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A Pilot Study of neoadjuvant and adjuvant mFOLFIRINOX in localized, resectable pancreatic adenocarcinoma.

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A Pilot study of neoadjuvant and adjuvant mFOLFIRINOX in localized, resectable pancreatic adenocarcinoma.

Patient eligibility:

1. Histological or cytological diagnosis of adenocarcinoma of the head, body or tail of the pancreas – no variants such as squamous cell, acinar cell, spindle cell or neuroendocrine tumors permitted.
2. A patent superior mesenteric (SMV)-portal vein (PV) confluence (assuming the technical ability to resect and reconstruct this venous confluence if needed), and a definable tissue plane between the tumor and regional arterial structures including the celiac axis, common hepatic artery, and SMA.
3. Confirmation of localized, resectable status by surgical oncology, per criteria in #2 and after presentation at a multidisciplinary conference.
4. No previous therapy for pancreatic cancer.
5. Karnofsky Performance status $\geq$ 80.
6. Age $\geq$ 21 years.
7. No currently active second malignancy.
8. No CVA within 6 months, no MI within 6 months.
9. Patients of reproductive age must agree to birth control methods.
10. Negative pregnancy test in females of reproductive potential.
10. Required Lab Values: Granulocytes: $\geq$ 1,500/μL
    Platelets: $\geq$ 100,000/μL
    Total bilirubin: $\leq$ 1.5 X ULN
    SGOT/SGPT: $\leq$ 2.5 x ULN
    Serum creatinine: $\leq$ 1.5 mg/dL, or creatinine clearance $\geq$ 60ml/min by Cockroft-Gault

Schema*:*

Confirmation of Eligibility

↓

mFOLFIRINOX x 4 cycles

↓

CT evaluation for reconfirmation of resectability.

↓ ↓

Resectable, proceed to surgery within 4-6 weeks — Unresectable, treat at MD discretion

↓ ↓

Successful resection — Unresectable → treat at MD discretion

↓

mFOLFIRINOX x 4 cycles starting 4-10 weeks after surgery

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1. OBJECTIVES

1.1 Primary Objective

To evaluate the percentage of patients able to complete the full course of preoperative chemotherapy and undergo a resection. This will be the primary determinant of success for this pilot study.

1.2. Secondary Objectives

1.2.1 To evaluate the percentage of patients able to complete all scheduled therapy, including preoperative chemotherapy, surgical resection and postoperative chemotherapy.

1.2.2 To assess treatment related toxicity and other adverse events (AE's) during preoperative, operative and postoperative therapy.

1.2.3 To assess the R0 resection rate.

1.2.4 To determine progression free survival and overall survival from the start of study treatment.

2. BACKGROUND

2.1 Study Disease

Pancreatic ductal adenocarcinoma is a highly lethal disease. It is estimated that in 2010 there were approximately 43,140 new cases in the United States and 36,800 deaths which ranks fourth among cancer related deaths[1]. At diagnosis, roughly 17,000 of the initial 43,000 patients have disease which appears to be localized to the pancreatic bed, but unfortunately, only a minority of these patients (15-20%) are immediately operable (on imaging studies their disease appears to be both localized to the pancreas and technically resectable with clear margins, and at surgery no unexpected findings preclude an R0 resection[2]). It should be noted that of those patients deemed immediately operable on clinical grounds, between 20 and 57% are found to have inoperable disease on exploration depending on the series and on the extent and nature of preoperative staging[3,4,5,6,7,8]. The majority of patients have locally advanced, borderline resectable or unresectable disease owing to involvement of critical

structures, most particularly sentinel blood vessels such as the SMA, celiac axis, hepatic artery, SMV, or portal vein. Furthermore, despite recent advances in systemic therapy, even those fortunate few able to undergo immediate surgery remain largely incurable, with a five year survival of slightly less than 20%[9,10].

The current standard of care for adjuvant therapy in resectable pancreatic cancer is based on the CONKO-001 study which randomized patients to 6 cycles of postoperative adjuvant therapy with gemcitabine versus observation alone[11]. Results favored adjuvant gemcitabine in both disease free survival (13.4 vs 6.9 months, $p<0.001$) and overall survival (24.2 months vs 20.5 months $p=0.02$) strongly supporting the use of adjuvant gemcitabine in the setting of both R0 and R1 resections. An RTOG study – 97-04 – concluded that gemcitabine was probably superior to 5FU when used pre and postoperatively in combination with 5FU/RT, with a HR of 0.82[12]. The role of radiation therapy in this setting remains controversial, with studies such as the GITSG trial (pro) and ESPAC 1 (con) criticized either for questionable design, outdated chemotherapy or unconventional radiation therapy[13,14]. Current studies in progress examining postoperative therapy include RTOG 0848 (phase III looking at adjuvant gemcitabine versus gemcitabine plus erlotinib plus/minus chemo/RT using fluorouracil), ACOSOG Z5041 evaluating gemcitabine plus erlotinib in the pre and postoperative setting and ESPAC 4 evaluating gemcitabine versus gemcitabine plus capecitabine.

Many studies have explored the use of neoadjuvant therapy in initially resectable, borderline resectable and unresectable disease. The majority of these have been single arm, single institution phase I/II studies, and results have been mixed[15,16,17,18,19]. Potential benefits of a neoadjuvant approach include: downstaging of disease with an increased percentage of margin negative and lymph node negative resections; no delay in systemic therapy aimed at eradicating micrometastatic disease; the detection of biologically aggressive tumors, as evidenced by early progression/metastases during this phase of therapy, thereby avoiding inappropriate surgery; and the greater likelihood of completing all intended therapy as opposed to postoperative treatment, where fully 22 – 35% of patients do not complete their intended program[20,21].

A comprehensive meta-analysis and systematic review of neoadjuvant therapy in both resectable and unresectable pancreatic cancer has recently been published [22]. The conclusion reached in resectable patients was that resection frequency and survival following neoadjuvant therapy was similar to that in patients undergoing primary resection followed by adjuvant therapy. In patients with initially unresectable disease, fully one third had resectable tumors following neoadjuvant therapy with survival comparable to initially resectable patients. In aggregate, these observations indicate that a neoadjuvant approach is feasible and effective, and that this sequence does not compromise resectability or survival, even in those patients with the best prognosis.

With respect to specific studies in resectable disease, investigators at MD Anderson Cancer Center have published their most recent results[23,24]. In their first study, 86 patients with resectable disease in the head of the pancreas received radiation therapy (30 Gy in 10 fractions over 2 weeks) plus 7 weekly infusions of gemcitabine at 400 mg/m2/week. 85% of these patients were taken to surgery and 74% were able to undergo the intended pancreaticoduodenectomy. Median survival for patients whose disease was resected was 34 months, but it was only 7 months for those whose disease could not be resected. In a

second study of patients with resectable adenocarcinoma of the pancreatic head, 90 patients were enrolled with the goal of administering chemotherapy alone for eight weeks, using gemcitabine and cisplatin, followed by combined low dose gemcitabine and radiation therapy (30 Gy in 10 fractions). Ultimately, 79 (88%) patients completed the full course of preoperative therapy and 62 of these (78%) patients were taken to surgery. 52 (66%) had their disease resected with a median survival of 31 months for those who had surgery, versus 10.5 months for those who did not. They concluded that initial combination chemotherapy with gemcitabine and cisplatin followed by chemotherapy/RT did not improve on the results achieved with chemotherapy/RT alone. This result is perhaps not surprising as gemcitabine, both alone and in doublet combinations, has simply not been active enough to materially impact on the outcome of this disease. Interestingly, the longer preoperative interval did not result in local tumor progression.

