HFHS- 13-03: A NEOADJUVANT PHASE II STUDY OF CHEMO-RADIOTHERAPY IN PATIENTS WITH RESECTABLE AND BORDERLINE RESECTABLE PANCREATIC CANCER

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Eligible patients with resectable and borderline resectable pancreatic cancer will be accrued onto protocol therapy, which would include a neo-adjuvant phase followed by surgical resection.

SCHEMA

Resectable and Borderline Resectable Pancreatic Cancer
Pre-study: Determine eligibility, baseline CT scan, surgical evaluation, Ca19-9
Sign Informed Consent
↓
2 cycles – FOLFOX6 (1 month)
↓
Gemcitabine/RT (5-6 weeks)
↓
Rest period 2 weeks
↓
Re-staging evaluation (CT scan to be done during the 2 weeks of rest)
↓
Surgery (To be performed no later than 6 weeks after completion of chemo-radiation)

***Note: If patient has evidence of distant disease progression at any restaging CT they will be removed from protocol treatment**

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1. INTRODUCTION

Pancreatic Cancer

There were an estimated 37,680 new cases of pancreatic cancer in the US in 2008 making it the 10th most common cancer. The estimated number of deaths, however, was 34,290 which places pancreatic cancer 4th among deaths caused by cancer[1]. A practical staging system for pancreatic cancer based on the approach to treatment separates patients into four categories: 1) resectable, 2) locally advanced unresectable, 3) metastatic disease, and 4) borderline resectable.

Resectable Disease

A small minority of patients fall into the category of resectable disease. Surgical treatment is most often the initial treatment and is offered with curative intent. However, median survival with surgery alone is only 13-20 months. Following resection, patients benefit from the addition of adjuvant radiation and/or chemotherapy[2-4]. Even in this most favorable group of patients, however, the 5 year survival is less than 30% in single institution series[5, 6]. A large majority of patients treated with surgery, with or without adjuvant therapy, progress with hepatic metastases.

Advanced Metastatic Disease

Patients presenting with evidence of distant metastasis at diagnosis are offered treatment with palliative chemotherapy. Gemcitabine has dominated systemic therapy for pancreatic cancer for most of the past decade. A pivotal study randomized 126 patients with advanced, symptomatic pancreatic cancer to either weekly gemcitabine 1000 mg/m^2 over 30 minutes or weekly bolus 5FU 600 mg/m^2 using clinical benefit response (CBR) as the primary endpoint[9]. The study found CBR more commonly in the gemcitabine treated patients (23.8% vs 4.8%, P=0.002). Gemcitabine also led to improved median survival (5.6 vs. 4.4 months) and 1 year survival (18% vs. 2%) as compared to 5FU. Tumor response was infrequent in both arms (5.4% gemcitabine vs. 0% 5FU). While gemcitabine as a single agent in advanced pancreatic cancer has utility, enthusiasm is muted considering the limited benefit it provides. The recent ACCORD trial evaluated gemcitabine vs. FOLFIRINOX (5FU, oxaliplatin and irinotecan) and determined that FOLFIRINOX was superior to gemcitabine in the treatment of metastatic disease, both in terms of overall survival (OS) and progression free survival (PFS). This pivotal trial has led to the acceptance of FOLFIRINOX as a standard in the first line treatment of metastatic pancreatic cancer[28]. It is noteworthy, however, that the toxicity caused by FOLFIRINOX was three times greater than gemcitabine. The role of irinotecan in the treatment of metastatic pancreatic cancer is unclear. A Phase II series suggests that the survival benefit with FOLFOX alone is very similar to that seen with FOLFIRINOX in the ACCORD trial[29]**.** Hence it is also reasonable to consider treatment with FOLFOX alone in the metastatic setting. Several trials addressing this important question are ongoing.

Borderline Resectable Disease

Patients with disease that falls somewhere between the first two categories, resectable and localized but unresectable, are designated as having borderline resectable disease. While not clearly unresectable, if surgery is the initial treatment, there is a high likelihood of an R1 or R2 resection with subsequent local recurrence[10-12]. Consequently, it is reasonable to provide chemotherapy and/or radiation with the intent of increasing the likelihood of a subsequent margin negative resection.

Historically, the rate of successful resection in borderline resectable pancreatic cancer following neoadjuvant treatment is in the range of 30%[13-15]. The variable reported rates of successful resection can be attributed to the variable definition of borderline resectable disease, different approaches to combining chemotherapy with radiation, and the surgeon's willingness and ability to perform vascular resection +/- reconstruction. As compared to R0 resection rates in resectable disease with up front surgery (60-80%), in recent studies investigating neoadjuvant therapies in resectable and borderline resectable disease, R0 resection rates have generally been reported in the range of 90%, suggesting an improvement in successful R0 resection rates following preoperative treatment [13, 14, 16, 17]. Additionally, in locally advanced borderline or unresectable disease, down staging with chemotherapy and radiation permitting resection yields post-surgery survival similar to that achieved in upfront resectable disease[17]. This suggests a significant benefit of neoadjuvant therapy, which aides in obtaining an R0 resection in borderline resectable disease.

