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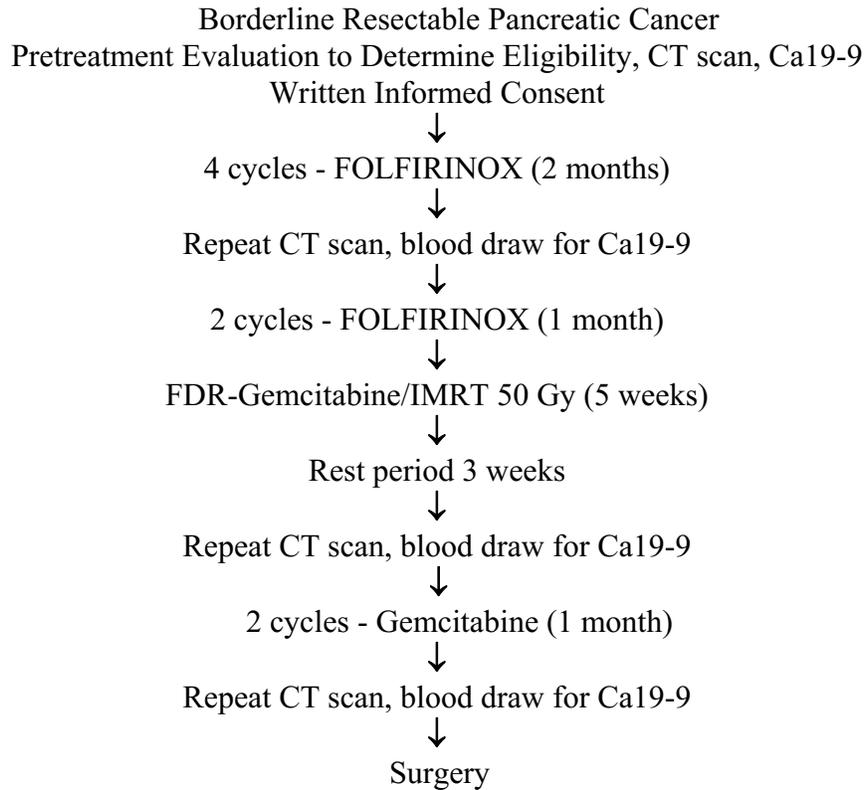
A Phase II Study of Neoadjuvant FOLFIRINOX and FDR-Gemcitabine with
Concurrent IMRT in Patients with Borderline Resectable Pancreatic Cancer

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SCHEMA



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

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1.0 OBJECTIVES

1.1 Primary Objective

To determine the frequency of achieving an R0 resection using a neoadjuvant regimen of FOLFIRINOX followed by IMRT concurrent with fixed dose rate (FDR)-gemcitabine in patients with borderline resectable pancreatic cancer.

1.2 Secondary Objectives

- 1.2.1 To estimate progression-free survival and overall survival as a function of time from study enrollment.
- 1.2.2 To evaluate tolerability and toxicity of the protocol treatment
- 1.2.3 To determine the primary tumor response rate to neoadjuvant chemotherapy alone and following combined modality treatment

2.0 BACKGROUND

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 pancreas cancer 4th among causes of cancer death¹. A practical staging system for pancreas 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 chemotherapy²⁻⁴. 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, fail with hepatic metastases.

Locally advanced unresectable disease

More often, patients present with disease that is localized but unresectable. This designation and frequency at presentation reflects the anatomic location of the pancreas and specifically the proximity to major intra-abdominal blood vessels. Median survival in this group of patients averages 6-11 months, with some suggestion of improvement for patients treated with combinations of radiation and/or chemotherapy^{7, 8}.

Advanced metastatic disease

Patients presenting with evidence of distant metastasis at diagnosis are offered treatment with palliative chemotherapy. Gemcitabine has defined systemic therapy for pancreas cancer for most of the past decade. A pivotal study randomized 126 patients with advanced, symptomatic pancreas cancer to either weekly gemcitabine 1000 mg/m² over 30 minutes or weekly bolus 5FU 600 mg/m² using clinical benefit response (CBR) as the primary endpoint⁹. 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 pancreas cancer has utility, enthusiasm is muted considering the limited benefit it provides.

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 recurrence¹⁰⁻¹². Consequently, it is rational to provide chemotherapy and/or radiation with the intent of increasing the likelihood of a subsequent margin negative resection.

Historically, the rate of 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 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 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 survival post-surgery similar to that achieved in upfront resectable disease¹⁷. This suggests a significant value to neoadjuvant therapy that aides in obtaining an R0 resection in borderline resectable disease.

There is currently no standard therapy approach for borderline resectable pancreas cancer. The goal of this study is to improve outcomes in patients with borderline resectable disease utilizing a planned course of neoadjuvant treatment designed to optimize R0 resection rate and local disease control using chemoradiation and control of distant disease using combination chemotherapy.

