Title: Neoadjuvant Modified FOLFIRINOX and Stereotactic Body Radiation Therapy in Borderline Resectable Pancreatic Adenocarcinoma

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PHASE II STUDY TO EVALUATE NEOADJUVANT MODIFIED FOLFIRINOX AND STEREOTACTIC BODY RADIATION THERAPY IN BORDERLINE RESECTABLE PANCREATIC ADENOCARCINOMA

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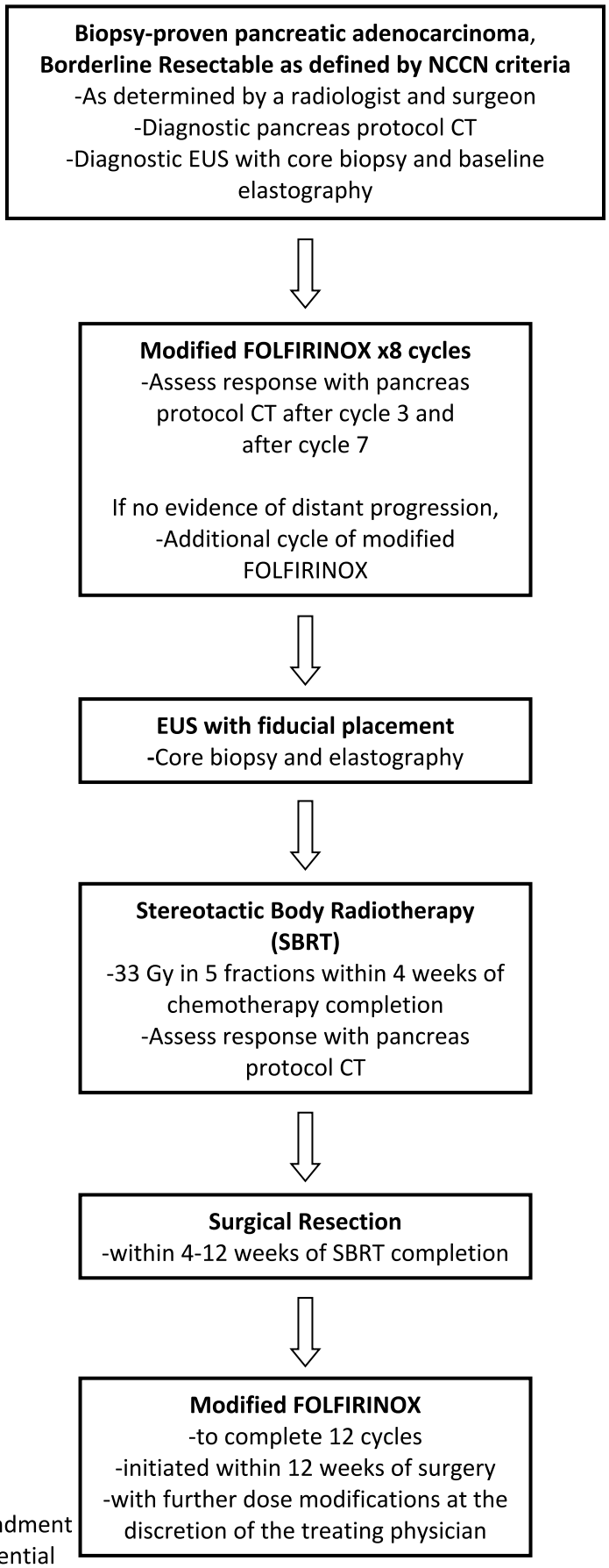
SCHEMA


Biopsy-proven pancreatic adenocarcinoma,
Borderline Resectable as defined by NCCN criteria
-As determined by a radiologist and surgeon
-Diagnostic pancreas protocol CT
-Diagnostic EUS with core biopsy and baseline elastography
Modified FOLFIRINOX x8 cycles
-Assess response with pancreas protocol CT after cycle 3 and after cycle 7
If no evidence of distant progression,
-Additional cycle of modified FOLFIRINOX
EUS with fiducial placement
-Core biopsy and elastography
Stereotactic Body Radiotherapy (SBRT)
-33 Gy in 5 fractions within 4 weeks of chemotherapy completion
-Assess response with pancreas protocol CT
Surgical Resection
-within 4-12 weeks of SBRT completion
Modified FOLFIRINOX
-to complete 12 cycles
-initiated within 12 weeks of surgery
-with further dose modifications at the discretion of the treating physician

1. BACKGROUND

1.1 Pancreatic Cancer

Pancreatic cancer is the tenth most common malignancy in the United States, yet the fourth leading cause of cancer death with a five year overall survival of less than 5%.[1] While surgery offers the only potentially curative treatment, only 15-20% of patients present with disease that is resectable, and in these patients the 5 year survival is at best 20%.[2-5] The poor survival outcomes are due to a high rate of metastatic progression, underscoring the need for more effective systemic regimens. In addition, 30% of patients die with progressive local disease.[6] Therefore strategies to identify this subset of patients and intensify local therapy may also improve survival outcomes.

Patients who are candidates for potential surgery have either resectable disease or borderline resectable disease. Resectable tumors have no arterial contact with the celiac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA), and no contact or less than 180 degrees of contact with the superior mesenteric vein (SMV) or portal vein (PV) with no vein contour irregularity. The category of borderline resectable pancreatic cancer (BRPC) was first described in 1999 to classify tumors that were between resectable and locally advanced unresectable disease, and could potentially benefit from pre-operative therapy for downstaging prior to attempted resection.[7] Since then, the definition of BRPC has evolved, and is primarily determined by pancreas protocol contrast-enhanced CT imaging to assess the relationship of the tumor to the vasculature. While slight variations in the definition of BRPC exist,[8] the NCCN guideline criteria provide an accepted consensus definition.[9] According to these guidelines, borderline resectable tumors include tumors of the pancreatic head and uncinate process that contact the CHA without extension to the CA or hepatic artery bifurcation, or contact less than 180 degrees of the SMA; or tumors of the body or tail that contact less than 180 degrees of the CA; and tumors contacting greater than 180 degrees of the SMV or PV, or with contour irregularity or short segment thrombosis of the vein, but with venous reconstruction feasible.

The potential for a resection with positive margins is increased when immediate resection is attempted in patients with BRPC.[10] In patients who undergo resection with microscopic (R1) or grossly positive margins (R2), survival rates are not improved over that of patients with locally advanced unresectable disease.[11-13] Moreover, a high rate of metastatic progression suggests that micrometastatic disease is likely present at diagnosis in a large subset of patients. Therefore neoadjuvant therapy is beneficial in patients with BRPC to increase the likelihood of achieving a margin negative resection, provide early control of occult micrometastatic disease, and select those patients without systemic progression who would benefit from surgical resection.

1.2 Adjuvant Therapy

Currently the standard of care management of patients with resectable pancreatic cancer entails six months of adjuvant chemotherapy with gemcitabine, or 5-Fluorouracil (5-FU), or gemcitabine with capecitabine.[5,14] The CONKO-001 trial demonstrated a survival benefit with the use of adjuvant gemcitabine versus observation (5-year overall survival of 21% vs. 9%, median survival 22.8 months vs. 20.2 months).[3] In the ESPAC-3 trial, survival outcomes were comparable with adjuvant gemcitabine vs. 5-FU, with median survival reported at 23.6 vs. 23 months, respectively.[5] Treatment-related adverse effects were significantly increased with adjuvant 5-FU vs. gemcitabine (14% vs. 7.5%), and therefore gemcitabine remains a standard adjuvant chemotherapy regimen. The ESPAC-4 trial was a large

randomized study that compared six months of adjuvant gemcitabine alone to gemcitabine with capecitabine. Results were recently presented at the 2016 ASCO annual meeting, and a significant survival benefit was demonstrated with the combination of gemcitabine and capecitabine compared to gemcitabine alone (median survival of 28 months vs. 25.5 months, and 5 year overall survival of 28.8 vs. 16.3%).[14] Based on these results, gemcitabine with capecitabine can be considered the preferred adjuvant chemotherapy regimen.

The role of post-operative radiation remains unclear. The early GITSG 9173 trial demonstrated a survival benefit with adjuvant 5-FU based chemoradiation compared to observation (median overall survival of 20 vs. 11 months), though the radiation approach is now considered outdated, as it was delivered in a split course fashion with a planned two week break mid treatment.[15] The subsequent ESPAC-1 trial was a 2x2 randomization comparing observation, chemotherapy alone with 5-FU/leucovorin, chemoradiation with 5-FU, and chemoradiation followed by maintenance chemotherapy.[4] A survival detriment was demonstrated with adjuvant chemoradiation, but multiple criticisms of the study design and analysis have called into question these results.[16,17] Recent large retrospective studies and an analysis of the National Cancer Database from our institution have demonstrated a survival benefit with adjuvant chemoradiation vs. observation or chemotherapy alone.[18,19] Therefore the role of post-operative radiation remains controversial, and the current RTOG 0848 phase III trial is examining the benefit of delayed chemoradiation after 6 months of adjuvant gemcitabine, compared to gemcitabine alone.

1.3 Neoadjuvant Therapy

Up to 25% of patients who undergo upfront surgery do not receive any adjuvant therapy due to post-operative complications or early metastatic progression.[13,20] Therefore, chemotherapy and/or radiation delivered in the pre-operative setting offers several advantages, particularly for patients with BRPC, foremost being the potential for downstaging to maximize the rate of margin negative resections. Additional advantages include early systemic therapy to address potential micrometastatic disease, and selecting those patients without early distant progression in whom surgical resection is beneficial.

Neoadjuvant therapy has not been compared to adjuvant therapy in a phase III trial, but multiple phase II and retrospective series have demonstrated promising outcomes. Prospective phase II studies have primarily focused on patients with resectable tumors, demonstrating the safety and feasibility of pre-operative gemcitabine-based chemotherapy with or without chemoradiation in these patients.[21-25]

Data specific to patients with BRPC is more limited.[26,27] In a retrospective series from MD Anderson Cancer Center, 160 patients with BRPC were identified of which 125 completed pre-operative therapy consisting of 2 to 4 months of gemcitabine-based chemotherapy followed by chemoradiation to 50.4 Gy in 28 fractions or 30 Gy in 10 fractions with concurrent 5-FU, paclitaxel, gemcitabine or capecitabine. 41% of patients were able to undergo resection after completing neoadjuvant therapy, and R0 resections were achieved in 94% of these patients. Survival was significantly prolonged in those patients who underwent resection (median overall survival of 40 months vs. 18 months for the cohort overall), which emphasizes the meaningful survival benefit associated with conversion to resectable disease.[28] Preliminary results from the multi-institutional Alliance Trial A021101 were presented at the 2015 ASCO annual meeting. In this study, 22 patients with BRPC were treated with 4 cycles of mFOLFIRINOX chemotherapy (oxaliplatin 85 mg/m^2, irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 on day 1 followed by 5-FU 2400 mg/m^2 x 48 hours) followed by chemoradiation to 50.4 Gy in 28 fractions with concurrent

capecitabine (825mg/m^2 twice daily). 15 patients (68%) underwent subsequent resection, while 7 patients had disease progression and 1 refused surgery. R0 resections were achieved in 14 of these 15 patients. Treatment-related toxicities were manageable, and the high rate of R0 resections supports the efficacy of pre-operative chemotherapy and chemoradiation in BRPC.[29] These studies report promising rates of R0 resection after neoadjuvant therapy (41-64%), though the optimal sequence and combination of neoadjuvant therapy has not been well defined.