There is currently no standard therapy approach for borderline resectable pancreatic cancer. The purpose of this study is to improve outcomes in patients with borderline resectable and resectable disease utilizing a planned course of neoadjuvant therapy, consisting of chemoradiation, in order to optimize successful R0 resection rates and local disease control, and combination chemotherapy to optimize control of distant disease .

Optimization of Local Disease Control Using Chemoradiation

In order to optimize local control of disease in borderline pancreatic cancer, chemoradiation can be given neoadjuvantly. Chemoradiation for pancreatic cancer has historically incorporated 5-fluorouracil. Gemcitabine has greater systemic efficacy than 5-fluorouracil in pancreatic cancer and is a potent radiosensitizer. Therefore, gemcitabine has been evaluated in combination with radiation therapy using conformal radiation techniques. Early studies using gemcitabine with radiation were hampered by limitations in radiation and or gemcitabine dose based on regional toxicity and poor distant disease control due to suboptimal doses of gemcitabine[24, 25]. However recent trials have demonstrated gemcitabine as a more potent radio-sensitizer with a more acceptable toxicity profile. Locoregional toxicity has been addressed by limiting the radiation field to the primary tumor alone and titrating the radiation dose [26,27].

Neoadjuvant Therapy

In resectable and borderline resectable pancreatic cancer, surgery is most often the initial

treatment. The adequacy of that resection is questionable, however, in that a significant minority of patients have positive margins and some patients have incomplete resection (R_2 resections)[18, 19]. Median survivals in patients with R_1 or R_2 resections are no different than that observed with non-operative therapy. Patients deemed to have borderline resectable disease are at even higher risk for a margin positive resection if treated initially with surgery. A reasonable strategy to address this problem is neoadjuvant therapy to try to increase successful resectability[12]. Compared with adjuvant therapy, neoadjuvant therapy has the potential advantage of an improved tolerance of combined modality treatment preoperatively, and a greater proportion of patients receiving all components of multimodality therapy completed over a shorter time interval. As many as 30% of resected patients fail to receive post-operative adjuvant therapy because of inadequate recovery from surgery or patient refusal. Treatment delays following surgery may impact efficacy of adjuvant treatment. In the ESPAC adjuvant trial, the median time to initiation of post operative chemotherapy was 46 days and for combined modality treatment 61 days[4]. Neoadjuvant treatment provides a more timely systemic therapy. Finally, patients that progress during neoadjuvant therapy have biologically aggressive disease and are spared a major operation which provides little benefit.

One of the potential downsides of neo-adjuvant treatment is: theoretical concerns of disease progression during treatment. However this has not been proved in clinical trials.

Summary and Rationale for This Study:

Considering the aggressive biology of pancreatic cancer, and the relatively limited survival with the current standard, which is surgery followed by adjuvant chemotherapy, we hereby propose this clinical trial to evaluate the safety and effectiveness of a novel neoadjuvant treatment strategy incorporating FOLFOX chemotherapy in combination with chemo-radiation with gemcitabine.

2. OBJECTIVES

Primary Objective:

1a. To evaluate frequency of achieving R0 resection in patients with resectable and borderline resectable pancreatic cancer treated with a neoadjuvant regimen of FOLFOX followed by RT concurrent with gemcitabine chemotherapy at standard dosing.

Secondary Objectives:

2a. To determine overall survival and progression-free survival as a function of time from study enrollment.
2b. To evaluate tolerability and toxicity of the protocol treatment.

2c. To evaluate radiographic primary tumor response rate using modified RECIST criteria

3. PATIENT SELECTION:

3.1 Conditions for Patient Eligibility:

3.1.1 Patients must have histologically or cytologically confirmed pancreatic adenocarcinoma of the pancreatic head or body

3.1.2 Patients must have radiographically-confirmed surgically resectable (or) borderline resectable disease at study entry staged at T1-3, N0-1 and M0 (see Appendix B for NCCN criteria for determining resectability status, borderline is at the discretion of the surgeon). Surgical resectability will be assessed by a surgeon experienced in pancreatic surgery in conjunction with a radiologist specializing in radiographic pancreatic imaging.

3.1.3 Age ≥18 years

3.1.4 Life expectancy of greater than 6 months in the opinion of the investigator, excluding the pancreatic cancer.

3.1.5 ECOG performance status ≤1 (see Appendix A).

3.1.6 **Required laboratory data:**

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin < 2mg/dl
- AST(SGOT)/ALT(SGPT) ≤5 X institutional upper limit of normal
- Creatinine <2.0 mg/dl
- Negative β-HCG for females
- Mg ≥LLN institutional lower limit of normal
- Calcium ≥ LLN institutional lower limit of normal
- Sodium ≥ LLN institutional lower limit of normal
- Potassium ≥ LLN institutional lower limit of normal
- CA 19-9

3.1.7 Disease assessment by CT scan within 4 weeks of study entry

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

3.2 **Conditions for Patient Ineligibility:**

3.2.1 Patients may not be receiving any other investigational agents.

3.2.2 Patients with metastatic disease are excluded from this clinical trial

3.2.3 History of allergic reactions attributed to 5FU, oxaliplatin and gemcitabine

3.2.4 No prior chemotherapy or radiation therapy for pancreatic cancer. Previous chemotherapy or radiation therapy for other malignancies is permitted.