Neoadjuvant therapy

In 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 (R₂ resections)^{18, 19}. Median survivals in patients with R₁ or R₂ 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 resectability¹². We have successfully and safely resected patients following gemcitabine based chemoradiotherapy²⁰⁻²². 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 postoperative chemotherapy was 46 days and for combined modality treatment 61 days⁴. 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 no benefit.

There are barriers to neoadjuvant treatment. These include biliary obstruction with a requirement for decompression of the biliary system, as well as a need to confirm diagnosis prior to treatment. Practical barriers to neoadjuvant therapy in this disease also include emotion, a desire by the patient and caregivers to have the tumor removed “before it’s too late.” Data do not support the concern of disease becoming unresectable during neoadjuvant therapy. Reports from two consecutive neoadjuvant trials from MD Anderson describe only one isolated local progression in more than 150 patients^{13, 23}.

Optimization of local disease control using chemoradiation

In order to optimize local control of disease in borderline pancreas cancer, chemoradiation can be given neoadjuvantly. Chemoradiation for pancreas cancer has historically incorporated 5-fluorouracil. Gemcitabine has greater systemic efficacy than 5-fluorouracil in pancreas 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}. Beginning in 1997, gemcitabine-based chemoradiation has been developed at the University of Michigan with a fundamentally different approach. Full dose gemcitabine is used to capitalize on maximal systemic efficacy and laboratory data that demonstrate maximum radiosensitization when cytotoxic concentrations of drug are used²⁶. Locoregional toxicity has been addressed by limiting the radiation field to the primary tumor alone and titrating the radiation dose. Over the subsequent decade, the advent of IMRT has allowed further escalation of radiation dose delivered to tumor. We are currently nearing completion of a phase I/II trial in patients with localized unresectable disease evaluating escalating doses of radiation delivered by IMRT with fixed-dose rate gemcitabine 1000mg/m². Based on preliminary results of efficacy and tolerability, we have selected a radiation dose of 50Gy delivered by IMRT in combination with gemcitabine given by fixed-dose rate. Among 50 patients with unresectable disease treated with this protocol, 10 were able to undergo resection with a 90% R0 resection rate suggesting significant efficacy in obtaining local control with this regimen.

Fixed-dose rate gemcitabine

Gemcitabine has traditionally been given as a rapid infusion over 30 minutes. However, accumulation of active phosphorylated metabolites of gemcitabine is dependent on infusion rate and can be optimized at a rate of 10mg/m²/min²⁷. Translation of increased active metabolite delivered by this fixed dose rate infusion to increased efficacy has been tested clinically. A phase II trial comparison of 1500mg/m² gemcitabine delivered by fixed dose rate with 2,200mg/m² given over 30 minutes yielded a median survival of 8 months vs. 5 months, respectively ($p=.013$)²⁸. A larger phase III trial compared gemcitabine 1500mg/m² given at a fixed dose rate with or without oxaliplatin (two separate arms) were compared to a single control arm of gemcitabine 1000mg/m² given over 30 minutes. Patients that received gemcitabine by fixed dose rate had an approximately 1-month increase in overall survival but this did not reach statistical significance²⁹.

Optimization of distant disease control using chemotherapy

Gemcitabine has been the cornerstone of systemic therapy for pancreas cancer over this past decade. Recently, a combination of 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) was reported to have significant efficacy in advanced pancreatic cancer. Preclinical data suggests synergy between irinotecan and 5FU as well as between oxaliplatin and 5FU. Results of a phase II trial in advanced disease were reported in 2005 demonstrating a 26% confirmed response rate and median overall survival of 10.2 months³⁰. A follow-up phase III trial comparing FOLFIRINOX with gemcitabine for patients ≤ 75 years of age with advanced pancreatic cancer was presented at ASCO 2010 revealing improvement in PFS (6.4 vs. 3.3 months, $p<.0001$) and improved disease control rate (CR+PR+SD) (70.2% vs. 50.9%, $p=.0003$). The most notable result was an impressive improvement in median overall survival with FOLFIRINOX compared to gemcitabine (11.1 vs 6.8 months, $p\text{-value} = <.0001$, HR=.57). The main toxicity was grade 3/4 neutropenia (45.7% vs. 18.7%, $p=.0001$) and increased risk of febrile neutropenia (5.4% vs. 0.6%, $p=.009$)³¹.

We hypothesize that the combination of the FOLFIRINOX regimen to provide maximal systemic disease control and FDR-gemcitabine with concurrent IMRT to address local disease, will achieve a significant improvement R0 resection rate in borderline resectable pancreatic cancer and enhance disease free and overall survival in this patient population.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients must have cytologic or histologic confirmation of carcinoma arising in the pancreas. Patients with neuroendocrine tumors are excluded.
- 3.1.2 Patients must be deemed to have borderline resectable disease (as defined in Table 1 below, adapted from NCCN Practice Guidelines in Oncology – v.2.2010) with no radiologic evidence of distant metastatic disease prior to registration. Specifically, patients must have at least one designation of borderline resectable and no designation of unresectable disease.
- 3.1.3 Patients must have a life expectancy of at least 12 weeks, a

Zubrod performance status of ≤ 1 and be willing and medically able to undergo surgical resection.