These findings are similar to those of other major centers reporting studies of neoadjuvant gemcitabine based chemoradiation for potentially resectable disease[25,26] and suggest that this is a valid strategy for further study in this setting.

Recently, investigators at the Institut Paoli-Calmettes and the Universite de la Mediterranee reported their results with a novel combination of docetaxel 30 mg/m2 weekly and RT of 45 Gy in 34 patients with resectable disease[27]. 32% had progression, 59% stable disease and 9% partial remission. 50% of the original cohort had pancreaticoduodenectomy with 100% R0 resection and a median survival of 32 months. The numbers are small and the overall resection rate disappointingly low, but the R0 resection rate and median survival for those resected is equivalent to patients receiving gemcitabine based regimens.

In locally advanced, unresectable disease, results have recently been reported from Austria with neoadjuvant gemcitabine/oxaliplatin without RT (39% of patients undergoing resection of disease with 69% R0 and 22 months median survival)[28], Italy with neoadjuvant PEFG/PEXG (cisplatin, epirubicin, 5-fluorouracil (F)/capecitabine (X), gemcitabine) or PDXG (docetaxel substituting for epirubicin) followed by RT plus X, F or G (14% resected with median survival 16.2 months)[29] and Japan with neoadjuvant gemcitabine 1000 mg/m2/wk and RT 50 Gy in T3 disease followed by postoperative 5FU liver perfusion (82% of patients with disease resected, 43% 5 year survival)[30]. In each of these studies, there is a mixture of borderline resectable and unresectable disease with the result that the interpretation of outcomes is problematic. However, it is clear that a neoadjuvant approach is feasible and active.

It is clear from an examination of the NCI CTEP database that the neoadjuvant approach has been widely embraced for future study. More than 40 active protocols are listed, including the following select few: a UVA study of hypofractionated RT plus chronomodulated capecitabine in resectable and borderline resectable disease; a UT Southwestern phase I study of SBRT or SBRT plus gemcitabine; an Emory phase I study of FOLFIRINOX and SBRT; a Fred Hutchinson study of GTX and oxaliplatin with IMRT and adjuvant gemcitabine; a UF phase II study of risk adapted gemcitabine plus abraxane; a European randomized phase II study of gemcitabine plus oxaliplatin pre and gemcitabine postop versus gemcitabine postop only; a Memorial Sloan Kettering pahse II study of gemcitabine plus oxaliplatin preop plus gemcitabine postop; and an ACOSOG study of gemcitabine plus erlotinib pre and postop.

Looking to the future there have been a number of recent innovations in chemotherapy. In an ongoing effort to discover non-gemcitabine based chemotherapy for those who have progressed on gemcitabine, and also a new regimen with more efficacy than those currently used in patients with pancreatic cancer, the combination of 5FU, leucovorin, oxaliplatin and irinotecan has been tested. This combination was initially studied in colorectal cancer, in a regimen known as FOLFOXIRI[31]. It was established that this combination was both tolerable and effective in this setting. Subsequently, the regimen was modified slightly to the current FOLFIRINOX format (oxaliplatin 85mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2 , 5FU 400 mg/m2 on day 1, then 5FU 2400 mg/m2 as a 46 hour continuous infusion) and tested in a phase II study in pancreatic cancer. 47 chemotherapy-naïve patients with metastatic disease were enrolled and 46 were treated[32]. Confirmed response rate was 26% with 4% complete responses. Median time to progression was 8.2 months and median overall survival was 10.2 months. Grade 3/4 toxicities included neutropenia (52%), nausea (20%), vomiting (17%), diarrhea (15%), and neuropathy (15%). No toxic death occurred. FOLFIRINOX was then tested after failure of previous gemcitabine therapy in metastatic disease and was deemed to be promising[33]. 13 patients were treated, with 9 evaluable for response - 6 had stable disease with a mean time to progression of 6.6 months, and 3 progressed.

As a consequence of the previously mentioned phase II study in chemo-naïve patients, a randomized phase II/phase III study comparing gemcitabine (G) to FOLFIRINOX (F) as first line treatment of metastatic pancreatic cancer was conducted [34]. This study was terminated prematurely by the study IDMC as it was determined that additional patient accrual would not add to the statistical power of the study. 342 patients were accrued with roughly one third of the primary disease involving the head of the pancreas. Overall objective response rate was 32% for F versus 9.4% for G. PFS was 6.4 months versus 3.4 months and overall survival 11.1 months versus 6.8 months, all in favor of F.

The overall survival rate of 11.1 months is the best result achieved thus far in a randomized phase III study of chemotherapy in metastatic pancreatic cancer. Notable toxicities of at least grade III/IV, which were all worse with F, were neutropenia (45.7 vs 18.7%), febrile neutropenia (5.4 vs 0.6%), fatigue (23.7 vs 14.2%), vomiting (14.5 vs 4.7%) and diarrhea (12.7 vs 1.2%). These results indicate that this is a notably active regimen with an encouraging response rate. However, the potential toxicities are significant, and it is a regimen that should be offered only to patients with ECOG 0-1 performance status and excellent supportive care. In this regard, in an attempt to ameliorate these toxicities, modifications to the published regimen have already been proposed by the French group and others. In their forthcoming study of FOLFIRINOX in the adjuvant setting, the French will omit the bolus of 5FU which contributes significantly to the myelosuppression but which is thought to have minimal impact on the therapeutic efficacy. In addition, most physicians now incorporate the routine use of neulasta with each treatment cycle. This study will similarly incorporate these modifications and the regimen will be named mFOLFIRINOX.

Thus, in the context of perioperative therapy, we have identified a regimen – FOLFIRINOX - with the best results to date in the treatment of metastatic disease and by inference, promise of improved outcome in those patients with resectable disease. If successful, this has the potential to improve DFS and overall survival (until now no better than 15-20% at 5 years) in these patients, and may establish a new paradigm for future studies .

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologic or cytologic diagnosis of adenocarcinoma of the pancreas.

3.1.2 Resectable primary tumor of the head, body or tail of the pancreas defined as a visible mass in the pancreas **and:**

3.1.2.1 No extrapancreatic disease
3.1.2.2 A patent superior mesenteric (SMV)-portal vein (PV) confluence (assuming the technical ability to resect and reconstruct this venous confluence if needed)
3.1.2.3 A definable tissue plane between the tumor and regional arterial structures including the celiac axis, common hepatic artery, and SMA.

3.1.3 Confirmation of resectability by surgical oncology consultation.

3.1.4 Presentation at a multidisciplinary conference at either University of Chicago or NorthShore University

3.1.5 No previous therapy for pancreatic cancer

3.1.6 Short removable metal stents rather than plastic stents are preferred but not required for palliation of initial obstructive jaundice

3.1.7 Karnofsky performance status 80 or better

3.1.8 Age $\geq$ 21 years

3.1.9 No currently active second malignancy

3.1.10 No CVA within 6 months, no MI within 6 months

3.1.11 The effects of mFOLFIRINOX on the developing human fetus are unknown. For this reason and because chemotherapy agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.12 Negative pregnancy test in females of reproductive age

3.1.13 Life expectancy of greater than 3 months.

3.1.14 Anticoagulation is permitted but patients may only be on lovenox for this purpose.

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

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ 1.5X upper limits of normal
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– creatinine	within normal institutional limits
OR	
– creatinine clearance	≥60 mL/min/ per Cockroft-Gault equation for patients with creatinine levels above institutional normal.