1.4 Advances in Chemotherapy

Though gemcitabine with or without capecitabine, or 5-FU are still considered the standard adjuvant chemotherapy options, FOLFIRINOX (oxaliplatin 85 mg/m^2 over 2 hrs, followed by irinotecan 180 mg/m^2 over 90 min and leucovorin 400 mg/m^2 over 2 hrs, followed by 5-fluorouracil 400 mg/m^2 bolus and 2,400 mg/m^2 46 hrs continuous infusion) has proven to be a superior regimen in the setting of metastatic pancreatic cancer. In the randomized phase III PRODIGE4/ACCORD 11 trial comparing FOLFIRINOX with gemcitabine in patients with metastatic disease, overall survival was significantly improved from a median of 6.8 months with gemcitabine to 11.1 months with FOLFIRINOX. Progression-free survival (PFS) was improved from 3.3 months to 6.4 months, and response rates increased from 9.4% to 31.6% with FOLFIRINOX.[30] Moreover, improvements in quality-of-life measures were reported with FOLFIRINOX compared to gemcitabine.[31] Despite these results, there has been reluctance to adopt the widespread use of full dose FOLFIRINOX due to significant increases in grade 3-4 toxicities, specifically neutropenia, fatigue, diarrhea, and vomiting.

Retrospective studies have evaluated the efficacy and tolerability of FOLFIRINOX administered with dose modifications,[32] including a retrospective analysis of patients with advanced pancreatic cancer treated at our institution with FOLFIRINOX between June 2010 and July 2011. The majority of the 35 patients analyzed received modest dose attenuations of irinotecan and/or 5-FU. These dose modifications resulted in improved tolerability with reduced rates of grade 3-4 toxicities, while maintaining comparable efficacy to that reported by Conroy et. al.[33] Therefore a phase II study was completed in patients with locally advanced pancreatic cancer (LAPC) and metastatic pancreatic cancer (MPC) to evaluate a modified FOLFIRINOX regimen with upfront 25% dose reductions of the 5-FU bolus and irinotecan and routine use of pegfilgrastim.[34] 31 patients with LAPC and 44 patients with MPC were enrolled. Rates of grade 3-4 adverse effects, including neutropenia, fatigue, and vomiting were significantly reduced compared to rates reported in the phase III trial. For MPC, the response rate was 35.1% and median overall survival was 10.2 months, consistent with comparable efficacy to full dose FOLFIRINOX. Results in patients with LAPC highlight the superiority of FOLFIRINOX compared to historical results with gemcitabine-based regimens. Median PFS and OS were prolonged at 17.8 months and 26.6 months, respectively. In comparison, median OS was just 15.2 months for patients without disease progression after induction gemcitabine plus or minus erlotinib who went on to receive chemoradiation in the recently published LAP07 randomized trial.[35] Of the 31 patients with LAPC treated with modified FOLFIRINOX in our institutional trial, 13 patients (41.9%) underwent R0 resections. 6 of these patients received chemoradiation prior to surgery. Similar promising outcomes with the use of FOLFIRINOX in the locally advanced setting have been reported in multiple retrospective series.[36-38]

Based on this institutional experience, a prospective phase II study is ongoing evaluating peri-operative modified FOLFIRINOX in patients with resectable pancreatic cancer.

1.5 Advances in Radiation Therapy

Studies evaluating the role of radiation therapy in the treatment of locally advanced pancreatic cancer have shown conflicting results. The ECOG 4201 study showed a modest but significant survival benefit with gemcitabine and concurrent radiation compared to gemcitabine alone (median overall survival of 11 months vs. 9.2 months, respectively).[39] Retrospective and phase II studies have shown a further survival benefit when chemoradiation is employed after a period of induction chemotherapy, thereby excluding those patients with early distant failure.[40-47] In the GERCOR combined analysis, patients received a minimum of 3 months of induction 5-FU or gemcitabine-based chemotherapy. Median overall survival was 15.0 months in those patients who went on to chemoradiation compared to 11.7 months with continued chemotherapy alone.[40] In contrast, the recently published LAP-07 trial demonstrated no improvement in overall survival with chemoradiation to 54 Gy with concurrent capecitabine compared to continued chemotherapy after 4 months of induction gemcitabine or gemcitabine plus erlotinib.[35] The addition of chemoradiation did prolong the time to second-line therapy, and provide a local tumor control benefit. Despite the conflicting results in these studies regarding the benefit of chemoradiation, the median overall survival after gemcitabine-based chemotherapy followed by chemoradiation ranged from 11 – 15.2 months and appears inferior to survival outcomes for patients with LAPC treated with FOLFIRINOX, where median overall survival reaches 26.6 months in our prospective institutional study.[34] This comparison emphasizes the importance of effective systemic therapy prior to chemoradiation. The efficacy of upfront FOLFIRINOX to control micrometastatic disease is likely critical to achieve the optimal benefit from local therapy. Therefore in the era of FOLFIRINOX, radiation therapy may have a greater impact on survival outcomes.

Conventional radiation entails daily treatments to a dose of 50.4 – 54 Gy in 1.8 to 2 Gy fractions over the course of five to six weeks using three-dimensional conformal techniques (3D-CRT) or intensity-modulated radiation therapy (IMRT). Consensus guidelines recommend treating the gross tumor volume with 1.5 – 2 cm expansions in the anterior, posterior, and lateral dimensions, and 2 – 3 cm expansions craniocaudally to take into account microscopic disease extension, motion of the tumor with respiration, and daily set-up variation.[48] The volume of irradiated adjacent normal tissue (duodenum and stomach), in part due to the rather generous margins employed around the tumor volume, limits the radiation dose that can be safely delivered. IMRT is a technique that relies on a computer-aided optimization process to generate a treatment plan in which the intensity of multiple radiation beams is varied across the treatment field in order to conform the radiation dose to the tumor target and reduce dose to neighboring normal structures. A recent retrospective study demonstrated reduced rates of acute grade 2 or higher gastrointestinal toxicities when IMRT vs. 3D-CRT was employed for definitive chemoradiation in patients with LAPC, suggesting that IMRT may allow for safe escalation of the radiation dose to the tumor using conventionally fractionated radiation.[49]

Stereotactic body radiotherapy (SBRT) is an emerging treatment option for patients with pancreatic cancer, in which highly focal radiation is delivered to the tumor most often with IMRT planning, allowing for dose escalation which may enhance local tumor control compared to conventional radiation. SBRT relies on methods to account for motion of the tumor target with respiration, including obtaining a 4-dimensional planning CT scan to visualize motion of the tumor, and respiratory gating for treatment only in pre-specified phases of the respiratory cycle or abdominal compression to reduce respiratory motion during treatment. Gold fiducial markers are placed in the tumor or surrounding pancreas to precisely align the pancreas on the day of treatment. These techniques allow for the delivery of highly conformal ablative doses of radiation in 5 or fewer treatments.[50]

Multiple phase I-II single institution studies have evaluated the use of SBRT for LAPC. Early studies from Stanford University explored single fraction treatment alone, as a boost after conventionally fractionated radiation, or in combination with sequential gemcitabine. While high rates of local control were reported at 1 year (94 – 100%), this was at the cost of increased grade 2 or higher acute GI toxicities (12.5 – 19%), and significant grade 2 or higher late GI toxicities (20-44%) including duodenal ulcers, and less commonly stenosis or perforation.[51-54] Subsequent studies utilized a multi-fraction approach (typically 3 to 5 treatments), and maintained effective local control (78 – 85% at 1 year) with reduced GI toxicities.[55-58] A recent phase II multi-institutional study evaluated gemcitabine followed by fractionated SBRT. Patients received up to 3 weeks of gemcitabine (1000 mg/m2) followed one week later by SBRT to 33 Gy in 5 fractions delivered over 1 to 2 weeks, and gemcitabine until disease progression or toxicity. The primary endpoint was late grade 2 or higher GI toxicities compared to historical controls. When compared to prior studies using single-fraction SBRT, GI toxicities were reduced to 2% grade 2 or higher acute toxicity, and 11% grade 2 or higher late toxicity. The median overall survival was 13.9 months. Local control at 1 year was 78% which compares favorably to historical controls treated with conventionally fractionated radiation, such as the recently published LAP-07 trial.[35,55] Therefore advantages of SBRT include the fact that the biologic effect of larger radiation fractions may provide a therapeutic benefit with improved local control compared to conventionally dosed radiation, and the shorter treatment course can be more easily integrated with other treatment modalities with less time off of effective multi-agent chemotherapy.

Given these promising local control outcomes, SBRT may also increase the rate of conversion to resectable disease for patients with BRPC or LAPC. While SBRT in the neoadjuvant setting has not been prospectively evaluated, a single institution retrospective experience from Moffitt Cancer Center reported on the safety and efficacy of pre-operative SBRT. Patients with LAPC or BRPC received induction chemotherapy (most commonly gemcitabine, taxotere, and capecitabine) followed by SBRT in 5 fractions. The tumor was treated to 25-30 Gy, and the region of tumor abutting vessels received a higher dose (35-50 Gy). Treatment was well tolerated, with no acute grade 3 or higher toxicities reported, and only 5.3% late grade 3 or higher toxicities. Rates of surgical complications were acceptably low. 54% (31/57) of BRPC patients underwent an R0 resection after neoadjuvant therapy, and the median overall survival was 16.4 months.[59] Updated results included a larger number of patients (n=23) receiving induction FOLFIRINOX. In this small retrospective experience, the combination of induction FOLFIRINOX and SBRT as neoadjuvant therapy was well tolerated. Most patients receiving FOLFIRINOX had LAPC, and R0 resections rates were significantly higher in FOLFIRINOX recipients versus other induction chemotherapy regimens (5 of 21 vs. 0 of 28, p = 0.011).[60] Finally, retrospective data from Johns Hopkins University presented in abstract form compared R0 resection rates for BRPC or LAPC patients receiving neoadjuvant chemotherapy alone or induction chemotherapy followed by SBRT. Rates of R0 resection were significantly higher in patients who received SBRT compared to those who received chemotherapy alone (87.2 vs. 48.6%).[61] Taken together, these single institution retrospective studies demonstrate the tolerability of neoadjuvant SBRT and report increased rates of R0 resections particularly for BRPC that warrants further evaluation in a prospective trial.