3.2.5 Patients with uncontrolled hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia or hypokalemia defined as less than the lower limit of normal for the institution, despite adequate electrolyte supplementation are excluded from this study.

3.2.6 Uncontrolled serious intercurrent illness including, but not limited to, ongoing or serious active infection requiring IV antibiotics for over 30 days, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia other than chronic, stable atrial fibrillation, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant or breastfeeding women are excluded from this study.

3.2.8 Known HIV-positive patients are ineligible.

3.2.9 Patients with unresectable disease are excluded from the protocol. (see Appendix B for NCCN criteria for determining resectability status). Surgical resectability must be confirmed by a surgeon experienced in pancreatic surgery.

3.2.10 Patients with pancreatic tail lesions will be excluded

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

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site has Institutional Review Board approval. Patients must have signed and dated all applicable consents and authorization forms. To register a patient to this study, the signed and dated eligibility checklist, along with any necessary supporting documentation, and the signed patient consent form will be forwarded to the responsible data manager. To complete the registration process, the data manager will assign a patient study number, in sequential order of consent, register the patient to the study, and contact the treating investigator and responsible research nurse to confirm registration.

5.0 TREATMENT PLAN

5.1 Chemotherapeutic Agent Administration

Treatment will be administered on an outpatient basis. Appropriate dose modifications for 5FU, oxaliplatin and gemcitabine are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2 FOLFOX

A cycle of treatment is 14 days. 2 cycles are intended prior to combined modality treatment, although this may be modified based on patient tolerance and toxicity experienced.

Starting dose levels are as follows:

Oxaliplatin 85mg/m^2 infused intravenously over 120 minutes on day 1.
Leucovorin 400mg/m^2 infused intravenously over 90 minutes on day 1.
5FU 400mg/m^2 as a bolus intravenous injection following leucovorin on day 1.
5FU 2,400mg/m^2 infused intravenously as a continuous infusion over 46 hours following the bolus 5FU, beginning on day 1.

A second cycle of treatment may begin when ANC $\geq$ 1,000/mm^3, platelets $\geq$ 75,000/ mm^3 and all other treatment related toxicity has resolved to $\leq$ grade 1.

Dose adjustments for toxicities may be found in Section 6.

5.3 Gemcitabine during Radiation Therapy

Combined modality treatment will begin 2 weeks (plus or minus 2 days) after the last FOLFOX administration, provided the ANC $\geq$ 1,000/mm^3, platelets $\geq$ 100,000/ mm^3 and all other treatment-related toxicity has resolved to $\leq$ grade 1.

Gemcitabine 1000mg/m^2 will be infused over 30 minutes on days 1, 8, 22, and 29 during the 5-week course of radiation treatment.

Dose adjustments for gemcitabine due to toxicity are detailed in section 6 and will be based on complete blood counts (done within 24 hours of starting the treatment), and non-hematologic toxicities experienced in the preceding week(s). If gemcitabine treatment is held for toxicity, radiation therapy will also be held and both treatments resumed when resolution of toxicity permits.

5.4 RADIATION THERAPY

Treatment Assignment:

All subjects will receive 45.0 Gy to the Clinical Tumor Volume (CTV) and 50.4 Gy to the Gross Tumor Volume (GTV) using Intensity Modulated Radiation Therapy (IMRT).

Physical Factors:

All subjects will undergo radiographic imaging required for radiation treatment planning purposes using a CT scanner. Digitally reconstructed radiographs from the CT will simulate the patient geometry during radiation treatment, including the localization and immobilization methods. A virtual treatment planning procedure is used to design treatment fields mathematically from the CT images.

Field Arrangement:

IMRT will be used to cover the primary or planning target volume (PTV), provided that the normal tissue constraints described below are met.

Beam Shaping:

A multileaf collimation system will be used to comply with field margin and normal tissue dose requirements.

Treatment Equipment:

Treatment will be administered on an isocentrically mounted megavoltage linear accelerator with photon energy ≥ 6 MV. Typically, the source-to-axis distance (SAD) will be 100 cm. IMRT will be delivered using dynamic MLC technique.

Target Volumes:

The PTV will be defined with CT-based treatment planning. Simulation of the clinical target volume (CTV) will be determined with intravenous bolus contrast administration given during CT and pre-CT oral contrast. GTV is the gross tumor volume. CTV (clinical tumor volume) will include GTV and surrounding nodal areas. PTV1 (planning tumor volume 1) is defined as CTV plus 1.0 - 1.5 cm margins in all directions. PTV2 (planning tumor volume 2) is defined as the GTV plus 1.0 - 1.5 cm margins in all directions.

Radiation Dose:

The prescription point will be designated at the intersection of the multiple beams. The PTV1 will receive a total cumulative target dose of 45 Gy delivered in 25 fractions at a daily fractional dose of 1.8 Gy. Following this, the PTV2 will receive a boost dose of 5.4 Gy in 3 fractions at a daily fractionated dose of 1.8 Gy. The

total dose to the GTV will be 50.4 Gy.

Beam Verification:

Beam verification films of each treatment field will be obtained during the first treatment until satisfactory. Thereafter, beam verification films will be obtained every week and at the time of any field modification. Daily KV-KV imaging may be used at the discretion of the treating physician. Standard IMRT QA procedures developed at our institution will be performed, including monitor units verification, intensity map verification, as well as point dose measurements.