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

3.2 **Exclusion Criteria**

3.2.1 Patients who have had previous chemotherapy or radiotherapy for pancreatic adenocarcinoma prior to entering the study.

3.2.2 Pathologic subtypes other than pure adenocarcinoma; acinar cell carcinoma, squamous cell carcinoma, spindle cell carcinoma, neuroendocrine cancer, and mixed types are not eligible.

3.2.3 Patients who are receiving any investigational agents.

3.2.4 Patients with borderline resectable, locally advanced or metastastatic disease.

3.2.5 History of allergic reactions attributed to 5FU, leucovorin, irinotecan or oxaliplatin or to compounds of similar chemical or biologic composition.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, active liver disease including viral or non-viral hepatitis and cirrhosis, chronic diarrhea or inflammatory disease of the colon or rectum, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study. mFOLFIRINOX is a regimen containing more than one chemotherapy agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with FOLFIRINOX, breastfeeding should be discontinued if the mother is treated with these agents. These potential risks may also apply to other agents

used in this study.

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

3.2.9 Currently active second malignancy other than non-melanoma skin cancer or carcinoma in-situ of the cervix. Patients are not considered to have a "currently active" malignancy if they have completed therapy and have no evidence of recurrence for at least 5 years.

3.2.10 Pre-existing neuropathy greater than grade 1.

3.2.11 Anticoagulants other than low molecular weight heparin.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study at both the University of Chicago and at NorthShore University by the Study Coordinator. Confirm all selection criteria listed in section 3.0 and then call the registrar (Michele Britto) at 847-570-2109 with the following information:

Provider of information
Study # and Institution
Treating Physician
Patient name and hospital ID number
Patient's zip code of residence
Date of signed informed consent
Race, gender, date of birth of patient
Diagnosis and date of initial diagnosis

Following registration, a copy of all pertinent records should be forwarded to Michelle Britto in order that patients begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon

as possible. These patients should still be kept in the database so that this may be tabulated and reported and the reasons for not receiving protocol therapy analyzed.

4.2 Registration Process

To register a patient, the following documents should be completed by the research nurse or data manager and faxed _*847-570-2918*_ or e-mailed _*mbritto@northshore.org)*_ to the Study Coordinator (phone 847-570-2109):

- Copy of required laboratory tests/pathology report/surgical oncology consultation
- Signed patient consent form
- HIPAA authorization form
- Eligibility Screening Worksheet, Registration Form
- All documents that support eligibility

The research nurse or data manager at the participating site will then call _*(847-5702109)*_ or e-mail *(mbritto@northshore.org)* the Study Coordinator within 2 working days to verify eligibility. To complete the registration process, the Coordinator will

- assign a patient study number
- register the patient on the study
- fax or e-mail the patient study number to the participating site

4.3 Data and Safety Monitoring Plan

Data Safety and Monitoring will occur monthly at NorthShore University protocol review meetings, which are led by senior level medical oncologists. At each meeting, all active studies are reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting and a Data Safety and Monitoring form will be filled out for this protocol and signed by either the chairperson or by his/her designee if he/she is not available. Biweekly telephone calls will take place between the principal investigators at NorthShore University and University of Chicago to review all toxicity and adverse event data. ***Please see Appendix B for full details.***

5. CHEMOTHERAPY TREATMENT PLAN

5.1 Agent administration

Treatment will be administered on outpatient basis. Appropriate dose modifications are described in Section 6. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 mFOLFIRINOX will be administered for 8 cycles (4 preoperatively and 4

postoperatively, 2 weeks per cycle) in the following fashion:

- Oxaliplatin 85 mg/m² IV infusion on Day 1 over 2 hours and then
- Leucovorin 400 mg/m² IV infusion on Day 1 over 2 hours immediately following oxaliplatin If there is a shortage of leucovorin, then a reduced dose of 40mg/m2 may be given. If unavailable, then leucovorin may be omitted and restarted when available.
- Irinotecan 180 mg/m² IV infusion on Day 1 over 90-120 minutes (infusion via a Y connector during the infusion of leucovorin)
- Fluorouracil 2.4 g/m² continuous IV infusion over 46 hours (1200 mg/m² per day for two days) immediately following leucovorin and irinotecan

Treatment is given every 2 weeks provided that blood counts and other toxicity criteria are met as below in sec 5.3.

Oxaliplatin 85 mg/m²	Leucovorin 400 mg/m²	Continuous 5-FU 2400 mg/m²	Pegfilgrastim 6 mg
2 hours	Irinotecan 180 mg/m² 1.5 - 2 hours	46 hours	

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Hematopoietic growth factor support

Due to the high incidence of neutropenia associated with the FOLFIRINOX regimen (42.5% in the ACCORD study), growth factor support will be mandated beginning with the first treatment cycle. This may consist of either pegfilgrastim (Neulasta, *PEG*-rmetHuG-CSF) 6 mg s.c. x 1 dose on discontinuation of the 5-FU pump; or filgrastim (Neupogen, G-CSF) 300 or 480 micrograms s.c. daily for 5 consecutive days, beginning 24 to 48 hours after discontinuation of the 5-FU pump (i.e., beginning day 4 or 5) of each 14-day cycle. The duration of G-CSF may be lengthened or decreased with subsequent treatment cycles, at the discretion of the treating physician, depending on count recovery at the start of the next treatment cycle.

Erythropoiesis stimulating agents may be used at the discretion of the treating physician and implemented in accordance with ASCO guidelines.

5.2.2 Anti-emetics

Patients should be premedicated prior to each treatment cycle of FOLFIRINOX with an HT-3 antagonist and dexamethasone. The addition of aprepitant (Emend) is

strongly encouraged. Other anti-emetics, such as lorazepam may also be provided as clinically necessary.

5.2.3 **Anti-diarrheals**

For symptoms of diarrhea (and/or abdominal cramping), patients will be instructed to take loperamide. This should be started at the earliest sign of loose stool, an increase in bowel movements by 1 to 2 episodes compared to baseline, or an increase in stool volume or liquidity. Dosing is as follows: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours (4 mg every 4 hours at night) until diarrhea-free for at least 12 hours. *Maximum 24-hour dose is 16 mg total*. Additional antidiarrheal measures may be implemented at the discretion of the treating physician. Patients should also be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.

5.2.4 **Antibiotics**

Prophylactic oral antibiotic therapy will not be given at the start of study treatment. However, antibiotics (i.e. oral fluoroquinolones) should be initiated for patients in the following instances: those who have (a) endobiliary stents with an ANC that falls below 500; (b) endobiliary stents who develop a fever above 38.5C; (c) diarrhea persisting for more than 48 hours despite loperamide; (d) fever with diarrhea, regardless of ANC. Administration of long-term prophylactic antibiotics following the first occurrence of any of the above scenarios may be considered only following discussions with the PI or one of the co-PI's.