- 3.1.4 Patients must have adequate organ function defined as follows: absolute neutrophil count of $\geq 1500/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$, serum Cr ≤ 1.5 mg/dl, total bilirubin < 2.0 mg/dl with relief of biliary obstruction if present (PTC tube or endobiliary stent).
- 3.1.5 Patients must be free of other active systemic malignancy, ongoing infection, or any other serious uncontrolled, concomitant systemic disorders or psychiatric condition that would interfere with the safe delivery of protocol therapy.
- 3.1.6 Patients with preexisting peripheral neuropathy \geq grade 2 are ineligible.
- 3.1.7 Pregnant or nursing women are ineligible and patients of reproductive potential must agree to use an effective contraceptive method during participation in this trial due to the unacceptable teratogenic toxicity of abdominal radiation and cytotoxic chemotherapy.
- 3.1.8 Patients must be aware of the investigational nature of the therapy and provide written informed consent.
- 3.1.9 Patients must have no history of previous chemotherapy for pancreatic cancer or any abdominal radiation therapy.
- 3.1.10 Patients may not have used any investigational agent within 4 weeks prior to enrollment into the study.

Table 1

SMV/PV: no contact	resectable
SMV/PV: contact <180 degrees without deformity	borderline
SMV/PV: contact <180 degrees with deformity	borderline
SMV/PV: contact ≥ 180 degrees w/o encasement of nearby arteries	borderline
SMV/PV: vessel occlusion short segment reconstructable	borderline
SMV/PV: vessel occlusion not reconstructable	unresectable
SMA: no contact	resectable
SMA: contact <180 degrees	borderline
SMA: contact ≥ 180 degrees	unresectable
Celiac axis: (head): no contact	resectable
Celiac axis: (head): any contact	unresectable
Celiac axis: (body/tail): no contact	resectable
Celiac axis: (body/tail): contact <180 degrees	borderline
Celiac axis: (body/tail): contact ≥ 180 degrees	unresectable

Hepatic artery: no contact	resectable
Hepatic artery: contact amenable to resection or reconstructable	borderline
GDA contact > 180 degrees up to hepatic with either short segment encasement or direct abutment of the hepatic artery without extension to celiac axis	borderline
Hepatic artery: contact not amenable to resection or reconstructable	unresectable

3.2 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

To register a patient a copy of eligibility checklist with supporting documents and the signed patient consent form will be forwarded to the responsible data manager. The data manager will verify eligibility. To complete the registration process, the data manager will assign a patient study number, register the patient on the study and contact the treating investigator to confirm registration.

5.0 TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for 5-Fluorouracil (5FU), irinotecan, oxaliplatin and gemcitabine are described in Section 7. Appropriate dose modifications for 5FU, irinotecan, 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 m-FOLFIRINOX

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

Starting dose levels as following:

Oxaliplatin 85mg/m² intravenously over 120 minutes on day 1.

Irinotecan 180mg/m² intravenously over 90 minutes on day 1.

5FU 2,400mg/m² infused intravenously as a continuous infusion over 46 hours following the bolus 5FU, beginning on day 1.

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

Dose adjustments for toxicities may be found in Section 6.3

5.3 Gemcitabine during Radiation Therapy

Combined modality treatment will begin approximately 3 weeks after last FOLFIRINOX administration provided ANC $\geq 1,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$ and all other treatment related toxicity has resolved to \leq grade 1.

Gemcitabine $1000\text{mg}/\text{m}^2$ infused over 100 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 6.5 and will be based on complete blood count the day treatment is due 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 Gemcitabine following Radiation Therapy

Two cycles (infusions) of gemcitabine alone are intended to be given, the first 21 to 28 days following completion of combined modality treatment.

A cycle of treatment is 14 days. A cycle of treatment may begin when ANC $\geq 1,000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$ and all other treatment related toxicity has resolved to \leq grade 1.

Treatment may be delayed for up to 2 weeks from time that a cycle is due, after which time that cycle of treatment will be dropped and not made up if conditions for treatment are not met.

Gemcitabine dosing is as follows:

Gemcitabine $1,000\text{mg}/\text{m}^2$ intravenously over 100 minutes on day 1. **Note:** If patient required treatment interruption and subsequent dose reduction of gemcitabine during combined modality therapy, then starting dose for gemcitabine following radiation therapy will be reduced per section 6.4.

5.5 Radiation Treatment

5.5.1 Radiation Dose

The prescribed dose will be 50.0Gy in 2.0Gy per fraction. Heterogeneity of -5% to +10% is permitted provided that normal-tissue constraints are met. The minimal PTV dose is dictated by the normal-tissue constraints. A maximal PTV dose of up to +10% is permitted provided that normal-tissue constraints are met. The mean PTV dose should be as close as possible to 50 Gy.