1.6 Study Rationale and Hypothesis

In summary, surgical resection is the only potentially curative treatment for patients with pancreatic cancer. Patients with BRPC have tumors in close contact with the vasculature but not to the extent that resection is prohibited. Nonetheless, retrospective studies have shown that immediate resection in these patients is associated with an increased risk of positive margins,[10] and a margin positive resection does not improve survival over that of patients with unresectable disease.[11-13] Moreover, even in those patients where a successful resection is achieved, there is a high rate of early metastatic progression suggesting that micrometastatic disease is often present at diagnosis. Therefore neoadjuvant therapy is likely to improve outcomes in patients with BRPC to increase the likelihood of achieving a margin negative resection, provide early control of occult micrometastatic disease, and select those patients without systemic progression who would benefit from surgical resection.

Superior survival outcomes have been demonstrated with FOLFIRINOX compared to gemcitabine in patients with metastatic disease. Our institutional prospective phase II trial demonstrated the tolerability and efficacy of modified FOLFIRINOX in patients with LAPC and MPC. Prolonged progression free survival and overall survival were seen in patients with BRPC and LAPC, and R0 resections were achieved in 42% of patients. In addition, retrospective and phase II studies have documented the tolerability of stereotactic body radiation therapy (SBRT) in LAPC and the potential for improved local control. Contact between the tumor and neighboring vasculature complicates or prohibits resection in the setting of BRPC, and therefore local therapy to potentially reduce the degree of contact may be of benefit. Given the superior outcomes with FOLFIRINOX and the potential for improved local response with SBRT, we propose to evaluate the efficacy of pre-operative modified FOLFIRINOX followed by SBRT in patients with borderline resectable pancreatic adenocarcinoma. We hypothesize that pre-operative modified FOLFIRINOX followed by SBRT will improve the rate of R0 resections compared to historical controls treated with standard gemcitabine-based chemotherapy and fractionated radiation prior to surgery.

2. OBJECTIVES

2.1 Primary Objective

To evaluate the R0 resection rate after neoadjuvant modified FOLFIRINOX and subsequent SBRT for borderline resectable pancreatic cancer.

2.2 Secondary Objectives

2.2.1 To evaluate the radiographic response to neoadjuvant therapy by comparing IV contrast CT scans before and after therapy.

2.2.2 To evaluate the pathologic response to neoadjuvant chemotherapy and stereotactic radiation.

2.2.3 To determine rates of recurrence (local only, systemic only, and both local and systemic), progression free survival, and overall survival.

2.2.4 To determine rates of grade 3 or greater gastrointestinal toxicity, including acute toxicities occurring within 3 months of treatment, and late toxicities occurring over 3 months after completion of radiation.

2.3 Exploratory Objectives

2.3.1 To prospectively assess quantitative *KRAS* mutation-associated circulating tumor DNA as a predictive marker of response to neoadjuvant therapy or a prognostic marker of outcomes.

2.3.2 To evaluate endoscopic ultrasound elastography measurements of tumor stiffness (change in strain ratio between the normal and tumor region before and after chemotherapy) as a predictor of outcomes.

2.3.3 To correlate response of CA19-9 to pre-operative therapy with outcomes.

2.3.4 To collect and bank serial serum and plasma specimens from subjects for future correlative biomarker studies.

2.3.5 To collect and bank tumor tissue from subjects prior to treatment (at the time of diagnostic EUS), after treatment with pre-operative FOLFIRINOX (at the time of fiducial placement for SBRT), and after SBRT (from the surgical specimen) for future correlative biomarker studies.

3. STUDY DESIGN

3.1 Description of Study

This is a Phase II open-label study to determine the efficacy of neoadjuvant mFOLFIRINOX followed by SBRT in patients with borderline resectable pancreatic adenocarcinoma. Patients will undergo a diagnostic endoscopic ultrasound (EUS) with core biopsy (or FNA if biopsy is attempted and unsuccessful) demonstrating pancreatic adenocarcinoma. Baseline elastography will be measured at the time of EUS, though patients will continue on study if elastography is not feasible. Borderline resectable disease will be defined by NCCN criteria, and determined centrally by review of a diagnostic pancreas protocol CT scan and/or MRI scan with contrast by a dedicated surgical oncologist and radiologist.

Patients will receive 8 cycles of mFOLFIRINOX every 2 weeks. mFOLFIRINOX will be dosed as follows*:* Oxaliplatin 85 mg/m^2, followed by folinic acid 400 mg/m2 infused over 120 minutes and irinotecan 135 mg/m^2 infused over 90 minutes, followed by 5-fluorouracil 300 mg/m^2 IV bolus, followed by 2,400 mg/m^2 continuous infusion for 46 hours. Levoleucovorin may be substituted for folinic acid at a dose of 200 mg/m2 infused over 120 minutes.

Patients will undergo a re-staging pancreas protocol CT scan after cycle 3 and after cycle 7. Patients without evidence of distant progression will continue on study. Patients will receive an additional 8th cycle of mFOLFIRINOX while radiation planning is underway. EUS will be performed for placement of fiducials to guide radiation delivery. Elastography will be performed and a core biopsy will be obtained at the time of EUS for correlative studies (patients will continue on study if elastography and core biopsy is not feasible). Stereotactic body radiotherapy (SBRT) will be delivered to the primary tumor and any adjacent involved nodes to 33 Gy in 5 fractions over the course of 2 weeks, and within 4 weeks of chemotherapy. All patients will be maintained on proton pump inhibitors beginning with the first SBRT treatment and continuing for at least 6 months after completion of SBRT, or at least until surgery if undergoing resection. After SBRT, patients will undergo re-evaluation with a pancreas protocol CT scan. Those patients who are resectable will undergo surgical resection between 4-12 weeks after completion of SBRT. Tissue from the resection will be banked for correlative studies. Post-operatively, patients will

receive 4 additional cycles of mFOLFIRINOX to complete a total of 12 cycles, with further dose modifications at the discretion of the treating medical oncologist.

Patients who complete the study treatment without disease progression will then enter a period of post-study surveillance which will include a history, physical exam, and laboratory assessments at three month intervals for three years and then 6 month intervals for two years, and CT scans at 6 month intervals for a total of three years, and then annually for an additional two years. After five years, patients will be followed annually until death.

3.2 Rationale for Study Design

Recent advances in the treatment of pancreatic cancer include the use of FOLFIRINOX, which has been shown to significantly improve overall survival compared to gemcitabine in patients with metastatic disease, and the use of SBRT which may provide a therapeutic benefit with improved local tumor response compared to conventionally dosed radiation. The improved tolerability and comparable efficacy of a modified FOLFIRINOX regimen was demonstrated in our published institutional retrospective and phase II studies. Moreover, survival outcomes for patients with LAPC or BRPC treated with mFOLFIRINOX as part of the phase II trial were significantly prolonged compared to historical results with gemcitabine-based regimens. An ongoing phase II study at our institution is evaluating the efficacy of peri-operative mFOLFIRINOX for patients with resectable disease. Given the improved outcomes achieved with FOLFIRINOX and the retrospective and phase II data demonstrating tolerability and potential for enhanced local tumor response with SBRT, we propose an open label phase II study to evaluate the efficacy of neoadjuvant mFOLFIRINOX followed by SBRT in patients with borderline resectable pancreatic adenocarcinoma. We hypothesize that the addition of SBRT as part of pre-operative treatment will be associated with a significant improvement in the rate of R0 resections compared to historical controls receiving pre-operative standard gemcitabine-based chemotherapy and fractionated radiation.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

The primary outcome of this study is the R0 resection rate in patients with BRPC treated with neoadjuvant mFOLFIRINOX and SBRT.

3.3.2 Secondary Outcome Measures

- **3.3.2.1** Radiographic response to neoadjuvant therapy
- **3.3.2.2** Pathologic response to neoadjuvant therapy
- **3.3.2.3** Local only, systemic only, and local or systemic rates of recurrence
- **3.3.2.4** Progression free survival
- **3.3.2.5** Overall survival
- **3.3.2.6** Grade 3 or greater acute and late gastrointestinal toxicity

3.4 Expected Accrual

We expect to accrue 28 patients over approximately 56 months. Approximately 40 resections for pancreatic adenocarcinoma are performed annually at Yale New Haven Hospital, of which approximately one third are for BRPC. Therefore we anticipate enrolling approximately 6 patients per year.

4. ON-STUDY GUIDELINES AND SAFETY PLAN

4.1 General On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they may not be considered as formal subject selection criteria, as part of this decision making process, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness that would prevent the patient from giving informed consent.
- Patient is not deemed a candidate for mFOLFIRINOX or SBRT based on overall condition and co-morbidities.
- A medical condition such as active/uncontrolled infection or cardiac disease that would make this protocol unreasonably hazardous for the patient in the opinion of the treating physician.

4.2 mFOLFIRINOX-Specific Safety Guidelines

Refer to section 7 for safety guidelines and recommendations for the management of toxicities related to FOLFIRINOX.

4.3 Radiation-Specific Safety Guidelines

The radiation fractionation scheme proposed in this study (33 Gy in 5 fractions) was evaluated in a prospective multi-institutional phase II study in which patients with locally advanced pancreatic cancer received gemcitabine followed by SBRT. The rate of grade 3 or higher acute GI toxicity was 2% and the rate of grade 3 or higher late GI toxicity was 8%.[55] Based upon this study and other published studies evaluating multi-fraction SBRT for pancreatic cancer, a rate of grade 3 GI toxicity of 20% or higher would be unexpected.[55-58] An interim safety analysis will be performed by the PI after 5 patients complete 3 months of follow-up after SBRT. Study accrual will continue during this time period. If the rate of grade 3 GI toxicity that is probably related to SBRT exceeds 20%, then accrual will be held and the protocol and consent will be revised.

Refer to section 7 for recommendations for the management of toxicities related to SBRT.