5.2.5 **Anticholinergics**

Prophylactic use of atropine prior to irinotecan dosing is strongly encouraged and should be on hand for any cholinergic reaction given the higher incidence of this problem in patients receiving irinotecan following oxaliplatin.

5.3 Dosing delays/dose modifications

Dose Modification Guidelines for FOLFIRINOX

These will be based on NCI Common Toxicity Criteria Version 4

** The dose of leucovorin is not modified for toxicity, but may be reduced for shortages.

Once a dose is decreased, re-escalation is not permitted. Patients are off study if they develop the same grade 4 toxicity despite a first dose reduction.

5.3.1. Hematologic toxicity

Do not treat until the granulocyte count is $\geq 1.5 \times 10^9$/L and the platelet count is $\geq 75 \times 10^9$/L.

5.3.1a. Doses according to the blood counts at the beginning of a cycle (Day 1)

Blood counts at D1 of each cycle	DELAY OF CYCLE	DOSE REDUCTION		
		Irinotecan	**Oxaliplatin**	**LV5FU**
Granulocytes < 1.5 x 10^9/L	Hold treatment until granulocytes ≥ 1.5 x 10^9/L (one or two weeks if necessary). In case of non recovery after 2 weeks delay, stop treatment*	1st occurrence: reduction of dose to 150 mg/m² 2nd occurrence: maintain the dose at 150 mg/m² 3rd occurrence: treatment discontinuation	1st occurrence : no reduction of dose 2nd occurrence: reduce the dose to 60 mg/m2 3rd occurrence: treatment discontinuation	Any occurrence: no change in 5FU infusion
Platelets < 75 x 10^9/L	Hold the treatment until recovery (platelets ≥75 x 10^9/L). In case of non recovery after 2 weeks delay, stop treatment	1st occurrence : no reduction of dose 2nd occurrence: reduce the dose to 150 mg/m²	1st occurrence: reduce the dose to 60 mg/m² 2nd occurrence: maintenance of the reduced dose 3rd occurrence: treatment discontinuation	1st occurrence: reduce the continuous infusion to 75% of the original dose

5.3.1b Doses according to subsequent blood counts or in case of infection

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Febrile neutropenia **or** **Grade 4 neutropenia (<500) for more than 7 days** **or** **Infection with concomitant grade 3-4 neutropenia**	1st occurrence: reduce the dose of irinotecan to 150 mg/m² 2nd occurrence: reduce also the dose of oxaliplatin to 60 mg/m² 3rd occurrence: treatment discontinuation
Grade 3-4 thrombocytopenia **[grade 3 <50,000 grade 4 <25,000]**	1st occurrence: reduce the oxaliplatin dose to 60 mg/m² and the continuous 5-FU dose to 75 % of the original dose 2nd occurrence: reduce also the dose of irinotecan to 150 mg/m² and the dose of continuous 5FU an additional 25 % 3rd occurrence: treatment discontinuation

5.3.2. Gastrointestinal toxicities

Patients must be instructed in the use of loperamide as treatment for diarrhea, and must have a supply of this drug upon starting mFOLFIRINOX. Patients should not be retreated with irinotecan until recovery from diarrhea (without loperamide for at least 24 h) has occurred.

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Diarrhea grade 1-2	No change in doses
Diarrhea grade 3-4 or Diarrhea + fever and/or neutropenia grade 3-4	1st occurrence: reduce the irinotecan dose to 150 mg/m^2 2nd occurrence: reduce also the oxaliplatin dose to 60 mg/m^2 and reduce the dose of continuous 5FU to 75 % of the original dose 3rd occurrence: treatment discontinuation
Diarrhea ≥ 48 h despite high dose loperamide	No reduction of the irinotecan, oxaliplatin or 5FU doses after complete recovery, unless either grade 3-4 diarrhea, or diarrhea + fever, and/or concomitant neutropenia grade 3-4 has occurred

5.3.3 Mucositis or "hand-foot" syndrome

In case of grade 3-4 toxicity, a reduction in dosage of 25% of continuous 5FU will be carried out for the subsequent cycles.

5.3.4 Cardiac toxicity

In case of angina pectoris or of myocardial infarction, 5FU and leucovorin has to be stopped.

5.3.5 Increase in bilirubin

In case of elevation of bilirubin, it is essential to exclude an obstruction of the biliary stent or progressive disease and to postpone chemotherapy. If bilirubin is ≥1.5xULN, irinotecan is held and should not be given until bilirubin is ≤ 1.5xULN.

5.3.6 Other toxicities

Any other toxicity ≥ grade 2, except anemia and alopecia, may require a reduction in the dose of irinotecan to 150 mg/m² and/or oxaliplatin to 60mg/m² and/or 5FU of 25% depending on the type of adverse event.

5.3.7 Peripheral neuropathy

The dose of oxaliplatin should be adjusted according to the table below:

Toxicity	**Duration of the toxicity**		
	≤ 7 days	**>7 days and <14 days**	**Persistent between the cycles**
Paraesthesia/dysesthesia without functional impairement (grade 1 NCI)	No change	No change	No change
Paraesthesia/dysesthesia with functional impairment but not impeding the activities of the daily lives (grade 2 NCI)	No change	No change	65 mg/m^2
Paraesthesia/dysesthesia with pain or functional impairment impeding the activities of daily life (grade 3 NCI)	65 mg/m^2	65 mg/m^2	Stop oxaliplatin
Paraesthesia/dysesthesia persistent, disabling	Not applicable	Not applicable	Stop oxaliplatin

If the oxaliplatin is stopped for neurotoxicity, irinotecan and the 5-FU will be continued.

Once the dose of any drug has been decreased, re-escalation is not permitted.
Patients are off study if they develop the same grade 4 toxicity despite a first dose reduction.
All dose adjustments should be based on the worst preceding toxicity, graded using the National Cancer Institute Common Toxicity Criteria (version 4.0).

5.4 Duration of Therapy

5.4.1 Including treatment delays due to adverse event(s), as specified in section 5.3, *initial preoperative* chemotherapy treatment with FOLFIRINOX will continue for 4 cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4.2 Following successful surgery, subsequent FOLFIRINOX will be given for 4 cycles or until one of the aforementioned criteria for stopping applies.

5.5 **Duration of Follow Up**

Patients will be followed every 3 months for 2 years and every 6 months for years 3-5 after completion or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.6 **Criteria for Removal from Study**

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. ADVERSE EVENTS: LISTING AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting to the local IRB (NorthShore or University of Chicago), to the data manager at NorthShore (Michelle Britto) and to MedWatch **in addition** to routine reporting.

6.1. **Adverse Event Lists for Commercial Agents**

6.1.1 Common, expected adverse events

5FU/leucovorin: diarrhea, esophagopharyngitis, leukopenia, infection, ulcerative stomatitis, gastrointestinal ulceration, thrombocytopenia, acute cerebellar

syndrome, myocardial ischemia, palmar-plantar erythrodysesthesia, and pneumopathy

Oxaliplatin: anemia, arthralgia, chest pain, dehydration, dyspnea, edema, hand-foot syndrome, hypokalemia, injection site reaction, leukopenia, neutropenia, neuropathy, cold sensitivity,persistent cough, pulmonary fibrosis, stomatitis, thrombocytopenia, thromboembolism.

