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ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY
 ALLIANCE A021101
**NEOADJUVANT FOLFIRINOX AND CHEMORADIATION FOLLOWED BY DEFINITIVE SURGERY AND
 POSTOPERATIVE GEMCITABINE FOR PATIENTS WITH BORDERLINE RESECTABLE PANCREATIC
 ADENOCARCINOMA: AN INTERGROUP SINGLE-ARM PILOT STUDY**
An Alliance trial conducted by CALGB, NCCTG, and ACOSOG*
Commercial agent(s): mFOLFIRINOX, capecitabine, gemcitabine
Limited Access Study

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Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, or (where available) Data Manager
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data directly to the NCCTG/Alliance:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	Research Base Operations Quality Assurance Office NW Clinic 3-24-CC 200 First Street SW Rochester, MN 55905 Attn: QAS for A021101 Note: NCCTG sites will submit all forms via NCCTG Remote Data Entry System. CALGB and ACOSOG participant sites will submit study data using paper CRF forms and a cover sheet located in the Forms Packet. Do not submit study data or forms to the CTSU Data Operations. Do not copy the CTSU on data submissions.
<p>The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.</p> <p>CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</p>		
<p>For patient eligibility or treatment-related questions contact the Study PI of the Coordinating Group.</p>		
<p>For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org.</p>		
<p>The CTSU Web site is located at https://www.ctsu.org.</p>		

The following cooperative groups have formally endorsed this trial. Institutions from these groups must enroll patients and submit data via the CTSU.

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NEOADJUVANT FOLFIRINOX AND CHEMORADIATION FOLLOWED BY DEFINITIVE SURGERY AND POSTOPERATIVE GEMCITABINE FOR PATIENTS WITH BORDERLINE RESECTABLE PANCREATIC ADENOCARCINOMA: AN INTERGROUP SINGLE-ARM PILOT STUDY

Pre-registration Eligibility Criteria

- Documentation of Disease:
 Cytologic or histologic proof of adenocarcinoma of the pancreatic head or uncinate process.
 Objective radiographic staging
 Borderline resectable primary tumor
 No potentially resectable disease
 No metastatic disease
 No locally advanced and unresectable disease
 No prior chemotherapy or chemoradiation for panc cancer
 No currently active second malignancy other than non-melanoma skin cancer
 No baseline peripheral sensory neuropathy \geq grade 2
 No known Gilbert's Syndrome or homozygosity for UGT1A1*2
 No history of pulmonary embolism in past 6 months.
 Age \geq 18 years
 ECOG Performance Status 0-1
 Non-pregnant and non-nursing

Required Pre-registration Lab Values

Granulocytes	$\geq 2,000 /\mu\text{l}$
Hemoglobin	$> 9 \text{ g/dL}$
Platelets	$\geq 100,000/\mu\text{l}$
Albumin	$> 3.0 \text{ g/dL}$
Creatinine	$\leq 1.5 \text{ x ULN}$
AST/ALT	$\leq 2.5 \text{ x ULN}$

Required Registration Laboratory Values

Bilirubin	$\leq 2 \text{ mg/dL}$
CA 19-9	$< 1000 \text{ U/mL}$ (from time point when bilirubin is $< 2 \text{ mg/dL}$)