Intensity-modulated radiotherapy (IMRT) will be planned based on a helical CT obtained in the treatment position following administration of oral and double-phase intravenous contrast. The treatment-planning CT scan will be obtained prior to initiation of the run-in chemotherapy whenever possible. For patients in which IV contrast is contraindicated based on severe allergy or decreased renal function, an MRI scan of the abdomen or CT without contrast should be performed.

5.5.2 Treatment Volumes

The gross tumor volume (GTV) will be the primary tumor plus any involved regional lymph nodes identifiable on CT scan.

The clinical target volume (CTV) will be defined as the GTV plus 0.5 cm.

The planning target volumes (PTV) will be the CTV plus 0.5 cm.

The normal structures to be contoured are: left and right kidneys, liver, stomach, duodenum, small intestine, spinal cord

5.5.3 Breathing and target motion management

Management of motion is mandatory. The use of Active Breathing Control (ABC) is preferred. The device should be used during acquisition of images and during treatment to reduce/eliminate breathing motion. Other acceptable methods include tracking or gating using an implanted pancreatic fiducial. If none of these methods is feasible, the Radiation Oncology co-investigator, Dr. Edgar Ben-Josef, should be contacted to discuss. Rarely, other methods may be deemed reasonable and would be allowed.

5.5.4 Normal-tissue dose-volume constraints

Structure	Constraints
Kidney(L & R)	Max dose $\leq 18\text{Gy}$; not more than 10% of the volume can be between 16 and 18Gy
Liver	Mean dose $\leq 30\text{ Gy}$; Minimize mean dose or NTCP
Stomach Small intestine	Max dose $\leq 50\text{Gy}$; 25% of the volume can be between 45 and 50Gy
Spinal cord	Max dose $\leq 45\text{Gy}$
Duodenum	Max dose $\leq 50\text{Gy}$; not more than 33% of the volume can be between 45 and 50Gy

5.5.5 Beam Arrangement

The following beam arrangement is recommended. In our experience, this arrangement results in excellent dose distributions that are hard to supersede. However, modifications are allowed if they result in a more favorable dose distribution.

Couch Angle	Gantry Angle
0	350
0	90
0	30
0	310
90	20
90	330

5.6 Duration of Therapy

Protocol treatment is defined as six cycles of FOLFIRINOX followed by gemcitabine and IMRT, then two further cycles of gemcitabine. Surgical exploration and an attempt at resection will be offered to all patients unless there is evidence of distant metastatic disease.

Patients will remain on protocol therapy until completion unless;

Intercurrent illness that prevents further administration of treatment

Unacceptable adverse events(s) despite protocol therapy interruption and dose modifications

Patient decision to withdraw from the study

General or specific changes in the patient's condition rendering the patient unacceptable for further treatment in the judgment of the investigator.

Development of distant metastatic prior to surgical treatment

5.7 Re-evaluation following 4 cycles of folfirinox chemotherapy

Patients will undergo repeat imaging including CT scan (or MRI) to evaluate for response/disease progression. It is anticipated that the large majority of patients will proceed to two additional cycles of chemotherapy, followed by combined radiation and chemotherapy after cycle 6, or if development of distant metastatic disease, patient will be off protocol therapy per Section 5.6.

5.8 Re-evaluation following combined chemotherapy and radiation

Patients will undergo repeat imaging including CT scan (or MRI) 3-4 weeks following completion of radiation to evaluate for response/disease progression. Patients without evidence of distant progression will continue with two more cycles of gemcitabine alone. If distant metastatic disease is demonstrated, patients will be

off protocol per section 5.6.

5.9 Re-evaluation following 2 additional cycles of chemotherapy

Patients will undergo repeat imaging including CT scan (or MRI) scan for final response evaluation and resectability. Patients will be discussed at the multi-disciplinary tumor conference. Patients without evidence of distant disease will be offered surgical exploration. Patients not offered surgery or with distant metastatic progressive disease will be off protocol treatment per section 5.6.

5.10 Surgical Therapy

The surgical procedure performed will be that required for complete resection as per the judgment of the operating surgeon. Generally, surgery should take place approximately 4-6 weeks following last chemotherapy administration. If surgery is delayed, imaging within 28 days of the surgery date will be available as clinically indicated, to confirm no distant disease precluding curative intent resection. Information regarding any surgical therapy will be recorded including the operation performed, whether vascular resection and reconstruction was required, completeness of the resection (R₀, R₁ or R₂), duration of the operation, blood loss, the length of stay and the need for re-admission within 30 days of surgery.