Irinotecan: anemia, diarrhea with or without abdominal cramping and sweating, dyspnea, fever, abdominal enlargement, dehydration, edema, upper respiratory tract infection, neutropenic fever, stomatitis, allergic reactions, including anaphylactoid reactions, and thrombocytopenia

6.1.2 Comprehensive list of adverse events

Please refer to the professional package inserts for a comprehensive list of adverse events.

6.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 6.1 above) for expedited reporting purposes only.

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

6.3 Routine Adverse Event Reporting

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

6.4 Serious or Unexpected Adverse Events Reporting

All serious (Grade 4 or 5 according to CTCAE v 4.0) or unexpected adverse events must immediately be reported to the local IRB at NorthShore University or the University of Chicago, to the data manager (Michelle Britto 847-570-2109) and to MedWatch (fax 1-800-FDA-0178) within 7 -10 days.

6.5 **Secondary AML/MDS**

AML/MDS events must be reported. In CTCAE v 4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment-related secondary malignancy.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the commercial agents administered in this study can be found in Sections 7.1 – 7.4.

7.1 Fluorouracil

7.1.1 Other Names:
5-Fluorouracil, 5-FU, Adrucil, Efudex

7.1.2 Classification
Antimetabolite

7.1.3 Mode of Action
Fluorouracil is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering with the synthesis of DNA. It also interferes with RNA synthesis. See introduction for elaboration.

7.1.4 Storage and Stability
Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

7.1.5 Dose Specifics
Initial dose following leucovorin on day 1 of every 2 week cycle: 2400 mg/m2 continuous infusion over 46 hours immediately following leucovorin. The 46 hour infusion should be prepared per institution guidelines.

7.1.6 Administration
IV infusion.

7.1.7 Incompatibilities
Incompatible with doxorubicin and other anthracyclines.

7.1.8 Availability
Commercially available in 500 mg/10 mL ampules and vials, and 1 g/20 mL, 2.5 g/50 mL, and 5 g/100 mL vials. Supply for this study will be commercial.

7.1.9 Side Effects

Hematologic: Leukopenia, thrombocytopenia, anemia; can be dose-limiting; less common with continuous infusion.
Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.
Gastrointestinal: Nausea, vomiting, anorexia; diarrhea, can be dose-limiting; mucositis, more common with 5-day infusion, occasionally dose-limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.
Neurologic: Cerebellar syndrome (headache and cerebellar ataxia).
Cardiac: Angina, noted with continuous infusion.
Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.
Hepatic: Hepatitis with hepatic infusion.

7.1.10 Nursing Implications
Monitor CBC, platelet counts.
Administer antiemetics as indicated.
Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.
Assess for stomatitis - oral care recommendations as indicated.
Monitor for neurologic symptoms (headache, ataxia).
Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.
Inform patient of potential alopecia.

7.1.11 References
Hansen R, Quebbeman E, Ausman R, et al. Continuous systemic 5-fluorouracil in advanced colorectal cancer: Results in 91 patients. J Surg Oncol 1989; 40:177-181.
Freeman NJ, Costanza ME. 5-Fluorouracil-associated cardiotoxicity. Cancer 1988; 61:36-45.

7.2 Irinotecan (CPT-11) (NSC-616348)

7.2.1 Other Names:
Irinotecan hydrochloride trihydrate [CPT- 1 1, (4S)-4, 1 1- diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy] -IHpyroano [3',4':6, 7l indolzino [1 ,2-bl quino line-3,14(4H, l2H)dione hydrochloride trihydrate] is a topoisomerase I inhibitor.

7.2.2 Classification
Topoisomerase I inhibitor

7.2.3 Toxicology
Human Toxicity: Virtually all Phase I and II studies of irinotecan have reported neutropenia and diarrhea as the dose-limiting toxicities. It is expected that these toxicities will also be encountered in this trial. Other Grade 2-3 toxicities seen include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia, thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss. Sporadic cases of pulmonary toxicity, manifested as shortness of breath and nonproductive cough, have also been reported.

7.2.4 Mode of Action
Causes single stranded DNA breakage by inhibition of the intranuclear enzyme toposisomerase-1. Leads to apoptotic cell death via defects in DNA repair.

7.2.5 Pharmacology

7.2.5.1 Pharmacokinetics: Several studies describing the pharmacokinetic characteristics of irinotecan (CPT-11) and its active metabolite, SN-38, when administered alone or in combination with other agents (including cisplatin) in patients with small cell or non-small cell lung cancer have been reported in published literature. CPT- 11 is converted by carboxylesterases to its more active metabolite, SN-38. In vitro, SN-38 is 250 to 1,000 fold more potent than CPT-11 in the inhibition of topoisomerase I activity. A reversible, pH-dependent hydrolysis converts the closed lactone E ring form of both CPT-11 and SN-38 to the open, carboxylate form of each compound. Only the closed ring (lactone) forms of CPT-11 and SN-38 are effective topoisomerase I inhibitors. The mean terminal half-life of SN-38 in plasma is slightly longer than that for CPT-11; 11.5 ± 3.8 hours versus 6.3 ± 2.2 hours for the lactone forms. Peak plasma concentrations for CPT-11 occur at the end of the infusion. The time to peak for SN-38 is highly inter-patient dependent occurring at variable times points 30 to 90 minutes after the end of infusion. Murine studies suggest that the liver may concentrate, convert CPT-11 to SN-38, and eliminate both compounds as well as the glucuronide conjugate of SN-38 (SN-38G) via biliary secretion. In rats, 55% of radiolabeled CPT-11 was excreted unchanged in the bile within 24 hours, while 21.7% was transformed to SN-38. It recently was demonstrated that plasma concentrations of SN-38G in patients occur 0.5 to 3 hr after the SN38 peak and plasma levels generally exceeded that of SN-38. Overall, 73% of the radioactivity could be recovered from the feces of rats and 25% from the urine. Bile concentrations of CPT-11 were 10 to 60 fold higher than plasma concentrations in one patient during the first 6 hours following administration, while bile concentrations of SN-38 were 2 to 9 fold higher. Renal clearance has not been reported to be a major route of elimination for these compounds in humans.

7.2.6 Formulation
The drug is supplied in two forms: 2 ml vials containing 40 mg of drug and 5 ml vials containing 100 mg of drug. The drug is supplied in brown vials and appears as a pale-yellow-to-yellow crystalline powder and pale yellow transparent solution when reconstituted.

7.2.7 Storage and Stability
Irinotecan vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. It is stable for at least three years at room temperature. Irinotecan is stable for 24 hours in glass bottles or plastic bags after reconstitution with D5W.

7.2.8 Dose Specifics
Irinotecan will be given at a dose of 180 mg/m2 intravenously over 90-120 minutes every 2 weeks.

7.2.9 Preparation
Irinotecan will be diluted with D5W to a total volume of 500 ml and infused intravenously over 90-120 minutes. Nothing else should be added to the bag.

7.2.10 Route of Administration
Intravenous administration only.

7.2.11 Incompatibilities
Do not mix with any other compound.

7.2.12 Availability
This drug is commercially available for purchase by a third party. This drug will not be supplied by the NCI.