Dosimetry:

The uniformity requirement will be +/- 5% of the total dose at the prescription point within the planning target volume.

Critical Normal Structures: QUANTEC Dose Constraint Parameters will be used as follows:

Kidneys (unilateral): <75% to get 20 Gy
Kidneys (bilateral): mean dose< 15 Gy
<55% to get 12 Gy
<32% to get 20 Gy
<30% to get 23 Gy
<20% to get 28 Gy
Spine: dose shall be limited to 45 Gy. of the volume of the liver
Liver: mean dose< 28 Cy, <70% to get 30 Gy

Radiation Treatment Modifications:

Radiation therapy will be withheld if ANC drops below 500/μL or if the platelet count is less than 50,000/μL. Treatment will be reinstituted when hematologic toxicity has improved to below grade 3 level.

Radiation will be withheld for 2 - 5 days or until symptoms resolve if severe nausea & vomiting occurs that does not resolve with antiemetics.

5.5 Surgical Resection:

Operative and surgical resection evaluation will be done at initial diagnosis as well as within 6 weeks after the completion of neoadjuvant treatment.

To determine resectability, radiologic computer tomography (CT) imaging, preferably a pancreas protocol CT, will be utilized to identify:

1. Absence of tumor extension to the adjacent visceral arteries (SMA, celiac, hepatic). Intact tissue plan between the tumor and the Superior Mesenteric Artery(SMA)/Common Hepatic Artery Interface;

2. A patent Superior Mesenteric Vein/ Portal Vein (SMPV) confluence, and the absence of tumor-induced unilateral shift or narrowing of any aspect of the SMPV confluence;

3. Absence of extrapancreatic disease;

The surgical procedure performed will be that required for a complete resection, and this will be based on the discretion of the operating surgeon.

Information regarding any surgical therapy performed will be recorded including: type of surgery performed, type of vascular reconstruction performed, if any, extent of resection R0, R1 (or) R2 resection, duration of the operation, length of post-operative hospital stay, complications, and need for re-admission within 30 days following surgical resection. Surgical resection will be performed for resectable pancreatic cancer as determined by the NCCN guidelines. All resection cases will be reviewed at Henry Ford Hospital's Multi-disciplinary GI Tumor Board.

DETAILS ON SURGICAL RESECTION

1. Pancreaticoduodenectomy with retroperitoneal lymphadenectomy will be performed for patients with ductal adenocarcinoma of the head of the pancreas.
This will be assessed prior to the operation with high-quality 3-D imaging of the pancreas and associated mesenteric vessels for optimal categorization of tumors.
Tumors will be considered resectable based on the following:

- No distant metastases
- No radiographic evidence of SMV and portal vein abutment, distortion, tumor thrombus, or venous encasement
- Clear fat planes around the celiac axis, hepatic artery, and SMA.
- **Those with venous involvement of the SMV/portal vein, namely tumor abutment, encasement, or short segment venous occlusion will be considered borderline resectable
- **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 will be considered borderline resectable
- **Tumor abutment of the SMA not to exceed >180 degrees of the circumference of the vessel wall will be considered borderline resectable

2. Recent evidence suggests that the optimal number of lymph nodes to be examined following standard pancreaticoduodenectomy should be greater than or equal to 15 (Tomlinson JS, Jain S, Bentrem DJ, Sekeris EG, Maggard MA,
Hines OJ, et al.Accuracy of staging node-negative pancreas
cancer: a potential quality measure. Arch Surg. 2007;142:767–23;

discussion 73–4.) Cooperation between both the operating surgeon and the surgical pathologist should ensure analysis of sufficient number of lymph nodes.

3. If, at the time of operation, vascular resection is required, vein resection and reconstruction will be performed if there is short segment invasion of the portal vein or PV/SMV confluence, providing adequate inflow and outflow veins are present.

4. Whipple specimens will be inked, examined, and reported in conformity with College of American Pathologists (CAP) or AJCC. Examination of the pancreatic margin, and bile duct margin will be assessed. In addition, it will be critical to examine the retroperitoneal margin as well as the SMA margin to accurately determine the resection status.

Safe achievement of an R0 margin is the main surgical objectives of the pancreaticoduodenectomy. The SMA margin is the most important driver of this outcome.

5.6 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue with chemo-radiotherapy as previously outlined prior to proceeding with surgical resection

5.7 Duration of Follow Up

Patients will be followed for 1 year after completion of neoadjuvant therapy or until removal (or) termination from study, or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be seen in follow-up every 3 ± 1 months for 1 year from completion of protocol therapy. At each interval visit, surveillance CT scans will be performed to assess local recurrence or metastatic disease. If patients choose to receive the adjuvant chemotherapy elsewhere other than the treating institution, a 3 month follow-up evaluation in the different institution is permissible. The data from the 3 month follow-up visit will be captured by the data managers and provided to the study principal investigator. Toxicity notations and disease status will be recorded. If it is not possible to coordinate a follow-up evaluation at 3 ± 1 months, then a follow-up phone call will be made to the patient by the treating physician, or clinical trials office designee, in lieu of a visit.