Registration Eligibility Criteria

Confirmation of radiographic staging by central reviewers

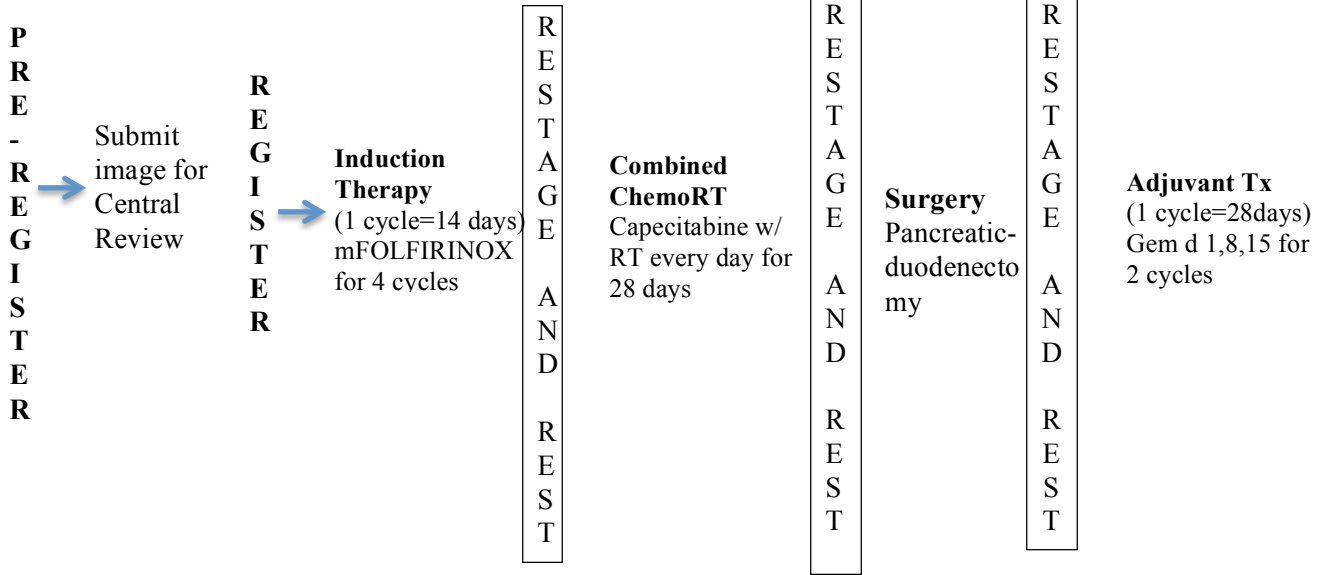


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1.0 INTRODUCTION

1.1 Rationale for Approach and Design

Borderline resectable pancreatic ductal adenocarcinoma (PDAC) represents a poorly-served but prevalent stage of PDAC. Although large randomized trials have established therapeutic standards for patients with resectable (1) and metastatic (2) PDAC, borderline resectable disease is still managed in a heterogeneous manner. A strong rationale exists for the use of preoperative therapy and surgery in patients with borderline resectable PDAC, but the majority of data relating to this disease stage have been generated from a handful of single institution case series in which patients received a variety of treatment regimens (3-6). No prospective trials specifically evaluating these patients or their treatment have been completed. Furthermore, the only multi-institutional trial ever designed to specifically study this population, Eastern Cooperative Group (ECOG) Trial 1200 (7), closed prematurely almost a decade ago for multiple reasons including the absence of a well-defined study population and the absence of therapeutic and surgical standards. Indeed, the ongoing failure to study borderline resectable PDAC can be attributed in large part to the historical absence of a standardized infrastructure of definitions, decision-making processes and technical procedures that is required to properly evaluate and treat this complex population (8).

Despite this historical background, a multi-institutional study of this stage of disease is now justified and appropriate given the following considerations. First, no standard therapeutic approach has been established for patients with borderline resectable PDAC. Furthermore, although a significant number of patients with borderline resectable PDAC exist nationwide, the number treated at most institutions is relatively small. Second, over the past decade the application of both neoadjuvant therapy and vascular resection for patients with localized PDAC has increased, indicating a growing understanding and acceptance of these two historically controversial treatment modalities. Finally, the recent publication of national “consensus statements” regarding borderline resectable PDAC suggests an awareness of, interest in, and dedication to, this unique patient population (9-10).