5. ELIGIBILITY CRITERIA

5.1 Disease Characteristics

5.1.1 Histologically confirmed pancreatic adenocarcinoma

5.1.2 Borderline resectable pancreatic adenocarcinoma, determined centrally by review of a diagnostic CT scan and/or MRI scan with contrast by a dedicated surgical oncologist and radiologist, or as determined by EUS, and defined according to one of the following four NCCN consensus guidelines:

-Tumors of the pancreatic head or uncinate process with:

-Solid tumor contact with the common hepatic artery (CHA) without extension to the celiac axis (CA) or hepatic artery bifurcation allowing for safe and complete resection and reconstruction, or

-Solid tumor contact with the superior mesenteric artery (SMA) of ≤180 degrees, or

-Presence of variant arterial anatomy such that the degree of tumor contact affects surgical planning

-Tumors of the pancreatic body or tail with:

-Solid tumor contact with the CA of ≤180 degrees, or

-Solid tumor contact with the CA of >180 degrees without involvement of the aorta and with intact and uninvolved gastroduodenal artery

-Solid tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) of >180 degrees, or contact of ≤180 degrees with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction

-Solid tumor contact with the inferior vena cava (IVC)

5.1.3 No evidence of extrapancreatic disease on diagnostic imaging (CT, MRI, or PET scan), or laparoscopy, including nodal involvement beyond the peripancreatic tissues and/or distant metastases

5.1.4 No evidence of invasion into the duodenum or stomach, as determined by EGD/EUS

5.2 Prior Therapy

5.2.1 No prior treatment (chemotherapy, biological therapy, or radiotherapy) for pancreatic cancer

5.2.2 No prior treatment with oxaliplatin, irinotecan, fluoruouracil or capecitabine

5.2.3 Patients who received chemotherapy >5 years ago for malignancies other than pancreatic cancer are eligible

5.2.4 No major surgery within 4 weeks of study entry

5.2.5 No other concurrent anticancer therapy

5.3 Patient Characteristics

- **5.3.1** ECOG Performance Status of 0-1
- **5.3.2** Age ≥ 18
- **5.3.3** No other malignancy within past five years (exceptions include basal cell carcinoma of the skin, cervical carcinoma in situ, and nonmetastatic prostate cancer)
- **5.3.4** No evidence of second malignancy at the time of study entry
- **5.3.5** No interstitial pneumonia or extensive and symptomatic interstitial fibrosis of the lung
- **5.3.6** No ≥ grade 2 sensory peripheral neuropathy
- **5.3.7** No uncontrolled seizure disorder, active neurological disease, or known CNS disease
- **5.3.8** No significant cardiac disease, including the following: unstable angina, New York Heart Association class II-IV congestive heart failure, myocardial infarction within six months prior to study enrollment
- **5.3.9** Not pregnant and not nursing
- **5.3.10** No other medical condition or reason that, in the opinion of the investigator, would preclude study participation
- **5.3.11** Laboratory parameters as follows:
    - Absolute neutrophil count ≥1,500/uL,
    - Platelet count ≥75,000/uL,
    - Hemoglobin ≥9 g,/dL,
    - Creatinine <1.5 X ULN or estimated GFR >30 ml/min,
    - Bilirubin ≤1.5 X ULN,
    - AST and ALT ≤3 X ULN,
    - Negative pregnancy test in women of childbearing potential
- **5.3.12** Able to be treated with SBRT only at the Smilow New Haven campus
- **5.3.13** Able to have fiducials placed in the pancreas

6. TREATMENT PLAN

This is a non-randomized phase II study. Treatment will be administered on an outpatient basis under medical supervision. Protocol treatment will begin within 14 days of registration.

6.1 Neoadjuvant mFOLFIRINOX

Patients will receive eight cycles of neoadjuvant mFOLFIRINOX – one cycle every two weeks (+/- 3 days). One cycle is defined as 14 days, and treatment will be initiated on day one of a two week cycle. The drugs will be dosed and administered as follows:

- Oxaliplatin 85 mg/m^2 IV infused over two hours, followed by
- Leucovorin 400 mg/m^2 IV (or levoleucovorin 200 mg/m^2 IV) over two hours
- Irinotecan 135 mg/m^2 IV over 90 minutes (concurrent with leucovorin during the last 90 min of the leucovorin infusion)
- 5-FU 300mg/m^2 IV bolus, then 2400 mg/m^2 continuous IV infusion over 46 hours

All patients will receive supportive care as follows:

- Pegfilgrastim (Neulasta™) on day 3, 4, or 5.

- Anti-emetics including palonosetron or ondansetron, aprepitant, and dexamethasone, according to standard institutional protocols.
- Atropine is administered per standard guidelines for cholinergic symptoms during irinotecan infusion of on day 1.
- Loperamide is administered per standard guidelines for chemotherapy-induced diarrhea.
- Patients will be counseled regarding potential sides effects and their management.

Re-staging pancreas protocol CT scans will be performed after 3 and 7 cycles of mFOLFIRINOX. MRI can be substituted for patients unable to undergo a CT scan. A PET scan is optional if necessary for re-staging.

6.2 Neoadjuvant SBRT

Patients without evidence of distant progression will receive SBRT directed at the primary tumor. An 8th cycle of mFOLFIRINOX will be administered during planning for SBRT. All patients will be maintained on proton pump inhibitors beginning with the first SBRT treatment and continuing for at least 6 months after completion of SBRT, or until surgery if undergoing resection.

6.2.1 Fiducials

Patients will undergo an EUS for placement of 1-5 gold fiducials to guide radiation delivery. The fiducials will be placed directly in the tumor or surrounding normal pancreas under endoscopic guidance. The fiducials will be used as a surrogate for tumor position on the day of each treatment. A core biopsy and elastography measurements will be obtained at the time of fiducial placement. If a core biopsy is attempted but not successful, or elastography is not feasible, patients can continue on study.

6.2.2 Simulation

CT simulation for radiation planning will be performed after the placement of fiducials. Patients will be NPO 3 hours prior to the scan, with the exception of oral contrast 30 minutes prior to the scan. Patients will be positioned supine in a custom vac-loc immobilization device. A dual phase (arterial and venous) IV contrast scan with 1.25mm slices will be obtained for target delineation. If the patient cannot tolerate IV contrast, the scan will be obtained without contrast and merged to diagnostic imaging (MRI, PET, and/or prior CT with contrast) for target delineation. A 4D-CT scan (with 2.5mm slice thickness) will then be obtained to characterize tumor motion with respiration. Abdominal compression will be applied for respiratory motion management, with the goal of decreasing motion of the fiducials to 5mm or less. The IV contrast and 4D scans will include from the carina to the iliac crests. Patients must begin SBRT within 3 weeks of the simulation scan.

6.2.3 Treatment Planning

The planning arterial and venous phase IV contrast scans will be fused to the 4D scan for target delineation. Diagnostic imaging including MRI or PET scans can also be fused to the treatment planning scans if deemed helpful for contouring the tumor. The tumor volume (GTV) will include the primary tumor and any involved peripancreatic nodes. An internal target volume (ITV) will be generated using the 4D scan to account for motion of the GTV with respiration. The planning target volume (PTV) will consist of a 2-3mm volumetric expansion of the ITV, except if the expansion includes the duodenum or

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stomach, in which case a non-uniform expansion margin is acceptable to limit dose to these surrounding normal tissues. Treatment planning will be carried out on the average of the 4D scan, using IMRT (including volumetric-arc therapy [VMAT]), or 3D conformal techniques.

The prescription dose will be 33 Gy in 5 fractions of 6.6 Gy over the course of 2 weeks.

The following normal tissue constraints will serve as guidelines for treatment planning, as per prior studies evaluating the dosimetric determinants of duodenal toxicity with SBRT and the dose constraints established in prior trials.[55,62] In the circumstance where the following constraints cannot be met, exceptions will be recorded and treatment can proceed with PI approval.

- Proximal Duodenum (the entire duodenum on the same axial plane as the PTV, and the duodenum 1 cm above and 1 cm below the PTV):
  - <1cc to 33 Gy
  - <9cc to 15 Gy
  - <3cc to 20 Gy
  - If <9cc to 15 Gy and/or <3cc to 20 Gy can not be met, <5cc of small bowel including duodenum to 18 Gy is acceptable
- Small Bowel:
  - <1cc to 33 Gy
  - <9cc to 15 Gy
  - <3cc to 20 Gy
  - If <9cc to 15 Gy and/or <3cc to 20 Gy can not be met, <5cc of small bowel including duodenum to 18 Gy is acceptable
- Stomach:
  - <1cc to 33 Gy
  - <9cc to 15 Gy
  - <3cc to 20 Gy
  - If <9cc to 15 Gy and/or <3cc to 20 Gy can not be met, <5cc of stomach to 28 Gy is acceptable
- Liver:
  - 50% <12 Gy
- Combined Kidneys:
  - 75% <12 Gy
- Spinal Cord:
  - <1cc to 8 Gy
  - 30 Gy point max

The following treatment planning goals will be achieved:

- No more than 1cc of the PTV can receive >130% of the prescription dose
- Greater than 90% of the PTV should receive 100% of the prescription dose
- If the above normal tissue constraints can not be met, then 100% of the ITV will receive at least 25 Gy

6.2.4 Treatment Delivery

Linac-based SBRT will be delivered to a total dose of 33 Gy in 5 fractions over the course of 2 weeks, or maximum of 3 weeks (21 days). The fiducials will be contoured to aid in target localization. A cone beam CT (CBCT) will be obtained in the treatment position on the Linac prior to each treatment. The fiducials will be visualized on the day of treatment CBCT, and the patient position will be adjusted to align the fiducials to match that of the planning CT scan.

6.3 Surgery

After completion of SBRT, patients will undergo re-evaluation for resection with a pancreas protocol CT scan, MRI if CT scan can not be tolerated, and PET or EUS if deemed necessary to determine resectability. Those patients who are determined to be potentially resectable will undergo a laparoscopy, followed by surgical resection within 4-12 weeks after completion of SBRT. For surgical resections occurring more than 12 weeks after SBRT, exceptions will be recorded and patients can remain on study with PI approval. Standard pathologic evaluation and staging will be performed.

6.4 Adjuvant therapy

Post-operatively, patients will be followed every 2 weeks in medical oncology, and receive 4 additional cycles of mFOLFIRINOX to complete a total of 12 cycles, with further dose modifications at the discretion of the treating medical oncologist. Adjuvant chemotherapy will commence within 12 weeks of surgery.

7. STUDY DRUGS, DOSE MODIFICATIONS, AND TOXICITY MANAGEMENT

7.1 Doses and Schedule of Study Drugs

Chemotherapy will consist of mFOLFIRINOX administered every two weeks, as described in Section 6 at the following doses:

- Oxaliplatin 85 mg/m^2 IV infused over two hours, followed by
- Leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2) IV over two hours
- Irinotecan 135 mg/m^2 IV over 90 minutes (concurrent with leucovorin during the last 90 min of the leucovorin infusion)
- 5-FU 300mg/m^2 IV bolus, then 2400 mg/m^2 continuous IV infusion over 46 hours

7.2 Study Drugs: Formulation, Storage, Availability, Preparation, and Toxicity

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment. Unused portions of injectable chemotherapeutic agents supplied as single-dose preparations should be discarded within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

7.2.1 Oxaliplatin (Eloxatin)

Availability
Oxaliplatin is commercially available as an aqueous solution in vials containing 50 mg and 100 mg at a concentration of 5 mg/mL. The vials do not contain any preservative and they are intended for single use.

Storage and Stability
Intact vials should be stored at room temperature. Solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration.