5.11 Duration of Follow Up

Following completion of protocol therapy and surgery, resected patients will undergo surveillance multi-slice spiral CT scans of abdomen at approximately 12, 18 and 24 months from protocol entry and/or as clinically indicated. Patients will be evaluated with interval history and physical examinations as well as CA 19-9 measurements at 3 month intervals to the 24 month assessment. Follow-up beyond two years will not be protocol directed but survival and disease free survival information will be collected. All evaluable patients will be followed until death. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

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 reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>).

6.1 General Considerations – m-FOLFIRINOX treatment

- a. A new cycle of treatment may begin when the ANC is $\geq 1,000/\text{mcl}$, the platelet count is $\geq 75,000/\text{mcl}$, and any treatment-related GI toxicity is resolved to \leq Grade 1.

- b. If the initiation of a new 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 \geq grade 3 neutropenia.
- d. Dose reductions for the agents in the m-FOLFIRINOX combination are as follows:

AGENT	INITIAL DOSE	Level -1	Level -2	Level -3
Irinotecan	180 mg/m ²	140 mg/m ²	110 mg/m ²	90 mg/m ²
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 accountable 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.

Agent(s) or FOLFIRINOX combination therapy will be discontinued if more than three dose reductions for toxicity are needed.

6.2 Supportive Care

White blood cell colony stimulating factors will not be administered as primary prophylaxis following the first cycle of FOLFIRINOX administration.

Subsequent growth factor use will be at the discretion of the treating physician.

6.3 Dose Modifications

- a. Dose modifications for toxicities during FOLFIRINOX

i. Hematologic Toxicities

	Dose Modification
ANC <1000/mm ³ And/or Platelets <75,000/mm ³	Hold all chemotherapy and re-evaluate weekly. When toxicity permits, treatment will be continued with one level dose reduction of irinotecan and oxaliplatin.

*Note: for platelets 75,000 – 99,000 continue FOLFIRINOX but 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 and antibiotic treatment of the event is completed. When treatment resumes, reduce agents one level including infusional 5FU if diarrhea and/or stomatitis are part of the adverse event profile
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*Note: 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 reduction in 5FU infusion and irinotecan 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 infusion and irinotecan 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 or irinotecan for neuropathy.

6.4 Other non-hematologic toxicities attributable to 5-FU, irinotecan, and/or oxaliplatin.

For all other \geq 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 \leq Grade 1 within 4 weeks, treatment may resume with 5-FU, irinotecan, and oxaliplatin at one lower dose level.

6.5 Dose modifications for toxicities during combined modality therapy (IMRT/Gemcitabine)

Agent	Initial Dose	Level -1	Level -2	Level -3
Gemcitabine*	1,000 mg/m ²	750 mg/m ²	600 mg/m ²	500 mg/m ²

*Note: all infusions by fixed dose rate 10 mg/m²/minute

Gemcitabine and IMRT may begin when the ANC is \geq 1,000/mcl, the platelet count is \geq 100,000/mcl, and any treatment-related toxicity to folfirinox is resolved to \leq Grade 1.

During combined modality treatment, gemcitabine will be given days 1, 8, 22 and 29 as per UMCC 06.018.

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

- i. Hematologic toxicity - dose adjustments of gemcitabine will be made based on the ANC and platelet counts taken on the day of therapy.

For ANC \geq 1,000 /mm³ and platelets \geq 75,000/mm³, full dose due will be given

For ANC of 500- 999/mm³ and/or platelets of 50,000 to 74,999/mm³, 50% of the gemcitabine dose due will be given.

For 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.

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

- ii. Hematologic toxicity - dose adjustments of gemcitabine will be made based on the ANC and platelet counts taken on the day of therapy.

For ANC \geq 1,000 /mm³ and platelets \geq 75,000/mm³, full dose due will be given

For 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.

For 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.

- iii. Non-hematologic toxicity- Dose adjustments of chemotherapy will be made following assessment of non-hematologic toxicity on the day of therapy.

Chemotherapy will be held for \geq Grade 3 toxicity in any organ system. 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.

- iv. 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.

6.6 Dose Modification for Gemcitabine following Radiation Therapy

There will be no modification of doses for these two cycles (infusions). The dose level of gemcitabine will be that given on day 22 of combined modality treatment, unless treatment had to be interrupted on or before day 29 for toxicity, in which case the investigator may choose to further reduce gemcitabine one dose level.

A cycle of treatment is 14 days. A cycle of treatment may begin when ANC \geq 1,000/mm³, platelets \geq 100,000/mm³ and all other treatment related toxicity has resolved to \leq grade 1.

Treatment may be delayed for up to 2 weeks after which time that cycle of treatment will be dropped and not made up if conditions for treatment are not met.