Nonetheless, given the historical context, feasibility remains an important issue. Although the critical need for prospective evaluation of these patients is clear, and interest in this disease stage is high, the ability to successfully evaluate therapies for patients with borderline resectable PDAC in a prospective, multi-institutional trial is unknown. A randomized phase II design is inappropriate for the initial study of borderline resectable PDAC because the patient accrual numbers associated with this design would be prohibitive. Furthermore, the paucity of historical data required by this design imposes important statistical restrictions on the scientific questions that can be posed with it. For these reasons, in this initial trial, we propose a single-arm pilot design. This design will allow:

- Rapid assessment of the feasibility of multi-institutional study of borderline resectable PDAC,
- Development and assessment of a standardized clinical and research infrastructure specific to this disease stage that is necessary to study it, and
- Definition of a new standard of care therapy for patients in whom such a standard does not currently exist, to which novel regimens will be compared in future studies.

Following rapid completion of this study, we will conduct a follow-up study of multimodality therapy that will utilize a randomized phase II design. This successor study will randomize patients to two arms: 1) the FOLFIRINOX/chemoradiation/ adjuvant gemcitabine regimen

described here, and 2) an experimental regimen based on the chemotherapy/chemoradiation/surgery/adjuvant therapy but which tests the activity of a refined chemotherapy regimen, more sophisticated radiation techniques, and/or a change in the postoperative regimen. The goal of the follow-up study will be to further improve the outcomes of this group of patients.

1.2 Trial Importance

The rationale for defining borderline resectable PDAC as a unique clinical entity worthy of investigation is based on five observations:

- “Localized PDAC” encompasses a group of cancers with heterogeneous tumor anatomy and biology,
- Macroscopic (R1) or microscopic (R0) resection is mandatory for long-term survival of patients with PDAC,
- Resection of the superior mesenteric/portal veins at pancreatectomy can be safe and effective in certain clinical scenarios,
- “Downstaging” of patients with substantial tumor involvement of the mesenteric arteries is rare following the administration of conventional cytotoxic agents, and
- Chemotherapy and chemoradiation may be used to select patients with limited vascular involvement and with favorable tumor biology who may benefit from subsequent surgery.

Within this context, patients with borderline resectable cancers can best be characterized as those with tumor involvement of the mesenteric vein or limited involvement of the mesenteric artery in whom potentially-curative tumor resection might reasonably be expected, but in whom attempts at resection would likely be compromised by positive surgical margins in the absence of venous resection or preoperative therapy. Given the clinical observations enumerated above, the goals of therapy and the clinical outcomes that can reasonably be expected following therapy, differ for three defined groups of patients with localized PDAC:

Substage	Therapeutic Goal	Surgery	Preoperative Tx	Vascular Resection
Resectable	Cure	Probable	Optional	Unlikely *
Borderline	Cure	Possible	Preferred*	Likely
Unresectable	Palliation	Improbable	N/A	N/A

*, based on current consensus

Recognition of borderline resectable PDAC as a unique clinical entity distinct from resectable and locally advanced cancer is therefore absolutely critical, both for optimal patient care, as well as for the proper evaluation of novel adjuvant therapies in patients with localized PDAC in clinical trials.

Each year, less than 5,000 patients with resectable PDAC undergo potentially curative resection in the United States. An additional 16,000 patients are diagnosed with locally advanced PDAC. Of these, perhaps 30%, or 5,000 patients annually, might be considered to have borderline resectable primary cancers using modern definitions (5, 10). In many—if not most—centers, such patients are often treated as if they are inoperable, and thus incurable. If these patients were treated with neoadjuvant therapy, and those who do not have evident

metastatic disease or local progression on conclusion were taken to surgery, then the number of patients with PDAC eligible for potentially curative therapy would significantly increase.

A rational treatment approach to patients with borderline resectable PDAC of the pancreatic head includes use of neoadjuvant chemotherapy and chemoradiation prior to surgery (9). For patients with borderline resectable cancers, this strategy offers multiple theoretical advantages over an initial surgical approach: 1) early delivery of effective systemic therapy to a group of patients in whom micrometastatic disease is ubiquitous, 2) higher probability of R0 surgical resection, 3) superior patient functional status at the time of therapy, 4) selection of patients with favorable cancer biology for attempted surgery, 5) better tumor oxygenation and drug delivery for chemoradiation, and 6) smaller radiation fields (compared to the adjuvant setting) resulting in less treatment-related toxicity. The use of a neoadjuvant treatment strategy ensures that all patients who undergo surgery receive all components of multimodality care. Furthermore, patients who do not undergo resection still receive active anticancer therapy.