Preparation
The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters or IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

Administration
Oxaliplatin will be administered by intravenous infusion over 120 minutes in patients receiving FOLFIRINOX. Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia.

Oxaliplatin is unstable in the presence of chloride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or other chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration.

Toxicity
The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen:

Acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include paresthesia, dysesthesia, and hypothesia of the hands, feet and perioral regions. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of patients receiving oxaliplatin with 5-FU and leucovorin.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested to order to minimize pharyngolaryngeal dysesthesia. Antianxiety agents (e.g. lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesias, dysesthesias, and hypothesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.
Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea.

Neutropenia is reported in 73% of patients receiving oxaliplatin with 5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dyspnea) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Recent reports of oxaliplatin extravasation suggest that tissue necrosis may result and that oxaliplatin should be considered a vesicant. No standard treatment exists for oxaliplatin extravasation although heat and sodium thiosulfate have both been suggested.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5-FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients.

For more information on toxicities associated with oxaliplatin, please see the package insert.

7.2.2 5-Fluorouracil (5-FU: Fluorouracil: Adrucil®)

Please refer to the package insert for complete product information.

Availability
5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials
Preparation
Inspect for precipitate: if found, agitate or gently heat in water bath.

Bolus injections are prepared using undiluted drug.

46-48 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the individual institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5 FU should not be mixed in the same solution with most parenteral antiemetics.

Storage and Stability
Intact vials should be stored at room temperature and protected from light. Slight yellow discolor does not usually indicate decomposition. Stability in ambulatory pumps varies according to the pump, manufacturer of drug, concentration and diluent. Please refer to appropriate reference sources for additional information.

Administration
In this study, 5-FU is administered as a 300 mg/m^2 IV bolus followed by 2400 mg/m^2 by IV infusion over 46 to 48 hours.

Toxicity
Nausea, diarrhea, vomiting (mild); stomatitis (5-8 days after treatment initiation); myelosuppression; granulocytopenia (9-14 days); thrombocytopenia (7-14 days); alopecia; loss of nails; hyperpigmentation: photosensitivity; maculopapular rash; palmar-plantar erythrodysesthesias: (42-82% receiving continuous infusion); CNS effects: cerebral ataxia (rare); cardiotoxicity: MI, angina: asymptomatic S-T changes 68%; ocular effects: excessive lacrimation and less commonly, tear duct stenosis.

Drug Interactions
Leucovorin enhances the cytotoxicity of 5-FU by forming a more stable tertiary complex with thymidylate synthase. Concomitant administration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Patients receiving both drugs should be followed with weekly INRs.

7.2.3 Leucovorin Calcium (Folinic Acid; Calcium Folinate; Citrovorum Factor; N 5-Formyltetrahydrofolate; 5-Formyl-FH4; Folinic Acid)

Levoleucovorin (200 mg/m2) may be substituted for leucovorin (400 mg/m2) in this study. Please refer to the package insert for complete product information for levoleucovorin and leucovorin.

Availability
Leucovorin calcium is commercially available in: 50 mg, 100 mg, 350 mg vials for reconstitution.

Storage and Stability
Intact vials should be stored at room temperature and protected from light. Solutions reconstituted with BWI are stable for at least 7 days at room temperature.

Preparation
Leucovorin may be reconstituted with Bacteriostatic Water for Injection (BWI) or with Sterile Water For Injection. Solutions should be further diluted in D5W, 0.9% NaCl or Ringers solution for infusion over two hours.

Administration
Leucovorin will be administered as a 400mg/m^2 IV infusion over 2 hours after oxaliplatin administration. Leucovorin may also be administered concurrently with oxaliplatin as a separate IV infusion.

Toxicity
The only adverse reactions associated with leucovorin are allergic reactions. These are extremely uncommon.

7.2.4 Irinotecan (CMT-11, Camptosar)

Availability
Irinotecan is commercially available in a concentration of 20mg/mL in 2mL, 5mL, and 25 mL vials.

Storage and Stability
Intact vials should be stored at controlled room temperature 59 to 86 degrees Fahrenheit (15 to 30 degrees Celsius) and protected from light. Solutions diluted in D5W are reported to be stable for 48 hours under refrigeration and protected from light. Irinotecan solutions should not be frozen as the drug may precipitate.

Preparation
Irinotecan is diluted in 5% dextrose (D5W) 500 mL to a final concentration of 0.12 – 1.1 mg/mL.

Administration
In this study, irinotecan is administered by IV infusion over 90 minutes

Toxicity
Virtually all phase I and II studies of irinotecan have reported neutropenia and/or late diarrhea (diarrhea occurring more than 24 hours after the irinotecan administration as the dose limiting toxicities (depending on the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia. Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after irinotecan administration; this syndrome is thought to be cholinergically mediated, and may be treated and subsequently prevented with atropine. Sporadic cases of pulmonary toxicity, manifested as shortness of breath, non-productive cough and transient infiltrates on chest x-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Occasionally, abnormalities of serum creatinine, hepatic enzymes, or thrombocytopenia have been observed.

Please refer to the package insert for further information regarding irinotecan.

Concerns related to adverse effects:

- Bone marrow suppression: [U.S. Boxed Warning]: May cause severe myelosuppression. Deaths due to sepsis following severe myelosuppression have been reported. Therapy should be temporarily discontinued if neutropenic fever occurs or if the absolute neutrophil count is <1000/mm^3. The dose of irinotecan should be reduced if there is a clinically significant decrease in the total WBC (<200/mm^3), neutrophil count (<1500/mm^3), hemoglobin (<8 g/dL), or platelet count (<75,000/mm^3). Routine administration of a colony-stimulating factor is generally not necessary, but may be considered for patients experiencing significant neutropenia.
- Colitis: Colitis, complicated by ulceration, bleeding, ileus, and infection has been reported.

- Diarrhea: [U.S. Boxed Warning]: Severe diarrhea may be dose-limiting and potentially fatal; two severe (life-threatening) forms of diarrhea may occur. Early diarrhea occurs during or within 24 hours of receiving irinotecan and is characterized by cholinergic symptoms (eg, increased salivation, diaphoresis, abdominal cramping); it is usually responsive to atropine. Late diarrhea occurs more than 24 hours after treatment which may lead to dehydration, electrolyte imbalance, or sepsis; it should be promptly treated with loperamide. Patients with diarrhea should be carefully monitored and treated promptly.
- Hypersensitivity reactions: Severe hypersensitivity reactions have occurred.
- Renal toxicity: Renal impairment and acute renal failure have been reported, possibly due to dehydration secondary to diarrhea.
- Disease-related concerns:
- Bowel obstruction: Patients with bowel obstruction should not be treated with irinotecan until resolution of obstruction.
- Hepatic impairment: Use with caution in patients with hepatic impairment.
- Hyperbilirubinemia: Patients with even modest elevations in total serum bilirubin levels (1-2 mg/dL) have a significantly greater likelihood of experiencing first-course grade 3 or 4 neutropenia than those with bilirubin levels that were <1 mg/dL. Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan. Use caution when treating patients with known hepatic dysfunction or hyperbilirubinemia; dosage adjustments should be considered.

7.3 Dose Modifications and Toxicity Management

All dose adjustments should be based on the worst preceding toxicity, graded using the National Cancer Institute Common Toxicity Criteria (version 4.0).

If more than one of the dose modifications apply, use the most stringent (i.e., the greatest dose reduction). Dose modifications are cumulative and permanent.

If treatment is held for any treatment-related toxicities for $\geq$ 3 weeks, patients should discontinue all protocol therapy.

The dose of leucovorin is not modified for toxicity, but is omitted if fluorouracil is omitted.

Dose modifications for toxicity are adapted from Conroy et al.[30]

7.3.1 Hematologic Toxicity

On day 1 of each cycle, hold all chemotherapy until the granulocyte count is ≥ 1500/ul and the platelet count is ≥75000/ul.

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

BLOOD COUNTS DAY 1	DELAY OF CYCLE	DOSE REDUCTION		
		irinotecan	**oxaliplatin**	**fluorouracil**
Granulocytes <1500/ul	Hold treatment until granulocytes ≥ 1500/ul	1st occurrence: reduce to 75% of previous dose 2nd occurrence: maintain previous dose 3rd occurrence: treatment discontinuation	1st occurrence : no reduction 2nd occurrence: reduce to 75% of previous dose 3rd occurrence: treatment discontinuation	1st occurrence: delete bolus 5FU
Platelets <75000/ul	Hold the treatment until platelets ≥75000	1st occurrence: no reduction 2nd occurrence: reduce to 75% or original dose 3rd occurrence: treatment discontinuation	1st occurrence: reduce to 75% of previous dose 2nd occurrence: maintain previous dose 3rd occurrence: treatment discontinuation	1st occurrence: reduce bolus and infusion to 75% of previous doses

Doses for neutropenic fever or nadir cytopenias:

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Febrile neutropenia **or** **Grade 4 neutropenia**	1st occurrence: reduce irinotecan to 75% of previous dose and delete the bolus 5FU dose 2nd occurrence: reduce oxaliplatin to 75% of previous dose 3rd occurrence: treatment discontinuation
Grade 4 thrombocytopenia	1st occurrence: reduce oxaliplatin and 5FU (bolus and infusion) to 75% of previous dose 2nd occurrence: reduce irinotecan and 5FU (bolus and infusion) to 75% of previous dose 3rd occurrence: treatment discontinuation

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7.3.2 Diarrhea

Patients must be instructed in the use of loperamide for diarrhea, and must have a supply of this drug upon starting FOLFIRINOX. Patients should not be retreated with irinotecan until recovery from diarrhea to ≤ grade1 (without loperamide for at least 24 h) has occurred. Diarrhea is attributed to chemotherapy UNLESS a specific infectious agent is isolated.

ADVERSE EVENTS	REDUCTION OF DOSE FOR SUBSEQUENT CYCLES
Diarrhea grade 3-4 **or** **Diarrhea + fever** **and/or** **neutropenia grade 3-4**	1st occurrence: reduce irinotecan to 75% of previous dose and delete bolus 5FU dose 2nd occurrence: reduce oxaliplatin and continuous infusion 5FU to 75% of previous doses 3rd occurrence: treatment discontinuation
Diarrhea ≥ 48 h despite high doses of loperamide	Hold FOLFIRINOX until resolves to ≤ grade1 for at least 24 hrs. No dose reductions after complete recovery, unless gr 3-4 diarrhea, or diarrhea + fever and/or concomitant neutropenia gr 3-4

7.3.3 Mucositis or Hand-Foot Syndrome

Grade ≥ 2: Hold treatment until toxicity resolves to a ≤ grade 1, then resume oxaliplatin, irinotecan, and leucovorin at 100% of the previous dose and fluorouracil (bolus + infusional 5-FU) at 75% of the previous dose for all subsequent doses. For subsequent grade ≥ 2 recurrence(s), hold treatment until toxicity resolves to a ≤ grade 1, then resume oxaliplatin, irinotecan, and leucovorin at 100% of the previous dose and fluorouracil (bolus + infusional 5-FU) at 75% of the previous dose.