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 as in the best interest of the patient.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1 Adverse Event Lists for Commercial Agents

- a. 5FU - Please refer to package insert for comprehensive list of adverse events. Side effects include anorexia, nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, nosebleed, stomatitis, esophagopharyngitis, alopecia, myelosuppression, maculopapular eruptions, dermatitis, fingernail changes, dry skin, hyperpigmentation, photosensitization, palmar-plantar erythrodysesthesia syndrome as manifested by tingling of the hands and feet followed by pain, erythema and swelling, acute cerebellar syndrome including ataxia, dizziness, and slurred speech; visual changes, lacrimation, uncontrolled eye movements, headache, myocardial ischemia, thrombophlebitis, angina, anaphylaxis, generalized allergic reaction, disorientation, confusion and euphoria.
- b. Irinotecan - Please refer to package insert for comprehensive list of adverse events. 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.
- c. Oxaliplatin - Please refer to package insert for comprehensive list of adverse events. The most common toxicities associated with oxaliplatin include fatigue, neutropenia, nausea, vomiting, diarrhea and neuropathy. An acute, reversible, primarily peripheral, sensory neuropathy of early onset and exacerbated by cold exposure is recognized. An acute syndrome of pharyngolaryngeal dysesthesia is seen in 1-2% of patients characterized by subjective sensation of dysphagia or dyspnea. A persistent primarily peripheral, cumulative dose sensory neuropathy characterized by paresthesias, dysesthesias, hypoesthesias and deficits in proprioception is also seen. Anaphylactic-like reactions have been reported and may occur within minutes of oxaliplatin administration. Fever, pain at the site of infusion, dehydration and electrolyte disturbances are not uncommon. Much less commonly, pulmonary fibrosis, renal dysfunction, and hemolytic-uremic syndrome have been reported.
- d. Gemcitabine - Please refer to package insert for comprehensive list of adverse events. Myelosuppression is the principal dose-limiting factor with gemcitabine therapy including leukopenia, thrombocytopenia and anemia. Non-hematologic toxicities include reversible hepatic enzyme elevations, gastrointestinal toxicity (nausea, vomiting, diarrhea, stomatitis), fever in the absence of infection, flu-like syndrome, rash, and peripheral edema. Rarely hemolytic-uremic syndrome, drug-induced pneumonitis and sepsis have been reported.
- e. Pregnancy and Lactation: Chemotherapy has been shown to cross the placenta and enter into fetal circulation in the rat. Administration of

chemotherapy has resulted in increased resorptions and embryolethality in rats. Also, in monkeys, chemotherapy results in abortion of embryos exposed. Because chemotherapy inhibits DNA, RNA and protein synthesis, adverse effects on peri and postnatal development might be expected and mothers should not nurse while receiving these drugs.

7.2 Reporting of Serious Adverse Events

All serious, unexpected adverse events possibly related to treatment should be reported as soon as possible and no later than 7 calendar days of knowledge of the event.

A serious adverse event is one that meets any of the following criteria:

- death
- initial or prolonged inpatient hospitalization
- life-threatening
- severe or permanent disability
- congenital anomaly
- is significant or unexpected for other reason

The following adverse events are excluded from SAE reporting:

Death > 30 days beyond protocol therapy completion where death of a patient is due to progression of the patient's cancer

Hospitalization under the following circumstances:

Hospitalization is secondary to expected cancer morbidity:

- Admission for palliative care or pain management
- Admission for management of biliary obstruction, or cholangitis
- Admission for management of deep venous thrombosis or pulmonary embolism.

Planned hospitalizations for surgical procedures.

Morbidity or mortality from surgical exploration and/or resection.

Common toxicities observed secondary to therapy, progressive disease and events secondary to progressive disease are generally excluded from reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

The University of Michigan will report unexpected, possibly, probably and definitely related to treatment SAEs to FDA, as appropriate.

Safety

US Regulations require that a sponsor reports Serious Adverse Events (SAEs) occurring with use of its product in a clinical trial if it is unexpected, and felt to be related to use of the drug. During the conduct of Investigator Initiated Trials (IITs), all SAEs that occur will be evaluated by the investigator for reportability to FDA. An Adverse Event should be identified, Serious Adverse Event and Expectedness determined and causality assessed by the investigator using the definitions that follow:

Definitions

An **Adverse Event** is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment.

A **Serious Adverse Event** is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
- Requires in-patient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect, or
- Is a medically important event:

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Note: The term "life-threatening" in the definition of "Serious Adverse Event" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

An **Unexpected Adverse Event** is not listed in the current Clinical Investigator's Brochure (CIB) / Package Insert or an event that may be mentioned in the CIB / Package Insert, but differs from the event because of greater severity or specificity.

For comparative drugs, expectedness is determined by using the pertinent reference text: the US Package Insert.

Causality is a determination of whether there is a reasonable possibility that the drug may have

caused or contributed to an adverse event. It includes assessing temporal relationships dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) or a lack of one or more likely causes.

Pregnancy Guidance

During the course of the trial, all female patients of childbearing potential should be instructed to contact the treating physician immediately if they suspect they might have conceived a child. In addition, a missed or late menstrual period should be reported to the treating physician. If a female patient, or an investigator, suspects a pregnancy prior to administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the patient must not receive study medications and must be withdrawn from the study.