5.8 Criteria for Removal from Neoadjuvant Study

Patients will be removed from this study when any of the following criteria are met:

- Intercurrent illness that prevents further administration of treatment;

- Unacceptable adverse events(s);

- Pregnancy;

- Patient decides to withdraw from the study;

- General or specific changes in the patient's condition which render the patient unsuitable for further treatment, in the judgment of the investigator;

- Patients with unresectable disease, noted on laparotomy (or) laparoscopic evaluation following completion of neoadjuvant therapy, will be removed from the protocol ;

- Patients who develop documented metastatic disease at any point during the trial period .

The reason for removal from study and the date the patient was removed must be documented in the Case Report Form.

5.9 **Adjuvant Therapy following Surgical Resection**

All patients who are enrolled in this study are eligible to receive adjuvant chemotherapy based on the discretion of their primary oncologist. These patients will be followed on protocol and details of their adjuvant therapy will be recorded.

6. DOSING DELAYS/DOSE MODIFICATIONS

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) version 4.0 for toxicity and Serious Adverse Event (SAE) reporting.

6.1 General Considerations – FOLFOX treatment

a. The second cycle of treatment may begin when the ANC is ≥ 1,000/mcl, the platelet count is ≥ 75,000/mcl, and any treatment-related GI toxicity has resolved to ≤ Grade 1.

b. If the initiation of the second cycle of treatment is delayed for > 4 weeks from date due, secondary to toxicity, the patient will be removed from protocol treatment.

c. Doses will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of ≥ grade 3 neutropenia.

d. There are no dose reductions for leucovorin. Dose reductions for the other agents in the FOLFOX combination are as follows:

AGENT	INITIAL DOSE	Level -1	Level -2	Level -3
5-FU Bolus	400 mg/m^2	200 mg/m^2	0	0

Oxaliplatin	85 mg/m^2	70 mg/m^2	60 mg/m^2	50 mg/m^2
5-FU infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	1200 mg/m^2

Note: laboratory abnormalities that are not directly attributable to treatment (i.e., hyperglycemia) or not clinically relevant (i.e., lymphopenia) do not require modification of dosing.

Efforts to attribute toxicity experienced to a single component or some combination of the cytotoxic agents will be made by treating investigator and doses of the responsible agent(s) modified according to that judgment. Dose adjustments for toxicity will be described in the clinical record.

Once doses are reduced for toxicity, they will not be subsequently increased.

An agent(s) may be discontinued (i.e., oxaliplatin for neuropathy or hypersensitivity) and protocol therapy continue with remaining agents.

An agent(s) or FOLFOX combination therapy will be discontinued if more than 2 dose reductions for toxicity are needed.

6.2 Supportive Care

White blood cell colony stimulating factors may be administered as primary prophylaxis following each FOLFOX administration.

6.3 Dose Modifications

a. Dose modifications for toxicities during FOLFOX

i. Hematologic Toxicities

	Dose Modification
ANC <1000/mm3 and/or Platelets <75,000/mm3	Hold all chemotherapy and re-evaluate weekly. When toxicity resolves, treatment will be continued with one dose level reduction of oxaliplatin and bolus 5FU.
Platelets ≥ 75,000/mm3-≤ 99,000/mm3	Reduce oxaliplatin one dose level
Febrile Neutropenia	If a patient experiences neutropenic fever at any point in the treatment cycle, chemotherapy will be delayed until ANC > 1,000/mm3 and antibiotic treatment of the event, if required, is completed. When treatment resumes, reduce agents oxaliplatin

	and infusional 5FU if grade III or IV diarrhea and/or stomatitis > are part of the adverse event profile, by one dose level

*Note: There are no dose reductions for anemia or lymphopenia

ii. Diarrhea

Grade	Dose Modification
3-4	Hold all chemotherapy. When diarrhea resolves to ≤Grade 1, chemotherapy may be resumed with a reduction in 5FU-bolus and 5FU infusion by one dose level.

*Note: No dose reductions of oxaliplatin for diarrhea.

iii. Mucositis

Grade	Dose Modification
3-4	Hold all chemotherapy. If mucositis resolves to ≤Grade 1, chemotherapy may be resumed with reduction in 5FU-bolus and infusion by one dose level.

*Note: No dose reductions of oxaliplatin for mucositis.

iiii Neuropathy

Grade	Dose Modification
3-4	Hold oxaliplatin. If neuropathy resolves to ≤Grade 2, oxaliplatin may be resumed with reduction of two dose levels or discontinued.

*Note: No dose reductions for 5-FU for neuropathy.

b. Other non-hematologic toxicities attributable to 5-FU and/or oxaliplatin.

For all other ≥ Grade 3 non-hematologic toxicities attributable to treatment and not described above, hold all protocol treatment and monitor toxicity at least weekly. If toxicity resolves to ≤ Grade 1 within 4 weeks, treatment may resume with 5-FU and oxaliplatin at one lower dose level.

c. Dose modifications for toxicities during combined modality therapy (RT/Gemcitabine)

Agent	Initial Dose	Level -1	Level -2
Gemcitabine*	750 mg/m^2	600 mg/m^2	500 mg/m^2

*Note: all infusions of Gemcitabine and RT may begin when the ANC is ≥ 1,000/mm3, the platelet count is ≥ 100,000/mm3, and any treatment-related toxicity to FOLFOX is resolved to ≤ Grade 1.