7.3.4 Cardiac Toxicity

For any cardiac arterial thrombotic event or ischemic event (angina, myocardial infarction) discontinue all protocol therapy.

7.3.5 Increased Bilirubin

In case of elevation of bilirubin, evaluation to exclude biliary obstruction or progressive disease is recommended. For bilirubin >1.5x ULN, omit irinotecan until bilirubin is <1.5x ULN.

7.3.6 Neurotoxicity

Toxicity Scale for the Sensory Neuropathies Associated with Oxaliplatin

	Symptoms
Grade 1	Paresthesias/dysesthesias* of short duration that resolve and do not interfere with function
Grade 2	Paresthesias/dysesthesias* interfering with function, but not with activities of daily living (ADL)
Grade 3	Paresthesias/dysesthesias* with pain or with functional impairment that also interfere with ADL.
Grade 4	Persistent paresthesias/dysesthesias* that are disabling or life threatening.
	* *May be cold-induced*

- For grade 2 neurotoxicity persisting between treatments: Reduce oxaliplatin to 75% of the previous dose for all subsequent cycles.
- For grade 3 neurotoxicity resolving to ≤ grade 2 between treatments: Reduce oxaliplatin to 75% of the previous dose for all subsequent cycles.
- For grade 3 neurotoxicity persisting between treatments: Discontinue Oxaliplatin. Patients should continue to receive other protocol therapy.
- For grade 4 neurotoxicity: Discontinue oxaliplatin. Patients should continue to receive other protocol therapy.

7.3.7 Other Toxicities

For ≥ grade 2 toxicity attributed to treatment and not described above (except fatigue, anemia and alopecia), hold treatment until toxicity resolves to ≤ grade 1 and resume treatment with the agent that is thought to be causing the toxicity at 75% of the previous dose and all other agents at full dose.

If grade 3-4 toxicity is clearly secondary to a single agent and is thought to be cumulative, the causative agent may be discontinued with the approval of the principal investigator. Similarly, a causative agent may be discontinued for grade 2 allergic reaction and must be discontinued for grade 3-4 allergic reaction.

7.3.8 Extravasation

Extravasation of oxaliplatin is reported to cause necrosis. Extravasation should be treated according to institutional guidelines.

7.3.9 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by the patient's BSA as calculated from actual weight.

7.4 Concomitant Medications

7.4.1 Anti-emetics:

Due to the emetogenic nature of this regimen, Emend will be administered with each cycle in addition to concomitant antiemetics at the discretion of the treating physician.

For symptoms of nausea and vomiting during radiation, anti-emetics (such as ondansetron or prochlorperazine) will be given one hour prior to SBRT, and as needed following SBRT.

7.4.2 Loperamide:

For symptoms of diarrhea and/or abdominal cramping that occur at any time during a treatment cycle or during radiation, patients will be instructed to begin taking loperamide. Loperamide should be started at the earliest sign of (1) a poorly formed or loose stool or (2) the occurrence of 1 to 2 more bowel movements than usual in 1 day or (3) an increase in stool volume or liquidity. Loperamide should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Patients may take loperamide 4 mg every 4 hours during the night. The maximum daily dose of loperamide is 16 mg/day.

7.4.3 Proton Pump Inhibitors (PPIs):

All patients will be prescribed proton pump inhibitors to start at least by the first SBRT treatment, and to continue for a minimum of 6 months after completion of SBRT, or at least until surgery for those undergoing resection.

7.4.4 Antibiotics:

Oral fluoroquinolone treatment may be initiated for ANC<500 or diarrhea for >24 hours despite loperamide, at the discretion of the treating physician.

7.4.5 Anticoagulants:

Prophylactic or therapeutic doses of Coumadin or low-molecular weight heparin are permitted.

7.4.6 Low-dose aspirin (≤ 325 mg/d):

Aspirin may be continued if the patient was on this prior to enrollment.

7.4.7 Growth Factors:

Pegfilgrastim (Neulasta) will be administered with each cycle of therapy but can be omitted after the first cycle at the discretion of the treating physician for hyper-leukocytosis on day 1 of treatment.

8. REQUIRED CLINICAL AND LABORATORY EVALUATIONS

To be completed within 14 days (2 weeks) before the first dose of study drug:

- All blood work, History, Physical Examination, and Performance Status

To be completed within 21 days (3 weeks) before the first dose of study drug:

- Imaging studies (CT or MRI, and PET scans)

To be completed within 42 days (6 weeks) before the first dose of study drug:

- Endoscopic Ultrasound (EUS)

CT with pancreatic protocol will be obtained at the following time points: (1) at baseline, (2) after cycle 3 of chemotherapy, (3) after cycle 7 of chemotherapy within 4 weeks prior to SBRT, and (4) pre-operatively within 4 weeks prior to surgery. For patients who cannot undergo CT, MRI is allowed.

Calendar of Assessments

Neoadjuvant mFOLFIRINOX:					
Tests & Observations	**Screening**			**Day 1 of each cycle**	**Day 3, 4, or 5 of each cycle**
	Within 14 days of starting study drug	**Within 21 days of starting study drug**	**Within 42 days of starting study drug**		
Scheduling Window (Days)				**(±3)**	**(±3)**
Surgical Evaluation			x		
History & Physical	x			x	
Height	x				
Weight/BSA	x			x	
Vital Signs	x			x	
Performance Status	x			x	
Toxicity Assessment	x			x	
Neulasta[Q]					x
Laboratory Studies[A]:					
CBC, Diff, Platelets	x			x	
Serum Chemistries[B]	x			x	
PT/INR[C]	x				
CA 19-9, CEA	x				
Pregnancy Test[D]	x				
Research Blood Collection[E]	x				
Staging:					
CT (or MRI)[F]		x			
EUS (with elastography)[G]			x		
Neulasta					x
Tissue:					
Core Biopsy[H]			x		

Neoadjuvant SBRT and Pre-Operative Evaluation:			
Tests & Observations	**Pre-SBRT (within 4 weeks prior to RT)**	**Weekly During SBRT**	**Pre-operative (within 4 weeks prior to surgery)**
Surgical evaluation			x
History & Physical	x	x	
Weight/BSA	x	x	
Vital Signs	x	x	
Performance Status	x	x	
Toxicity Assessment		x	
Laboratory Studies:			
CBC, Diff, Platelets	x		x
Serum Chemistries[B]	x		x
PT/INR[C]			x
CA 19-9, CEA	x		x
Research Blood Collection[E]	x[I]	x[J]	x[K]
Staging:			
CT (or MRI)[F]	x		x[K]
EUS (fiducials and elastography)[G]	x		x[L]
Tissue:			
Core Biopsy[H]	x		

Adjuvant mFOLFIRINOX and Post-Treatment Follow-Up:					
Tests & Observations	**Day 1 of 1st adjuvant cycle (within 12 weeks of surgery)**	**Day 3, 4, or 5 of each cycle**	**Day 1 of each subsequent cycle**	**Post-Treatment Follow-Up[N]**	**30-day follow-up**
Scheduling Window (Days)	**(±3)**	**(±3)**	**(±3)**	**(± 14)**	**(± 7)**
History	x		x	x	x
Physical Exam	x		x	x	x
Weight/BSA	x		x	x	x
Vital Signs	x		x		
Performance Status	x		x	x	
Toxicity Assessment	x		x		
Neulasta[Q]		X			
Laboratory Studies[A]:					
CBC, Diff, Platelets	x		x	x	
Serum Chemistries[B]	x		x	x	
CA 19-9, CEA	x			x	
Research Blood Collection[E]	x			x[O]	
Staging:					
CT (or MRI)[F]				x[P]	x
Tissue:					
Surgical Resection[M]					

Long Term Follow-up Period[N]:			
Tests & Observations	**Every 3 months (for the first three years after completing mFOLFIRINOX)**	**Every 6 months (three years after completing mFOLFIRINOX for the next two years)**	**Annual (five years after completing mFOLFIRINOX)**
Scheduling Window (Days)	**Every 3 months ±14 days**	**Every 6 months ±14 days**	**Annually ± 14 days**
History	x	x	x
Physical Exam	x	x	x
Weight/BSA	x	x	x
Performance Status	x	x	x
Laboratory Studies[A]:			
CBC, Diff, Platelets	x	x	x
Serum Chemistries[B]	x	x	x
CA 19-9, CEA	x	x	x
Research Blood Collection[E]	x	x	x

Follow-up Period[N]:		
Staging:	**Every 6 months (first three years after completing mFOLFIRINOX)**	**Annually (three years after completing mFOLFIRINOX for two years)**
Scheduling Window (Days)	**Every 6 months ±14 days**	**Annually ±14 days**
CT (or MRI)[F]	x	x

A Laboratory studies must be drawn within 24 hours of administration of drugs

B Serum chemistry panel will include serum creatinine, BUN, electrolytes (Na, K, Cl, Bicarb), AST/ALT, Alk Phos, Bili, and albumin

C PT/INR should be monitored weekly for those taking coumadin or warfarin

D For women of child-bearing potential only

E 3 purple top tubes (30 mls) at diagnosis, and 2 – 3 purple top tubes (20 – 30 mls) at each follow up time point, for cryopreservation of plasma and buffy coat

F CT should be performed using pancreatic protocol when possible. For patients who are unable to undergo CT, MRI may be used

G If elastography is not feasible, patients can remain on study

H At the time of diagnosis, core biopsies will be attempted with one specimen sent to pathology for diagnosis and a separate specimen to be banked for correlative studies. If core biopsies are not successful, a FNA is acceptable for diagnosis. At the time of EUS for fiducial placement, a core biopsy will be obtained and banked for correlative studies. Patients can continue on study if core biopsy is not feasible at the time of fiducial placement.

I At the time of CT simulation

J On the day of fraction 3 and fraction 5 of SBRT

K CT scan and plasma and serum samples will be done within 4 weeks prior to surgery

L Endoscopic ultrasound is optional if deemed necessary for surgical assessment

M Tissue from the surgical specimen will be banked for correlative studies

N Initiated within 4 weeks of completing all treatment and continued every 3 months for three years, then every six months for two years, then annually or until disease recurrence or death

O At completion of 12 cycles of FOLFIRINOX, at follow up every 3 months for 3 years, then every 6 months for 2 years, then annually until recurrence or death, and at the time of disease progression

P Initiated within 4 weeks of completing all treatment, then every 6 months for three years, and then annually for 2 years or until disease recurrence

Q Administered with each cycle of therapy but can be omitted after the first cycle at the discretion of the treating physician for hyper-leukocytosis on day 1 of treatment.