Throughout the entire pregnancy, additional contact should be made with the patient, and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the study investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

If a male patient is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the risk to the fetus. In addition, the treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

Upon live-birth delivery, minimum information that should be collected includes date of birth, length of pregnancy, sex of infant, major and minor anomalies identified at birth. Outcomes can be obtained via mailed questionnaires, maternal interviews, medical record abstraction, or a combination of these methods.

8. PHARMACEUTICAL INFORMATION

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

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 unopened vials at room temperature and protect from light.
- e. Supplier – 5-FU is commercially available.

8.2 Irinotecan (CPT-11)

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

- a. Description – Irinotecan hydrochloride trihydrate [CPT- 11, (4S)-4, 1 1- diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy] -1Hpyroano [3',4':6, 7] indolizino [1,2-b] quino line-3, 14(4H, 12H)dione hydrochloride trihydrate] is a topoisomerase I inhibitor.
- b. Pharmaceutical Data – 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. Formulation: The drug is supplied as 20mg/mL solution in 2, 5, 25 mL vials.
- c. Administration – Irinotecan must be diluted prior to administration in D5W (preferred) or 0.9% sodium chloride to a final concentration of between 0.12 to 0.28 mg/mL. When diluted in D5W, and stored refrigerated (at 2-8C) protected from light, the solution is physically and chemically stable for 48 hours. Irinotecan is infused intravenously over 90 minutes. Other drugs should not be added to the bag.

- d. Storage and Stability - Irinotecan vials must be stored at room temperature (15-30° C) protected from light. Irinotecan is stable for 24 hours in glass bottles or plastic bags after reconstitution with D5W.
- e. Supplier – Irinotecan is commercially available.

8.3 Oxaliplatin

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

- a. Description – Oxaliplatin (cis-[(1R,2R)-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 monoquo 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 aqueous solution at 25o 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

8.4 Gemcitabine

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

- a. Description – Gemcitabine hydrochloride (2',2'-difluoro-2'deoxyctidine) is a deoxyctidine 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. To reconstitute, add 5 mL of sodium chloride 0.9% injection to the 200 mg vial or 25 mL of sodium chloride 0.9% injection to the 1 g vial to a concentration of 38mg/mL. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% sodium chloride solution or dextrose 5% solution to concentrations as low as 0.1 mg/mL. Gemcitabine 0.1 and 10 mg/mL solutions diluted with sodium chloride 0.9% injection or dextrose 5% injection are chemically stable for up to 35 days at room temperature or under refrigeration when stored in polyvinyl chloride bags. Because these solutions contain no preservative, they should be used within 24 hours of preparation.
- c. **Administration** – Intravenous infusion over 100 minutes.
- d. **Storage and Stability** – Store at controlled room temperature.
- e. **Supplier** – Gemcitabine is commercially available

9.0 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 of start of therapy.

	Pre-Study	Cycles 1-4	Re-Eval	Cycles 5-6	Chemo XRT	Re-Eval	Cycles 7-8	Re-Eval	Surgery	Post
Performance Status	X	X	X	X	X	X	X	X		X
History/Physical	X	X	X	X	X	X	X	X		X
CBC,diff, plts ^a	X	X	X	X	X	X	X	X		X
Serum Chemistry ^b	X	X	X	X	X	X	X	X		X
Ca 19-9	X		X			X		X		X
Urine/serum pregnancy ^c	X									
CT chest/abdomen ^d	X		X			X		X		X
Tumor Measurement	X		X			X		X		
Surgery									E	
Radiation					B					
5FU, Irinotecan, Oxaliplatin		A		A						
Gemcitabine					C		D			
Toxicity Evaluation		X	X	X	X	X	X	X		X

^a prior to chemotherapy administration, at re-evaluation visits and per post treatment follow-up

^b comprehensive chemistry panel to include albumin, alkaline phosphatase, ALT or AST, glucose, total bilirubin, creatinine and electrolytes

^c in women of childbearing potential only

^d at intervals post treatment noted in section 5.11

A FOLFIRINOX section 5.2

B IMRT section 5.5

C FDR-gemcitabine section 5.3

D FDR-gemcitabine section 5.4

E Surgical exploration/resection see section 5.10

Post therapy follow-up at 3-month intervals through 2 years. 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

Any of above with vascular resection and reconstruction

Exploratory laparotomy (no resection)

With gastric bypass

With biliary bypass

With both

Duration of operation, Blood loss, Complete resection

Pathologic findings; Tumor size, Grade, Nodal status

Microscopic assessment of margins, including retroperitoneal margin (R₀ vs. R₁ vs. R₂)

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, University of Michigan 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. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Study Monitoring

- a. Study Forms - University of Michigan will maintain on-study forms, eligibility checklists, flow sheets and off-study forms for each patient entered in the study database
- b. Data and Safety Monitoring Committee

Composition of the Committee

This committee will be comprised of the Principal Investigator, co-Investigators (if available) and data manager, the Study Coordinator and the protocol's Statistician.