During combined modality treatment, gemcitabine will be given days 1, 8, 22 and 29.

During gemcitabine/RT the dose of gemcitabine for **days 8 and 29** will be based on toxicities experienced as follows:

i. Hematologic toxicity

	Dose Modification
ANC ≥ 1,000 /mm3 and platelets ≥ 75,000/mm3	Full dose due will be given
ANC of 500- 999/mm3 and/or platelets of 50,000 to 74,999/mm3	50% of the gemcitabine dose due will be given
ANC < 500/mm3 or platelets < 50,000/mm3	Gemcitabine treatment **and** radiation therapy will be held. Combined modality treatment will resume upon recovery to values permitting chemotherapy with one dose level reduction of gemcitabine

* Note: dose adjustments of gemcitabine will be made based on the ANC and platelet counts taken within 24 hours of the start of therapy.

During combined gemcitabine/RT, dose of gemcitabine for **day 22** will be based on toxicities experienced as follows:

ii. Hematologic toxicity

	Dose Modification
ANC ≥ 1,000 /mm3 and platelets ≥ 75,000/mm3	Full dose due will be given
ANC of 500- 999/mm3 and/or platelets of 50,000 to 74,999/mm3	75% of the gemcitabine dose due will be given. If gemcitabine is dose reduced on this day, this dose will be dose due on day 29 and starting dose of post-combined modality therapy.
ANC < 500/mm3 or platelets < 50,000/mm3	Gemcitabine treatment **and** radiation therapy will be held. Combined modality treatment will resume upon recovery to values permitting chemotherapy with one dose level reduction of gemcitabine

* Note: dose adjustments of gemcitabine will be made based on the ANC and platelet counts taken within 24 hours of starting therapy.

iii. Non-hematologic toxicity-Any organ system

Grade	Dose Modification
≥ Grade 3	Hold all chemotherapy. If gemcitabine is held, radiation therapy will also be held while appropriate physical, laboratory, radiologic assessments are undertaken to define cause and direct supportive therapy. Treatment may be resumed upon recovery to toxicity < grade 2 at the discretion of the physician investigator.

*Note: Dose adjustments of chemotherapy will be made following assessment of non-hematologic toxicity on the day of therapy.

If combined modality therapy is interrupted, when resumed, chemotherapy will be given on the first day of the next week of radiation therapy with gemcitabine dose reduced one level to complete the treatment cycle. A maximum of four doses of chemotherapy will be given during the course of radiation therapy.

d. General Guidelines

A cycle of FOLFOX treatment is 14 days. A second cycle of FOLFOX treatment may begin when ANC ≥ 1,000/mm^3, platelets ≥ 100,000/ mm^3 and all other treatment related toxicity has resolved to ≤ grade 1.

FOLFOX treatment may be delayed for up to 2 weeks, after which time the second cycle of treatment will be dropped and not made up if conditions for treatment are not met. The patient may then be continued on to the combined modality treatment, once toxicities are resolved to grade 0 or 1.

Protocol therapy may be shortened and patient may go directly to surgery following combined modality therapy in a scenario where toxicities and/or response and resectability suggest surgery is in the best interest of the patient.

7. ADVERSE EVENT REPORTING:

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for reporting of adverse events (AEs).
Serious Adverse Events (SAE) and adverse events will be carefully recorded, and SAEs will be reported to Henry Ford Hospital's IRB if they meet the IRB's SAE reporting criteria.

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory

finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Definition of an SAE: Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy, including a male patient's impregnation of his partner, occurring on study must be reported to the IRB as a medically significant event.

SAEs (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable, or definite) should be reported to the IRB if the reporting criteria is met.

8. PHARMACEUTICAL INFORMATION

8.1 5-Fluorouracil (5-FU)

Please refer to the FDA-approved package insert for additional information.

a. Description – 5-FU is an antimetabolite considered to act primarily as an inhibitor of thymidylate synthase.

b. Pharmaceutical Data – Kinetics: After IV injection, it is distributed widely throughout the tissues of the body and diffuses readily across the blood-brain barrier. The mean half-life of elimination from plasma is 16 minutes. Drug is primarily metabolized by the liver. Formulation: 5-FU is a colorless to faint yellow solution supplied in 10 ml single use vials. Each 10 ml contains 500 mg fluorouracil. The pH is adjusted to approximately 9.2 with sodium hydroxide.

c. Administration – Intravenous.

d. Storage and Stability - : Store unopen vials at room temperature and protect from light.

e. Supplier – 5-FU is commercially available.

