized acquired, hereditary, or congenital immunodeficiency disease including cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia?	☐ ☐ ☐
Eligibility: ☐ Patient satisfies all criteria ☐ Patient not formally eligible, but admitted to this study because (state reason): _____	
ELIGIBILITY reviewed and confirmed. Investigator Signature _____ Date _____ Printed Name of Investigator: _____	

APPENDIX D:

FDA MEDWATCH form

Available on-line at <http://www.fda.gov/medwatch/SAFETY/3500.pdf>

APPENDIX E: Common Toxicity Criteria

Toxicity will be scored using NCI CTC Version 5.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 5.0 can be downloaded from the CTEP homepage:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

All appropriate treatment areas have access to a copy of the CTC Version 5.0.