Scheduled Meetings

The committee will hold monthly data and safety monitoring meetings. Participants will include, whenever possible, the investigator(s), data manager, and statistician. Minutes from these meetings will be submitted to the Cancer Center DSMB.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

Definition of primary endpoint

Any eligible patient who receives at least one dose of chemotherapy according to the protocol will be considered evaluable for the primary study endpoint. R0 resection will be defined as gross total resection with pathology review demonstrating margins negative for microscopic disease.

12.2 Definition of secondary endpoints

Progression-Free Survival: Time from date of registration to the date of documented progressive disease, development of distant metastatic disease, non-protocol disease related therapy, death, or recurrence following surgical resection whichever occurs first. Patients who experience therapy related death will be considered to have experienced a PFS-event. Otherwise, the patient will be considered censored at last follow-up.

Overall Survival: Time from date of registration to date of death or last follow up whichever occurs first. Death regardless of cause will be considered an event. Otherwise, the patient will be considered censored at last follow-up.

Toxicity: Toxicity encountered during the study will be evaluated using the NCI Common Toxicity Criteria Version 4.0. Patients receiving any treatment will be evaluable for toxicity.

12.3 Sample Size/Accrual Rate

Thirty-one patients meeting eligibility criteria will be accrued and treated on this clinical trial. The sample size is based upon the statistical testing of the primary study hypothesis, the R0 resection rate following the neoadjuvant treatment regimen. Previous clinical experience treating borderline resectable pancreatic cancer patients with chemotherapy and chemoradiotherapy in the neoadjuvant setting yielded a 30% R0 rate at time of surgery. With the addition of the FOLFIRINOX chemotherapy regimen, we hope to improve the R0 rate to 55%. Thirty-one patients are necessary to test that hypothesis using a two-sided test with 5% type I error and 20% type II error (80% power). The University of Michigan historically sees 400 new patient consultations for pancreatic cancer per year. Between 10 and 15% of those patients are deemed to have borderline resectable disease. We therefore anticipate between 40 and 60 patients per year will be eligible for this protocol. Due to dismal survival rates in this lethal disease and the lack of a widely accepted standard of care, it is our experience that patients have strong interest in participating in clinical trials. Given that we have no competing trial for this patient population, we anticipate completing accrual to this study in 62 months.

12.4 Analysis of Endpoints

Analytic plan for primary objective: Since the primary study endpoint will be determined in some patients only after several months, halting enrollment for formal interim outcome monitoring will result in significant gaps in accrual and increase total study duration. We, therefore, plan to enroll in a single stage, 31 patients evaluable for the primary endpoint. The R0 rate and exact 90% binomial confidence interval will be reported.

Analytic plan for secondary objectives: Progression-Free Survival and Overall Survival as a function of time since enrollment will be estimated according to the method of Kaplan and Meier³².

Toxicity - The proportion of treated patients experiencing any clinically significant (Grade 3 or worse) toxicity will be determined; specific toxicities of all grades will be tabulated.

12.5 Interim stopping rules: It is important for the utility of this treatment regimen, that neoadjuvant FOLFIRINOX be tolerated, as to not delay initiating chemoradiation and surgery. Although some chemotherapy treatment related delays are expected, as outlined in Section 6, a high proportion of patients should complete adjuvant FOLFIRINOX chemotherapy on schedule. We expect, that at least 2/3 (66.7%) of patients should begin cycle 3, day 1 (C3D1) of neoadjuvant FOLFIRINOX chemotherapy between days 29 and 43 on protocol (days from C1D1). In order to assess this expectation, we will conduct an interim analysis for chemotherapy delay after 15 patients (approximately 50% of our required sample size) have been treated on trial. If less than 7 patients have received D1C3 by day 43 on protocol, we will close the trial to new accrual. If 7 or more patients have reached the D1C3 treatment milestone, then the trial will continue until 31 evaluable patients have been treated on study. The stopping-rule is based upon the exact binomial confidence interval. When 6 or fewer patients can reach this treatment milestone, the 90% confidence interval excludes 66.7%, our minimum expectation. The following table indicates the probability the trial will stop due to this rule for various levels for the true probability of reaching the C3D1 treatment milestone.

Probability of patients having C3D1 by day 43	Probability of stopping at interim analysis
0.35	0.75
0.40	0.61
0.45	0.45
0.50	0.30
0.55	0.18
0.60	0.10
0.65	0.04
0.70	0.02

12.6 Reporting and Exclusions

Evaluation of toxicity - All patients will be evaluable for toxicity from the time of their first treatment with protocol therapy.

Evaluation of response - Patients will be evaluable for the primary endpoint if they receive any protocol therapy. Patients will remain evaluable for the primary endpoint regardless of any reason for discontinuation from the protocol including but not limited to: death, withdrawal due to toxicity, and voluntary withdrawal.

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