8.2 Oxaliplatin

Please refer to the FDA-approved package insert for additional information.

a. Description – Oxaliplatin (cis-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N,N*] [oxalate(2-)-*O,O*] is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane with an oxalate ligand as a leaving group. Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives by displacement of the labile oxalate ligand. Several reactive species are formed including the monoaquo and diaquo DACH platinum which covalently bind with macromolecules. Crosslinks are formed between adjacent guanine *N7* positions. These crosslinks inhibit DNA replication, transcription and repair. Reactive oxaliplatin derivatives are present as a fraction of unbound platinum in plasma ultrafiltrate. The decline of platinum levels following oxaliplatin administration is triphasic, characterized by two short distribution phases (t1/2(alpha) 0.43 hrs, t1/2 (beta) 16.8 hrs) and a long terminal phase (t1/2 (gamma) 391 hrs). At the end of a 2 hour infusion approximately 15% of the administered platinum is present in the systemic circulation with the remaining 85% rapidly distributed into tissues or eliminated in urine. The major route of elimination is renal excretion and the renal clearance of ultrafilterable platinum is significantly correlated with GFR.

b. Pharmaceutical Data– Oxaliplatin is supplied as a sterile, preservative free, aqueous solution in clear glass single-use vials containing 50 mg, 100 mg or 200 mg of oxaliplatin at a concentration of 5 mg/ml. The solution must be further diluted in 250-500 ml 5% dextrose for injection and is stable up to 24 hours under refrigeration or for 6 hours at room temperature. Needles or IV infusion sets containing aluminum must not be used.

c. Administration – Intravenous.

d. Storage and Stability – Store lyophilized powder under normal lighting conditions at 25° C. Store aqueous solution at 25° C; excursions permitted to 15-30° C. Do not freeze and protect from light (keep in original outer carton).

e. Supplier – Oxaliplatin is commercially available

8.3 Leucovorin

Please refer to the FDA-approved package insert for additional information.

a. Description – Leucovorin is a mixture of the diastereoisomers of 5-formyl derivative of tetrahydrofolic acid. The active component is the (-)-L-isomer known as Citrovorum factor.

b. Pharmaceutical Data– Kinetics: Leucovorin is rapidly absorbed from the gastrointestinal tract after oral administration and enters the general body pool of

reduced folates. Serum folate half-disappearance time is around 3.5 hours. Oral tablets yielded areas under the serum folate concentration-time curves (AUCs) that were 12% greater than equal amounts of leucovorin given intramuscularly and equal to the same amounts given intravenously. After IV administration, peak concentration was at 10 minutes. Terminal half-life of its active metabolite, 5-methyl derivative, was 6.2 hours. IM administration revealed similar terminal half-life. Formulation: Leucovorin is provided in vials containing cryodessicated/leucovorin calcium powder which is reconstituted in sterile diluent.

c. Administration – Intravenous

d. Storage and Stability – Store dry powder, reconstituted solution and tablets at controlled room temperature. Protect from light. When reconstituted with Bacteriostatic Water for Injection, the resulting solution must be used within seven days. If reconstituted with Sterile Water for Injection, use immediately and discard any unused portion. Because of the benzyl alcohol contained in Bacteriostatic Water for Injection, when doses greater than 10 mg/m2 are administered, Sterile Water for Injection should be used.

e. Supplier – Leucovorin is commercially available.

8.4 Gemcitabine

Please refer to the FDA-approved package insert for additional information.

a. Description – Gemcitabine hydrochloride (2',2'-difluoro-2'deoxycytidine) is a deoxycytidine analog with structural and metabolic similarities to cytarabine. Gemcitabine is metabolized intracellularly by nucleoside kinases to active di- and triphosphate nucleosides. The active nucleosides interfere with ribonucleotide reductase and compete with dCTP for incorporation into DNA, respectively, resulting in inhibition of DNA synthesis. Gemcitabine pharmacokinetics are linear and are described by a two compartment model. Half-life varies with age, gender, and infusion length; for a short infusion it is generally less than 70 minutes. Nearly all of an administered dose is recovered in the urine as active drug (<10%) or inactive uracil metabolite. The maximum plasma concentrations of the inactive metabolite are achieved 30 minutes after discontinuation of the infusions, and the metabolite is excreted in the urine without undergoing further biotransformation. The metabolite does not accumulate with weekly dosing, but its elimination is dependent on renal excretion, and could accumulate with decreased renal function.

b. Pharmaceutical Data – Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 g of gemcitabine as the hydrochloride salt, with mannitol and sodium acetate. Gemcitabine is reconstituted with 0.9% sodium chloride without preservatives and used within 24 hours.

c. Administration – Intravenous infusion over 30 minutes on days 1, 8, 22 and 29

d. Storage and Stability – Store at controlled room temperature.

e. Supplier – Gemcitabine is commercially available

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done within 4 weeks prior to start of therapy.

	Pre-Study	Pre-Cycles 1-2	Re-Eval (Pre chemo/XRT)	Weekly during Chemo/ XRT	Re-Eval (Post chemo/XRT)	Surgery	Post Surgery and Follow up Q 3 months from the end of neoadjuvent treatment
Protocol Window							
Performance Status	X	X	X	X	X		X
History/Physical	X	X	X	X	X		X
CBC,diff, plts[a]	X	X	X	X	X		X
Biochemical profile[b] MG, Calcium	X	X	X	X	X		X
Ca 19-9	X		X		X		X
Urine/serum pregnancy[c]	X						
CT chest/abdomen	X				X		X
Tumor Measurement	X				X		
Assessment by radiation oncologist	X						
Assessment by surgeon	X				X		
Surgery						D	
Radiation				B			
5FU, Oxaliplatin, Leucovorin		A					
Gemcitabine				C			
Toxicity Evaluation		X	X	X	X		X

[a] within 24 hours prior to chemotherapy administration, at re-evaluation visits and per post treatment followup

[b] comprehensive biochemical profile to include albumin, alkaline phosphatase, ALT or AST, glucose, total bilirubin, creatinine, MG, Ca++ and electrolytes

[c] in women of child bearing potential only

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A FOLFOX section 5.2
B RT section 5.3
C Gemcitabine section 5.4
D Surgical exploration/resection section 5.10

Post therapy follow-up at 3 month intervals through 1 year post completion of neoadjuvant therapy. All times are approximate.