9. CRITERIA FOR RESPONSE AND PROGRESSION

Response to treatment will be assessed by the treating physicians and investigators according to RECIST version 1.1,[63] as follows:

9.1 Definitions

9.1.1 Measurable Disease:

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm 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.

9.1.2 Non-Measurable Disease:

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

9.2 Methods of Measurement

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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Computed tomography (CT) / MRI - CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should

be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

9.3 Baseline Documentation of Target and Non-Target Lesions

9.3.1 Target Lesions:

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

9.3.2 Lymph Nodes:

These merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. All other pathological nodes (those with short axis $\geq$10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

9.3.3 Non-Target Lesions:

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent.”

9.4 Evaluation of Best Overall Response

In general, the patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria as outlined below and summarized in Table 1:

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

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Table 1: Response Assessment in Patients with Measurable Disease

TARGET LESIONS	NON-TARGET LESIONS	NEW LESIONS	OVERALL RESPONSE	BEST RESPONSE FOR THIS CATEGORY ALSO REQUIRES:
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once >6 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR, or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response, PR=partial response, PD=progressive disease, SD=stable disease

Every effort should be made to document the objective progression even after discontinuation of treatment

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented.

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

9.5 Evaluation of Response for Non-Measurable Disease

When the patient has only non-measurable disease, the same general concepts apply here as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in

protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

It is assumed that at each protocol specified time point, a response assessment occurs. When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2: Response Assessment in Patients with Non-Measurable (Non-Target) Disease

NON-TARGET LESIONS	NEW LESIONS	OVERALL RESPONSE
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response, PD=progressive disease, NE=inevaluable

10. SUBJECT DISCONTINUATION

Patients will receive 8 cycles of neoadjuvant mFOLFIRINOX followed by SBRT, surgical resection, and post-operative mFOLFIRINOX to complete 12 cycles. Treatment will continue unless there is evidence of disease progression, or unacceptable toxicity as specified in section 7.3 of the protocol. Any patients deemed unresectable at the time of surgery will be discontinued from study treatment.

Patients who complete the study treatment phase without disease progression will enter a post-study surveillance phase. They will undergo history, physical exam, measurement of weight, evaluation of performance status, and laboratory assessments (including CBC, serum chemistries, liver function tests, CA 19-9, CEA, and a research blood collection, as specified in the study calendar) at three month intervals for three years, then every six months for two years, then annually or until disease recurrence or death. Cross-sectional imaging with CT or MRI will be performed at 6 month intervals for three years, and then annually for two additional years or until disease recurrence. After five years, patients will be followed annually until death; surveillance imaging and lab assessments are optional after five years.

In addition, subjects who meet the following criteria should be discontinued from study treatment:

- Any grade 3 or 4 toxicity that does not resolve within 3 weeks of holding treatment.
- Unwillingness or inability of subject to comply with study requirements
- Determination by the investigator that it is no longer safe for the subject to continue therapy, or that the constraints of this protocol are detrimental to the patient's health
- The patient no longer wishes to continue protocol therapy

All subjects will be followed for survival.

11. STUDY DISCONTINUATION

APPROVED BY THE YALE UNIVERSITY IRB 3/16/2020

The Principal Investigator has the right to terminate this study at any time if the incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects.

12. STATISTICAL METHODS

The primary endpoint of this phase II study is the R0 resection rate after neoadjuvant mFOLFIRINOX and SBRT in patients with BRPC.

In the largest reported series of patients with BRPC, 125 patients received pre-operative therapy consisting of 2 to 4 months of gemcitabine-based chemotherapy followed by fractionated chemoradiation. 41% of patients underwent a subsequent resection, and R0 resections were achieved in 94% of these patients, for an overall R0 resection rate of 39% for all patients initiating pre-operative therapy.[28] Superior outcomes have been demonstrated with FOLFIRINOX compared to gemcitabine chemotherapy, and a local control benefit has been suggested with SBRT compared to fractionated chemoradiation. Thus, we propose an increase in the R0 resection rate from 40% in historical controls treated with standard gemcitabine-based chemotherapy and fractionated radiation prior to surgery to 65% with pre-operative FOLFIRINOX and SBRT.

A total of 28 patients will be enrolled in a Simon two-stage design with a provision for early stopping for lack of efficacy. The primary endpoint is the rate of achieving R0 resections. Patients needing to drop out of this study prior to surgery, for disease progression or treatment related toxicity, will be considered as failing to achieve the R0 resection rate. The null hypothesis is this rate is 40% based on both reported historical rates as well as our experience at Yale-New Haven Hospital. Under the alternative hypothesis, we will judge pre-operative modified FOLFIRINOX followed by SBRT effective if the R0 resection rate is 65% or higher. The optimal Simon two-stage design will terminate early if 5 or fewer of the first 13 patients fail to achieve an R0 resection. Otherwise we continue and enroll the remaining 15 patients for a total of 28. If 15 or more out of the full 28 achieve R0 resection then we reject the null hypothesis. This design has 90% power and significance level 0.1. The probability of stopping early under the null hypothesis is 57%.

Secondary endpoints include radiographic response to neoadjuvant therapy, pathologic response to neoadjuvant therapy, rates of recurrence (local only, systemic only, and both local and systemic), progression free survival, overall survival, and rates of grade 3 or greater acute and late gastrointestinal toxicity. We will compare levels of KRAS mutation-associated circulating tumor DNA, CA19-9, and elastography measures with outcomes including R0 resection using logistic regression, and progression free survival and overall survival using proportional hazards regression. We will code IV contrast scans as binary and compare the before/after treatment within the same subject using the McNemar test for matched pairs. We have not powered this study for these secondary and exploratory measures. Future correlative biomarker studies will be studied using standard bioinformatics methods. Progression free survival, and overall survival will be estimated using Kaplan-Meier analysis. The Cox proportional hazards regression model will be used to determine if survival outcomes are associated with patient characteristics or treatment-related toxicities.

We anticipate accrual will be completed in two years based on the fact that approximately 40 resections for pancreatic adenocarcinoma are performed annually at Yale New Haven Hospital, of which around a third are for BRPC.

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13. ADVERSE EVENTS ANALYSIS, DEFINITION, AND REPORTING

13.1 Safety Analysis

Safety will be analyzed for patients treated in this study.

At each visit, a brief focused history will be obtained and any indication of treatment related toxicity will be evaluated by appropriate examination and/or laboratory/radiographic studies.

Safety analyses will include summaries of adverse event rates and changes in laboratory results, as well as number of CTCAE toxicity grades for both laboratory and non-laboratory data.

The evaluation period should extend from date of first treatment until at least 30 days (or longer if so specified) from the last dose or until resolution from all acute toxicities associated with the drug administration.

13.2 Definition of Adverse Event Terms

Adverse Event – Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite, per NCI – CTEP).

Serious Adverse Event (SAE) – Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death,
- a life-threatening adverse drug experience,
- in patient hospitalization or prolongation of existing hospitalization,
- any persistent or significant disability/incapacity,
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

“Serious” Versus “Severe” Adverse Events – There is a distinction between serious and severe AEs. Assessment of seriousness will be made solely by the serious criteria listed above. Severity of AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events v3.0. Therefore, serious events will not be automatically considered severe. For example, a stroke that results in only a limited degree of disability may be considered a mild (not severe) stroke, but it would still meet serious criteria and thus, be captured as an SAE. Similarly, severe events may not always be serious. An example would be an episode of severe, transient nausea which persists for several hours. This would be classified as a “severe” episode of nausea, but if it did not require treatment, intervention, or somehow meet other serious criteria, it would not be considered an SAE.

Life-threatening Adverse Drug Experience – Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Unexpected Adverse Drug Experience – Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

13.3 Toxicity Grading

Toxicities will be graded according to the current version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The full text of the NCI CTCAE is available online at: http://ctep.cancer.gov/

If a certain event or symptom is not described in the CTCAE grades, use the following grading scale:

- Mild: awareness of event but easily tolerated
- Moderate: discomfort enough to cause some interference with usual activity
- Severe: inability to carry out usual activity
- Very Severe: debilitating, significantly incapacitates patient despite symptomatic therapy

13.4 Toxicity Attribution

Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after occurrence of the event, including diagnostic tests to assess the cause of the event. Clinically relevant data include, but are not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered.

An adverse event is associated with the use of the drug when there is a reasonable possibility that the experience may have been caused by the drug.

Attribution Standards per NCI – CTEP:

- Unrelated: The Adverse Event is clearly not related to the investigational agent(s)
- Unlikely: The Adverse Event is doubtfully related to the investigational agent(s)
- Possible: The Adverse Event may be related to the investigational agent(s)
- Probable: The Adverse Event is likely related to the investigational agent(s)
- Definite: The Adverse Event is clearly related to the investigational agent(s)

14. YALE PRINCIPAL INVESTIGATOR SAE REPORTING REQUIREMENTS

14.1 Expedited Reporting of Unexpected SAES

AEs classified as "serious" and "unexpected" that are possibly, probably, or definitely attributed to drug administration, or SAEs whose frequency exceeds expectations, require expeditious handling and reporting.

The PI will promptly investigate all safety information related to an adverse experience. If the results of the PI's investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug administration) is so reportable, the PI will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

Reporting to the Yale Human Investigation Committee
All SAEs, whether originating at Yale or a collaborating center, meeting the criteria for expedited reporting will be reported to the Yale University Human Investigation Committee (HIC) using HIC Form 6A within 48 hours of discovery.

The Yale University Human Investigation Committee expedited reporting criteria are:

a. Serious AND unanticipated AND possibly, probably or definitely related events; and
b. Anticipated Adverse Events occurring with a greater frequency than expected.

The HIC does not require reporting of any other Adverse Event type. A copy of the HIC Adverse Event Policy is available at: http://info.med.yale.edu/hic/policy/AdverseEventPolicy.pdf

14.2 Duration of Reporting of SAEs

From the date of first treatment until 30 days (unless otherwise specified) subsequent to last treatment or withdrawal of subject, new onset adverse events will be captured. Follow-up and reporting of these events will follow the same procedure as for AEs observed during the study period. In addition, any unexpected Serious Adverse Event that occurs more than 30 days after drug administration but is possibly, probably or definitely attributed to drug administration will be recorded and reported.

15. YALE SAFETY REPORTING AND MONITORING (DSMP)

The principal investigator at the Yale Cancer Center will monitor the clinical trial for safety. The principal investigator will assess all expedited adverse events and will periodically review all adverse events observed on the trial. Yale Cancer Center standard operating procedures (SOPs) for assessment and reporting of adverse events are followed which are in compliance with FDA 21 Code of Federal Regulations Part 312.32 and 312.33.