At present, data supporting a neoadjuvant approach to borderline resectable PDAC are essentially limited to single-institution retrospective reviews (3-6). The ECOG opened a multi-institutional trial in 2003 to explore therapy for this stage of disease but it was terminated early owing to lack of accrual (7). Since then, a universally-accepted radiographic definition of borderline resectable PDAC has not been established, and standardization of preoperative assessment and staging, surgical decision-making and technique, and integration of drug therapy and chemoradiation has not been accomplished (8). Because of this absence of standardization, patients with borderline resectable cancers are often treated as inoperable, and are therefore denied a chance at cure.

This proposed study will prospectively define a group of patients with borderline resectable PDAC and will evaluate the efficacy of a promising—potentially curative—multimodality regimen. The design of the experimental regimen is consistent with previously published consensus recommendations (9). Critically, this study will establish and utilize standardized definitions of and procedures for: 1) the radiographic definition of borderline resectable PDAC, 2) selection criteria for a neoadjuvant strategy, 3) the indications for operative intervention following induction therapy, 4) surgical technique, and 5) pathologic review of the surgical specimen (11).

1.3 Definition of Borderline Resectable PDAC

No universally accepted definition of borderline resectable PDAC exists (8). Two major definitions have been proposed, neither of which was based on prospective data. The MD Anderson anatomic definition (5) differs from that recently proposed by the American Hepato-Pancreato-Biliary Association (AHPBA), Society of Surgical Oncology (SSO), and Society for Surgery of the Alimentary Tract (SSAT) (10), particularly with regards to the classification of tumors with minimal involvement of the mesenteric veins. The MD Anderson definition was developed within the context of a bias toward the use of preoperative therapy for both resectable and borderline resectable cancers. That definition includes only patients with outright venous occlusion in the borderline resectable category—any more limited involvement is considered potentially resectable disease. The AHPBA/SSO/SSAT definition, on the other hand, was developed as the basis for recommendations regarding treatment sequencing among a group consisting of investigators largely supporting the use of preoperative therapy only for patients with more advanced disease in whom vein resection might be required. This definition classifies primary cancers with any degree of vein involvement—from slight abutment to outright venous occlusion—as borderline resectable.

The definition of borderline resectable PDAC we include here is not inconsistent with either of these “consensus” definitions. The definition we include here:

- conforms to the spirit of previously proposed definitions of this disease: i.e., it clinically classifies a group of patients for whom margin negative resection is unlikely in the absence of vein resection or preoperative therapy,
- is consistent with prior radiographic data demonstrating that tumor involvement of more than ½ the circumference of a blood vessel is a highly specific predictor of unresectability in the absence of vascular resection (Lu 1997),
- is objective, reproducible, easy to implement, and does not rely on subjective, descriptive terminology,
- will provide a standard, data-driven definition for subsequent use.

1.4 Neoadjuvant Therapy for Borderline Resectable PDAC

No randomized controlled trial specific to borderline resectable PDAC has yet been completed. The ECOG failed to complete a randomized phase II study of chemoradiation with gemcitabine versus induction chemotherapy using gemcitabine/cisplatin/5-FU followed by chemoradiation with 5-FU (7) due to poor accrual. However, both preoperative regimens were tolerated.

Several institutions have reported single-center experiences with this stage of disease. In the largest, 84 patients with anatomically borderline resectable tumors were treated at MD Anderson with 5-FU- or gemcitabine-based chemoradiation, typically preceded by systemic chemotherapy prior to planned resection (5). Of this group, 38% underwent resection—97% of which were R0. The median survival of all patients was 21 months: 40 months for resected patients and 15 months for patients who did not undergo resection. These investigators subsequently demonstrated the benefit of chemoradiation therapy at the oncologically critical superior mesenteric artery margin among patients with this disease stage (13). Other preoperative strategies have been used successfully by other investigators, including: Fox Chase Cancer Center has examined chemoradiation followed by chemotherapy (3), the University of Cincinnati examined gemcitabine based chemotherapy (14), and the University of Virginia examined chemoradiation alone with capecitabine as the concurrent agent (6).