10. MEASUREMENT OF EFFECT

10.1 Primary Tumor Response

Diagnostic imaging and RECIST criteria will be used to evaluate and record response of the primary tumor as defined below.

Complete Response (CR): Disappearance of measurable and evaluable disease without the appearance of any new lesions.

Partial Response (PR): At least 30% decrease in the LD of the primary lesion without the appearance of any new lesions.

Progression (PD): At least 20% increase in the LD of the primary lesion or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

10.2 Surgical Data

The following information regarding any surgical therapy will be recorded:

Operation performed

Standard Whipple (pancreaticoduodenectomy)
Pyloric-preserving Whipple
Total Pancreatectomy
Distal/Subtotal Pancreatectomy
Laparoscopic/Robotic Distal Pancreatectomy
Biliary Bypass
GastroJejunostomy
Laparoscopy or Laparotomy, abort

Any of above with vascular resection and reconstruction

V1 (patch)
V1a (venorraphy no patch)
V2 (primary, SV ligation)
V3 (graft, SV ligation)
V4 (primary, no SV ligation)
V5 (graft, no SV ligation)
V6 (splenorenal shunt)
IVC (any)
Common Hepatic Artery (any)
Right Hepatic Artery (any)
Left Hepatic Artery (any)
Other:

Extent of Visceral Extension:
Colon, stomach, adrenal, other

Metastatic Disease
Liver, Peritoneum, other

Exploratory laparotomy (no resection)
With gastric bypass
With biliary bypass
With both

Duration of operation, Blood loss, blood product transfused, #units transfused, and complications/notable events.

Pathologic findings: Tumor size, grade, nodal status, lymphovascular invasion, perineural invasion, microscopic assessment of margins, including retroperitoneal margin (R_0 vs R_1 vs. R_2).

- **RO Resection:** Complete resection with no microscopic residual tumor (margins microscopically negative according to the pathologist).
- **R1 Resection:** Complete resection with no grossly visible tumor as defined by the surgeon, but microscopic cancer may be left behind (margins are microscopically positive according to the pathologist).
- **R2 Resection:** Partial resection, with grossly visible tumor left behind.

Length of stay, need for re-admission within 30 days of discharge.

10.3 Assessment of Pathologic Response

The surgical pathology slides will be reviewed at the Department of Pathology,

Henry Ford Hospital. All histologic slides from surgical resections will be reviewed by a single pathologist and assessment of therapeutic response will be graded using a system previously described by Evans et al as per the table below.

Grade	Histologic Appearance
I	Characteristic cytologic changes of malignancy are present, but very little (<10%) or no tumor cell destruction is evident
II	In addition to characteristic cytologic changes of malignancy, 10%-90% of tumor cells are destroyed
IIa	Destruction of 10%-50% of tumor cells
IIb	Destruction of 51%-90% of tumor cells
III	Few (<10%) viable-appearing tumor cells are present
IIIM	Sizable pools of mucin are present
IV	No viable tumor cells are present
IVM	Acellular pools of mucin are present

11. STATISTICAL CONSIDERATIONS

Planned Data Analysis

Primary Objective: The proportion of patients who achieve R0 resection will be estimated, along with a 95% confidence interval for that proportion.

Secondary Objectives: 2a Kaplan-Meier survival estimates will be made for progression-free survival and for overall survival.
2b Tolerabilitiy and toxicity will be assessed by estimating the proportion of patients with dose limiting toxicities, and 95% confidence intervals for those proportions.
2c The proportions of patients with CR, PR, PD or SD will be estimated along with 95% confidence intervals.

Justification of Sample Size

With a total sample size of 20, the 95% confidence interval width will be equal to ±0.22 if the proportion is ~0.5. For proportions greater or less then 0.5, the confidence interval width will be narrower. For instance, for a proportion around 0.2, the confidence interval width will be 0.175.

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13. APPENDIX

APPENDIX A

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX B

CRITERIA DEFINING RESECTABILITY STATUS

RESECTABLE
- HEAD/BODY/TAIL
  - No distant metastases
  - Clear fat plane around celiac and superior mesenteric arteries (SMA)
  - Patent superior mesenteric vein (SMV)/portal vein

BORDERLINE RESECTABLE[1]
- HEAD/BODY
  - Severe unilateral or bilateral SMV/portal impingement
  - Less than 180 degree tumor abutment on SMA
  - Abutment or encasement of hepatic artery, if reconstructible.
  - SMV occlusion, if of a short segment, and reconstructible.
- TAIL
  - SMA or celiac encasement less than 180 degree

UNRESECTABLE
- HEAD
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- BODY
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- TAIL
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
- Nodal status
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

[1] For any tumors where there is a higher likelihood of an incomplete (R1 or R2) resection, it is suggested that chemoradiation be given prior to surgery.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.