7.2.13 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

7.2.14 Nursing/Patient Implications
Premedicate with antiemetics in anticipation of mild to moderate nausea and vomiting. When used in combination with 5-fluroruracil 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 section 5.5.2).
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

7.3 Oxaliplatin

7.3.1 Generic Name
Oxaliplatin

7.3.2 Other name
L-OHP

7.3.3 Classification:
Platinating agent

7.3.4 Mode of Action
Oxaliplatin has properties similar to those of a bifunctional platinating agent,producing DNA cross-links and other damage to DNA.

7.3.5 Storage and Stability
Oxaliplatin should be stored at controlled room temperatures between 20° to 25°C in the light-proof packaging provided.
Oxaliplatin injection: Store between 20°C and 25°C (68°F to 77°F) with excursion permissible between 15°C and 30°C (59°F to 86°F). Do not freeze. For long-term storage, protect product from light (keep vial in outer carton). Stable for 3 years under these conditions.
Diluted Solutions
After dilution in 250-500 mL of 5% Dextrose in Water, diluted solutions are stable for 6 hours at room temperature (20°C to 25°C; 68°F to 77°F) or up to 24 hours under refrigeration (2°C to 8°C; 36°F to 46°F).

7.3.6 Dose Specifics
85 mg/m² intravenously over 2 hours every 2 weeks, for 4 cycles both pre- and postoperatively.

7.3.7 Preparation
Oxaliplatin injection: Withdraw the calculated dose of the 5 mg/mL solution from the vial(s) and then dilute with 250 mL to 500 mL Dextrose 5% in Water to give an oxaliplatin concentration between 0.2 mg/mL and 2.0 mg/mL. **Do not reconstitute or dilute oxaliplatin with a sodium chloride solution.**
Do not use administration needles or intravenous infusion sets containing aluminum items (risk of degradation of oxaliplatin upon contact with aluminum) for the preparation or administration of either the oxaliplatin for injection or the oxaliplatin injection.

7.3.8 Route of Administration
Intravenous.

7.3.9 Incompatibilities
Do not combine with alkaline medications or media (such as basic solutions of 5-FU, trometamol) which cause oxaliplatin to degrade. Do not use needles or IV infusion sets containing aluminum items for the preparation or administration (risk of degradation of oxaliplatin on contact with aluminum). Since little or no compatibility data exist on oxaliplatin at present, it should not be mixed or combined with anything

other than 5% dextrose injection USP. The reconstitution or final dilution must never be performed with a sodium chloride solution.

7.3.10 Availability
For this clinical trial, the supply of oxaliplatin will be commercial.

7.3.11 Side Effects
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 AGC < 1.0 x l09L), 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 <1.0 x l09L fever >38.5°C), infection (documented clinically or microbiologically with grade 3 or 4 neutropenia (ANC <1.0 x l09L), 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 laryngopharyngeal
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 (noncardiac 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.

7.3.12 Nursing Implications
Monitor CBC, platelet counts.
Administer antiemetics as indicated.
Monitor for diarrhea. Encourage fluids and treat symptomatically.
Monitor for neurological symptoms (paresthesias, dysesthesias, etc.).
Instruct patient on the care of access devices.
Inform patient of expected side effects.
Respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, and tachypnea) have been observed in patients administered with oxaliplatin. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold oxaliplatin until interstitial lung disease is ruled out for cases of grade >3.
All patients must be premedicated for nausea and vomiting (see below).
Patients on this study should be counseled to avoid cold drinks and exposure to cold water or air because the neurotoxicity often seen with oxaliplatin appears to be exacerbated by exposure to cold. The period of time during which the patient is at risk for these cold-induced sensory neuropathies is not well documented. Patients should exercise caution regarding cold exposure during the treatment period.
Peripheral sensory neuropathies can occur at any time after receiving oxaliplatin therapy. There have been deaths reported, especially in the elderly, while receiving Oxaliplatin/5-FU 130 mg/m², 5-FU 320 mg/m², Leucovorin 20 mg day 1-5 every three weeks. Patients had hypotension, weakness and diarrhea. They were not all neutropenic. These were thought to result from diarrhea complicated by enteric sepsis with dehydration and hypotension. Any patient with fever, grade 3 diarrhea, or grade 4 neutropenia/ANC with or without fever should be monitored closely, and hospitalization should be considered for fever, appropriate hydration, intravenous antibiotic therapy appropriate for gram positive and negative sepsis, and support for clinically significant deterioration. Patients should be supported aggressively until neutropenia and fever resolve.
Among over 50,000 patients that have been treated with Oxaliplatin, 11 patients developed respiratory problems. Four deaths occurred in these 11 patients, 2 of which were due to pulmonary fibrosis. As the relationship of such toxicity to Oxaliplatin cannot be confirmed, patients must be monitored closely for unexplained respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, and tachypnea) and Oxaliplatin must be held until interstitial lung disease is ruled out for cases of grade > 3.
Antiemetic premedications will be given as used for any platinum-containing regimen. The antiemetic regimen will be defined by the participating institution.

Antiemetic agents for platinum-induced nausea and vomiting are also effective for the prevention and treatment of oxaliplatin-induced nausea and vomiting.

List of warnings and cautions:
Any patient with unexplained severe hemolysis, hemoglobulinemia, and renal failure with increase in creatinine should be evaluated for hemolytic uremic syndrome (HUS). Oxaliplatin should be held in the event of hemolysis with renal failure until its etiology is determined in order to exclude the potential for HUS. Oxaliplatin should not be restarted if there is HUS. Evaluation for HUS should include CBC, differential, platelets, PT, PTT, fibrinogen, FDP, AT III, VWF, ANA, C3, C4, CH50, anti-platelet antibody, platelet-associated IgG, and circulating immune complexes. Renal evaluation should include creatinine, BUN, and urinalysis.

7.4 Leucovorin

7.4.1 Other Names:
Leucovorin, Wellcovorin, Citrovorum factor, folinic acid, 5formyltetrahydrofolate, LCV

7.4.2 Classification
Tetrahydrofolic acid derivative

7.4.3 Mode of Action
Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin. Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidilate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidilate synthetase.

7.4.4 Storage and Stability
All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10 mg/mL, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/mL the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light. The oral solution, 1 mg/mL, is stable for 14 days refrigerated and 7 days at room temperature.

7.4.5 Dose Specifics
400 mg/m2 diluted in 250 cc of D5W. Leucovorin is only compatible with D5W and is administered as a 2-hour infusion on day 1 of each 2 week cycle.

7.4.6 Preparation
The 50 and 100 mg vials for injection are reconstituted with 5 and 10 mL of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/mL solution. The 350 mg vial is reconstituted with 17 mL of sterile water resulting in a 20 mg/mL solution.

	60 seconds	30 seconds

The 60 mg bottle for oral solution is reconstituted with 60 mL of aromatic elixir provided, resulting in a 1 mg/mL oral solution

7.4.7 Administration
Leucovorin will be given as an intravenous infusion over 2 hours.

7.4.8 Compatibilities
Leucovorin (0.5-0.9 mg/mL) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin (0.03, 0.24 and 0.96 mg/mL) is stable for 48 hours at room and refrigeration temperatures when admixed with floxuridine (FUDR, 1, 2 and 4 mg/mL)
in normal saline. Leucovorin is also compatible with fluorouracil.

7.4.9 Availability
Commercially available as a tablet (5, 10, 15, 25 mg), cryodessicated powder for oral solution, and in parenteral formulations (3 and 5 mg ampule; 50 mg, 100 mg and 350 mg vial). Supply for this clinical trial will be commercial.