The clinical trial data consisting of all required observations, AEs, and laboratory data will be entered into a computerized database (OnCore) in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is assured by periodic auditing conducted by the Yale Cancer Center Office of Protocol Review and Monitoring, which reports to the

Yale Data and Safety Monitoring Committee (DSMC). Safety data will be submitted to DSMC at least once yearly or more often as required by the DSMC. On a regular interval basis, status reports of all laboratory parameters, AEs and SAEs are reviewed by the PI to view composite data across subjects. Regular meetings are held to discuss ongoing patient treatment and adverse events.

The Yale DSMC will perform an interim safety analysis after enrollment of 10 patients to determine whether there are any safety issues and to assess whether it is safe to continue enrollment. Enrollment will be suspended until approval is granted from the DSMC to proceed completion of enrollment.

Possible actions taken by the PI or the Yale DSMC if a new unexpected toxicity is identified from the above safety review, or if the periodic review of all adverse events and laboratory data indicates a pattern of incidence or severity of toxicity that raises a safety concern, can be to:

- Revise consent form
- Amend the protocol
- Suspend the protocol

All AEs found to be expected or non-serious, will be included in the Annual Report.

16. RETENTION OF RECORDS

U.S. FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the principal investigator for 2 years after the investigation is discontinued.

17. RESEARCH ETHINCS AND HUMAN SUBJECT PROTECTION

17.1 Subject Selection

This protocol will seek to accrue patients 18 years of age or older as described in the study inclusion criteria.

17.2 Informed Consent Process

The informed consent dialogue with the research subjects will include a discussion of the natural history of their condition and alternative therapies that a person might consider (e.g. supportive care only, administration of conventional chemotherapy agents, or participation in a research study).

17.3 Confidentiality

Data collected on each patient will be maintained in a research folder kept in a locked room. Data entered into a computerized database will be kept on a computer that is password protected and kept in a locked room. In all publications and presentations resulting from this research project, the research subject's anonymity will be protected to the maximum extent possible. Authorized Medical Department personnel and personnel from the cancer center and IRB may have access to their research file in order to verify that the research subject's rights have been safeguarded. In addition, their name will be given

to the Clinical Studies Unit, a contracting office who will register the research subject onto this study and verify their eligibility.

17.4 Patient Rights

If the research subject suffers any physical injury as a result of their participation in this study, immediate medical treatment is available at the treating institution. Although no compensation is available, any injury as a result of his participation will be evaluated and treated in keeping with the benefits or care to which he is entitled under applicable regulations.

If the research subject has any questions regarding this research project, he may contact Dr. Kimberly Johung or site investigator or coordinator or IRB. If he has any questions regarding his rights as an individual while participating in a research project at the Yale Cancer Center (YCC), he can contact one of the Research Administrators, Clinical Investigation Department, who will answer the research subject's questions or refer him to a member of the committee for the Protection of Human Subjects for further information. If the patient believes that he has been injured as a result of this project, he may call the legal office of YCC.

Participation in this research project is voluntary. A patient's refusal to participate will involve no penalty or loss of benefits to which he is entitled under applicable regulations. If the chooses to participate, he is free to ask questions or to withdraw from the project at any time. If he should decide to withdraw from the research project, he will notify the PI either directly or indirectly through the research nurse, to make sure the reasons for withdrawal are recorded and to ensure that everything is in order. A patient's withdrawal will involve no loss of benefits to which he is entitled.

The investigators may terminate the research subject's participation in this project for the following reasons: growth of cancer, intolerance of treatment, inability to comply with the protocol guidelines for treatment and follow-up, or if the patient chooses to stop protocol therapy, or at the specific request of MEI. Any new significant finding developed during the course of the research which may affect his willingness to participate further will be explained to the research subject.

18. EXPLORATORY STUDIES

18.1 *KRAS* mutation-associated circulating tumor DNA

Activating mutations in the *KRAS* oncogene are present in over 90% of pancreatic adenocarcinomas, resulting in constitutive activation of signaling pathways that promote cell proliferation, transformation, and invasion.[64] Single point mutations in codon-12 at G12 are most common, while codon-13 (G13D) or codon-61 (Q61L or Q61H) mutations are more infrequent.[65]

Circulating tumor DNA (ctDNA) has emerged as a promising non-invasive biomarker that may correlate with treatment response and prognosis.[66] At our institution, Dr. Abhijit Patel has developed methods for quantitative detection of cancer-specific mutations in ctDNA from peripheral blood samples. Mutation hotspot regions of plasma DNA are amplified, and deep sequencing is used to quantify the rare DNA containing tumor-specific mutations.[67] Given the high frequency of *KRAS* mutations in pancreatic tumors, we will collaborate with Dr. Patel to evaluate levels of *KRAS* mutation-associated circulating tumor DNA in BRPC patients enrolled on this study. Levels of *KRAS* mutated ctDNA will be correlated with radiographic and pathologic response to neoadjuvant therapy, onset of local and

systemic recurrences, and survival outcomes. Blood samples for ctDNA analysis will be collected at the following time points:

-At diagnosis (within 2 weeks prior to initiation of chemotherapy)
-After 8 cycles of mFOLFIRINOX (at the time of CT simulation)
-On the day of fraction 3 and fraction 5 of SBRT
-After SBRT (within 4 weeks prior to surgery)
-Day 1 of adjuvant mFOLFIRINOX (within 12 weeks of surgery)
-At completion of adjuvant mFOLFIRINOX
-At follow up every 3 months for 3 years, then every 6 months for 2 years, then annually until recurrence or death
-At the time of disease progression

18.2 EUS Elastography

Endoscopic ultrasonography (EUS) provides high-resolution images of the pancreas, and it is considered one of the most accurate methods for the diagnosis and staging of pancreatic malignancy.[68] EUS elastography is a method for the real-time evaluation of tissue stiffness, which has been used for the analysis of superficial organ lesions, such as those of the breast and prostate.[69,70] Elastographic images are an index of tissue elasticity, which may be related to histopathologic features. Studies have shown EUS elastography to be a promising technique with a high accuracy for the differential diagnosis of solid pancreatic tumors.[71,72]

EUS elastography is performed with the linear Olympus EUS (PA, USA) and the Prosound F75 equipment (Japan).[73,74] The results of the elastography evaluation are defined by the quotient strain ratio between the normal and tumor regions.[75] Two different areas (A and B) from the region of interest are selected for quantitative elastographic analysis. Area A is a representative area of the tumor and includes the largest possible area of tumor. Area B is a soft peripancreatic reference area outside the tumor. The quotient B/A (strain ratio) is considered the measure of the elastographic evaluation. The quoted mean strain ratio for pancreatic adenocarcinoma is 18.12 (95% CI, 16.03–20.21).[75]

In a neoadjuvant study, tumor stiffness was determined by elastography at baseline and 4 weeks after treatment with gemcitabine and nab-pacitaxel. The strain ratio was used as a measurement of tumor stiffness, and diminished from a value of 36 pre-treatment to 18 post-treatment (p=0.002), suggesting that tumors became softer after treatment. There was a statistically significant correlation between the changes in elastography ratio and CA 19-9 response (p=0.019).[76]

Therefore we propose to measure the strain ratio by EUS elastography at the time of diagnostic EUS and after neoadjuvant FOLFIRINOX when fiducials for SBRT are placed under EUS guidance. The change in strain ratio will be compared with outcomes including radiographic and pathologic response to treatment, recurrence, and survival endpoints.

18.3 Immunomodulatory Effect of SBRT

Pancreatic tumors are characterized by a dense desmoplastic stroma and infiltration of predominantly immunosuppressive leukocytes including tumor-associated macrophages (TAMs) and regulatory T cells with rare effector T-cells, which together promotes evasion of the immune system.[77,78] While immune

checkpoint inhibitors have shown promising activity in melanoma, lung cancer, and other malignancies, responses in patients with advanced pancreatic cancer have been disappointing,[79-81] likely in part due to the immunosuppressive pancreatic tumor microenvironment. Radiotherapy has both immune stimulatory and suppressive effects. Radiation triggers the release of tumor antigens, recruits effector T cells through induction of chemokines, and increases expression of co-stimulatory molecules and death receptors on tumor cells which enhances antitumor immunity. Radiation can also stimulate immunosuppressive leukocytes and induce expression of PD-L1.[82-84] Recent reports have suggested that radiation and immune checkpoint inhibitors can act synergistically to promote anti-tumor immunity.[82]

To better understand the immunomodulatory effect of stereotactic radiation on the pancreatic tumor and tumor microenvironment, we propose to characterize the tumor-infiltrating lymphocyte (TIL) population and expression level of PD-1 and PD-L1 in pancreatic tumors before and after stereotactic radiation. It is rare to have tissue available for analysis after SBRT, as SBRT is most often employed as a non-invasive treatment in place of surgery. Because SBRT will be performed pre-operatively in this study, core biopsies obtained at the time of fiducial placement prior to SBRT can be compared to surgical specimens in those patients who undergo successful resections after SBRT.

Dr. Kurt Schalper at our institution has developed assays for quantitative assessment of PD-1, PD-L1, and TIL subtypes from paraffin-embedded tissue using multiplexed quantitative fluorescence with automated quantitative analysis (AQUA).[85,86] Preliminary studies in collaboration with Dr. Schalper demonstrate the feasibility of quantitative immunofluorescence to measure PD-L1 expression in paraffin embedded core biopsy specimens from pancreas (Figure 1 below). In addition, high-throughput sequencing of T cell receptor (TCR) genes can be performed on tumor samples before and after SBRT to quantify T cell clonality, and determine whether stereotactic radiation triggers T cell clonal expansion.

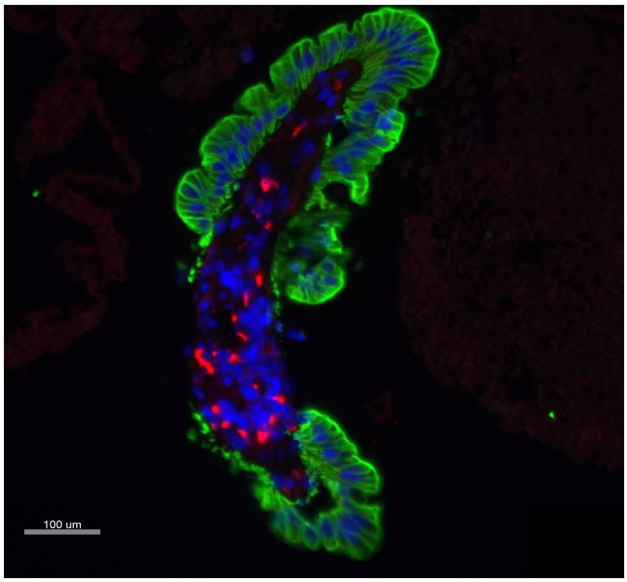

Figure 1: PD-L1 protein expression using quantitative immunofluorescence in a pancreas core biopsy specimen (PD-L1 protein in the red channel; DAPI nuclear stain in the blue channel; cytokeratin in the green channel). PD-L1 expression localizes to immune cells.

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