7.4.10 Side Effects
Dermatologic: Skin rash.
Gastrointestinal: Nausea, upset stomach, diarrhea.
Allergic: Skin rash, hives, pruritus.
Pulmonary: Wheezing (possibly allergic in origin).
Other: Headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

7.4.11 Nursing Implications
Observe for sensitization reactions.
When given with fluoropyrimidines monitor closely for diarrhea and stomatitis.

8. STUDY CALENDAR

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

Baseline history, physical and blood work are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. Laboratory evaluations should be repeated within 24 hours prior to initiation of the next cycle of therapy. [Cycle 1 refers to week of first actual therapy with mFOLFIRINOX.]

	Pre-Study	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Week +4 weeks after Cycle 4 completion	Week +4-6 After Cycle 4 completion	Cycle 5[e]	Cycle 6	Cycle 7	Cycle 8	Week +4 after completion of Cycle 8	Off Study[d]
Informed consent	X												
Demographics	X												
Medical history	X		X	X	X	X		X	X	X	X	X	X
Toxicity Assessment			X	X	X	X			X	X	X	X	
Physical exam	X		X	X	X	X		X	X	X	X	X	X
Vital signs	X	X	X	X	X	X		X	X	X	X	X	X
Height	X												
Weight	X	X	X	X	X	X		X	X	X	X	X	X
Performance status	X	X	X	X	X	X		X	X	X	X	X	X
CBC w/diff, plts	X		X	X	X	X		X	X	X	X	X	X
Serum chemistry[a]	X		X	X	X	X		X	X	X	X	X	X
Pregnancy test[b]	X							X					
CA 19-9	X			X		X		X		X		X	X
Radiologic evaluation[c]	X					X		X				X	
Chemotherapy		X	X	X	X			X	X	X	X		
Surgery							Exact timing per surgeon						

a. Specific minimal lab tests required –Na, K, Mg, Phosphorus, Glucose, BUN,CO2, Chloride Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphotase, SGOT, SGPT b. May be serum or urine.

c. CT scan of chest/abdomen/pelvis **or** MRI of abdomen/pelvis plus CXR if CT scan cannot be done.

d. Follow up visits and studies per usual standard of care but not less than every 3 months for years 1-2 and every 6 months for years 3-5.

e. Cycle 5 starts 4-10 weeks after surgery depending on patient recovery

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect

For the purposes of this study, RECIST 1.1 will be used. Patients should initially be re-evaluated for response 4 weeks after completion of 4 cycles of chemotherapy. Response and progression will be assessed in this study by evaluation at GI tumor board, with the presence of a minimum of one hepatobiliary surgeon, one medical oncologist and one radiologist. Should this not be possible, then an ad hoc meeting of these individuals should be convened forthwith for the purposes of making this determination.
If patients are not deemed resectable after the initial phase of chemotherapy, then the patient is off study and therapy will proceed at the discretion of the treating physicians.

9.1.1 Definitions

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

Evaluable for objective response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. These patients will have their response classified according to the definitions stated in Section 12.6.2

9.1.2 Disease Parameters

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

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease and will exclude the patient from participation in this protocol.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Target lesions. The only target lesion relevant to this study is the pancreatic primary and any additional disease will render the patient ineligible for this study.

Non-target lesions. These are not permissible on this study.

9.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is the only permitted method for this study.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable as a substitute.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. The use of PET-CT is discouraged in this study.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

FDG-PET: This test is neither required nor encouraged for this study.

9.1.4 Response Criteria

This study is unique in that the response evaluation is geared towards the maintenance of resectable status, no evidence of locally progressive or metastatic disease, and ultimately undergoing a resection.

9.1.4.1 **Tumors considered resectable according to current NCCN guidelines include the following:**

a. No distant metastases.

b. No radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement.

c. Clear fat planes around the celiac axis, hepatic artery, and superior mesenteric artery (SMA).

9.1.5 Progression-Free Survival (PFS)

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

9.1.6 Overall Survival (OS)

OS is defined as the duration of time from start of treatment to time of death from any cause.

10. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 6.0 (Adverse Events: List and Reporting Requirements).

10.1 Data Reporting

10.1.1 Method

Note: **All** adverse events that have occurred on the study must be reported via the monitoring method identified above.

11.1.2.1 Responsibility for Data Submission

Study participants are responsible for submitting data and/or data forms to the Coordinating Center *within 2 weeks of each cycle along with source documentation for CRFs* to allow time for Coordinating Center compilation, and Principal Investigator review.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoint(s).

12.1.1 Primary Endpoint

To evaluate the percentage of patients able to complete the full course of preoperative chemotherapy and undergo a resection. This will be the primary determinant of success for this pilot study.

Early withdrawals due to toxicity, disease progression, or intercurrent illness will be considered failures.

11.1.2 Secondary Endpoints

11.1.2.1 To evaluate the percentage of patients able to complete the full course of therapy, including preoperative chemotherapy, surgical resection and postoperative chemotherapy.
111.2.2 To assess treatment related toxicity and other adverse events (AEs) during preoperative and postoperative therapy and the safety of this approach.
11.1.2.3 To assess the R0 resection rate.
11.1.2.4 To determine progression-free survival and overall survival from the start of study treatment.

11.2 **Stratification factors.**

Not applicable.

11.3 **Sample size with power justification.**

This pilot study will be conducted using a minimax two-stage design to test the null hypothesis that the success rate is 50% or less versus the alternative that it is at least 75%. Nine patients are to be enrolled in the first stage. If four or fewer patients meet the criteria for success, the trial would be terminated. Otherwise, an additional twelve patients (for a total of 21) are to be enrolled, and if fourteen or more successes are observed then the regimen will be considered worthy of additional evaluation in this disease. This design yields at least 0.85 probability of a positive result if the true success rate is at least 75% and at least 0.90 probability of a negative result if the true success rate is at most 50%.

11.4 **Plans for analysis including plans for formal interim analysis.**

The proportion of patients completing preoperative therapy and undergoing resection will be calculated, and a confidence interval constructed based on the binomial distribution. Progression-free and overall survival will be calculated by using the method of Kaplan and Meier. The frequency of various AEs (worst grade) will be tabulated.

Because surgery-related deaths are of concern after administration of FOLFIRINOX, there will be close monitoring of this adverse event. Specifically, a stopping rule developed by Goldman[35] will be used as a guide for early termination due to surgery-related deaths. The trial may be halted if there is evidence that the true mortality rate is increased from an acceptable level of 3% to an upper limit of 10% assuming an alpha level of 5% and power of 80%. The stopping rule requires that early termination be considered if 3 deaths occur in the first 14 or fewer patients or four deaths in the first 31 or fewer patients. Additionally, febrile neutropenia, platelet counts less than 20,000, and diarrhea requiring hospitalization are also of concern. A stopping rule, based on an acceptable level of 10% and upper limit of 20%, requires that early termination be considered if 4 such adverse events occur in the first 4 patients, 5 such adverse events occur in the first 10 or fewer patients, 6 such adverse events in the first 17 or fewer patients, or 7 such adverse events in the first 24 or fewer patients. Delayed time to surgery and delayed wound healing are also of concern and will be reported and tabulated carefully. In order to monitor these events very closely, there will be a weekly telephone call between site PI's, and any events of concern will be immediately disseminated for discussion by all investigators. A monthly report will be generated for distribution to all investigators to update the group on the status of the study and of the patients on the study. Any concerns will receive immediate attention by the PI's.

11.5 **Reporting and Exclusions**

11.6.1 Evaluation of toxicity – All patients will be evaluable for toxicity from the time of their first treatment with FOLFIRINOX

11.6.2 Evaluation of response – All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) completion of all preoperative therapy with a resection; 2) completion of all preoperative therapy but unable to undergo resection; 3) early progressive disease or intolerable toxicity necessitating withdrawal from study, 4) early death from malignant disease, 5) early death from toxicity, or 6) early death because of other cause which results in inability to complete preoperative therapy; 7) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 2-7 should be considered to have a treatment failure. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

If a patient has completed all preoperative therapy, continues to have localized disease only, but is unable to undergo resection for technical reasons, then further treatment with Radiation Therapy and concomitant chemotherapy is encouraged as per standard of care protocols. In the event that a patient should become resectable following this additional treatment, postoperative adjuvant therapy with 4 cycles of mFOLFIRINOX is encouraged. While the patient will be scored as a treatment failure for the specific endpoints of this study, PFS and OS will be determined and tabulated on all such patients.

REFERENCES

[1]Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD,

[2] Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009 Jul;16(7):1727-33.

[3] Ahmed SI, Bochkarev V, Oleynikov D, Sasson AR. Patients with pancreatic adenocarcinoma benefit from staging laparoscopy. J Laparoendosc Adv Surg Tech A. 2006 Oct;16(5):458-63.

[4] Shah D, Fisher WE, Hodges SE, et al. Preoperative prediction of complete resection in pancreatic cancer. J Surg Res. 2008 Jun 15;147(2):216-20

[5] Croome KP, Jayaraman S, Schlachta CM. Preoperative staging of cancer of the pancreatic head: is there room for improvement? Can J Surg. 2010 Jun;53(3):171-4

[6] Soriano A, Castells A, Ayuso C, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol 2004;99:492-501.

[7] Bipat S, Phoa SSK, van Delden OM, et al. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis and determining resectability of pancreatic adenocarcinoma: a metaanalysis. J Comput Assist Tomogr 2005;29:438-45.

[8] Doucas H, Sutton CD, Zimmerman A, et al. Assessment of pancreatic malignancy with laparoscopy and intraoperative ultrasound. Surg Endosc 2007;21:1147-52.

[9] Sohn T, Yeo C, Cameron J et al. Resected adenocarcinoma of the pancreas – 616 patients: results, outcomes and prognostic indicators. J Gastrointest. Surg. 2000;4:567-79.

[10] Geer R, Brennan M. Prognostic indicators for survival after resection of pancreatic adenocarcinoma. Am J Surg. 1993;165:68-72.

[11] Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297:276-77.

[12] Regine W, Winter K, Abrams R, et al. Fluorouracil vs gemcitabine chemotherapy before and

after fluorouracil based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA. 2008;299:1019-26.

[13] Klinkenbijl J, Jeekel J, Sahmoud T et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: a phase III trial of the EORTC gastrointestinal tract cooperative group. Ann Surg. 1999;230:760-82.

[14] Neoptolemos J, Stocken D, Friess H et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350;1200-10.

[15] Palmer DH, Stocken DD, Hewitt H, Markham CE, Hassan AB, Johnson PJ, Buckels JA, Bramhall SR. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol. 2007;**14**:2088–2096.

[16] Hoffman JP, Lipsitz S, Pisansky T, Weese JL, Solin L, Benson AB 3rd. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol. 1998;**16**:317–323

[17] White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, Gottfried MR, Baillie J, Branch MS, Jowell PS, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. Ann Surg Oncol. 2001;**8**:758–765.

[18] Pisters PW, Wolff RA, Janjan NA, Cleary KR, Charnsangavej C, Crane CN, Lenzi R, Vauthey JN, Lee JE, Abbruzzese JL, et al. Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. J Clin Oncol. 2002;**20**:2537–2544.

[19] Yeung RS, Weese JL, Hoffman JP, Solin LJ, Paul AR, Engstrom PF, Litwin S, Kowalyshyn MJ, Eisenberg BL. Neoadjuvant chemoradiation in pancreatic and duodenal carcinoma. A Phase II Study. Cancer. 1993;**72**:2124–2133

[20] Pendurthi T, Hoffman J, Ross E, et al. Preoperative versus postoperative chemoradiation for patients with resected pancreatic adenocarcinoma. Am Surg. 1998;64:686-92

[21]Spitz F, Abbruzzese J, Lee J et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol. 1997;15(3):928-37.

[22] Gillen S, Schuster T, Buschenfelde C, Friess H, Kleeff J. Preoperative/Neoadjuvant therapy in pancreas cancer: A systemic review and meta-analysis of response and resection percentages. PLoS Med April 2010 7:4: 1-14

[23] Evans D, Varadhachary G, Crane C, et al. Preoperative gemcitabin-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008 Jul 20;26(21):3496-3502.

[24] Varadhachary G, Wolff R, Crane C et al. Preoperative gemcitabine and cisplatin followed by gemcitabine based chemoradiation for resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008 Jul 20;26(21):3487-95.

[25] Small W, Berlin J, Friedman G, et al. Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial. J Clin Oncol 2008 Feb 20;26(6):942-7.

[26] Meszoely I, Wang H, Hofman J, et al. Preoperative chemoradiation therapy for adenocarcinoma of the pancreas. The Fox Chase Cancer Center experience, 1986-2003. Surg Oncol Clin N Am 2004;13:685-696

[27] Turrini O, Moureau-Zabotto L, Rouanet P, et al. Neoadjuvant docetaxel based chemoradiation for resectable adenocarcinoma of the pancreas: New neoadjuvant regimen was safe and provided interesting pathologic response. Eur j Surg oncol 2010 oct;36(10):987-92.

[28] Sahora K, Kuehrer I, Eisenhut A, et al. NeoGemOx: Gemcitabine and oxaliplatin as neoaduvant treatment for locally advanced, nonmetastasized pancreatic cancer. Surgery 2010 Sep 2 Epub

[29] Reni M, Cereda S, Balzano G, et al. Outcome of upfront combination chemotherapy followed by chemoradiation for locally advanced pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2009 Nov;64(6): 1253-9

[30] Ohigashi H, IshikawaO, Eguchi H, et al. Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer. Ann Surg 2009 Jul;250(1):88-95

[31] Falcone A, Masi G, Allegrini G, et al. Biweekly chemotherapy with oxaliplatin, irinotecan, infusional fluorouracil, and leucovorin: a pilot study in patients with metastatic colorectal cancer. JCO 2002 Oct 1;20 (19):4006-14.

[32] Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer – a Group Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. JCO 23;(6) 2005:1228-1236

[33] Breysacher G, Kaatz O, Lemarignier C, et al. Safety and efficacy of FOLFIRINOX in metastatic pancreatic cancer after first line chemotherapy. GI ASCO 2010 abstr 269

[34] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. NEJM May 2011: 364;19 1817-1825.

[35] Goldman AI: Issues in designing sequential stopping rules for monitoring side effects in clinical trials. Control Clin Trials 8: 327-337, 1987.