A national consensus statement was recently published (9). This statement advises that patients with borderline resectable PDAC should be treated first with chemotherapy, and then consolidated with chemoradiation and surgery if appropriate.

1.5 Neoadjuvant Therapy for Resectable PDAC

With respect to specific studies in resectable disease, investigators at MD Anderson Cancer Center have published their most recent results (15,16). In the first study, 86 patients with resectable disease in the head of the pancreas were enrolled and received radiation therapy (30 Gy in 10 fractions over 2 weeks) plus 7 weekly infusions of gemcitabine at 400 mg/m². 85% of patients were taken to surgery and 74% underwent pancreaticoduodenectomy. Median survival for the resected patients was 34 months and was 7 months for those who could not be resected. In the second study in patients with resectable adenocarcinoma of the pancreatic head, a combination of gemcitabine and cisplatin was administered for eight weeks followed by combined low dose gemcitabine and radiation therapy of 30 Gy. Ultimately, 78% of patients were taken to surgery and 66% were resected with a median survival of 31 months for those who had surgery, versus 10.5 months for those who did not. These findings are similar to those of other centers reporting results with preoperative chemoradiation for potentially resectable cancers (17,18). In a comprehensive meta-analysis and systemic review of the use

of preoperative therapy (19), 74% of treated patients with resectable PDAC underwent resection. The median survival was 23.3 (range 12 – 54) months among patients who did.

In aggregate, the studies of neoadjuvant therapy show that preoperative multimodality therapy is feasible and tolerable in patients with resectable and borderline resectable PDAC. Patients who undergo surgery following such therapy have better outcomes than patients who do not.

1.6 “Neoadjuvant” Therapy for Locally Advanced PDAC

With respect to the administration of “preoperative” therapy in locally advanced, unresectable disease, recent results have been reported from Austria with neoadjuvant gemcitabine/oxaliplatin without RT (39% of patients resected with 69% R0 and 22 months median survival (20), Italy with neoadjuvant PEFG/PEXG/PDXG followed by RT with capecitabine, 5-FU or gemcitabine (14% resected with median survival 16.2 months) (21) and Japan with neoadjuvant gemcitabine 1000 mg/m²/wk and RT 50 Gy in T3 disease followed by postoperative 5-FU liver perfusion (82% of patients resected, 43% 5 year survival) (22).

In studies like these, enrollment of both borderline resectable (in whom surgery is feasible) and locally advanced cancers (in whom surgery is unlikely regardless of therapy) prohibits accurate interpretation of study results. Furthermore, the degree to which patients were seriously considered for operation following chemotherapy/chemoradiation in these and similar studies is unclear. Indeed, a recently published systematic review of phase II studies in which patients with locally advanced disease were reportedly re-evaluated for surgery following therapy found resection rates of 8.3 – 64.2% (median 26.5%) with a median survival of all patients ranging from 9 – 23 (median 13.3) months (23). It is also important to note that in most studies like these, the standards for exploration following treatment vary. In the meta-analysis described above (19), for example, the methods to assess tumor response prior to surgery were clearly reported in only 39.6% of evaluated studies; in 55% the criteria were either not clearly defined or not stated at all. In that review, estimated median survival was 20.5 (range 9 – 62) months for the 33% of treated patients with locally advanced cancers who underwent resection following therapy.

1.7 Palliative Therapy for Locally Advanced PDAC

Patients with locally advanced PDAC treated with palliative strategies have a median OS of 8 – 14 months (24-28). Patients with locally advanced PDAC treated with chemotherapy followed by chemoradiation may have a slightly more favorable (15 months) survival (29).

1.8 FOLFIRINOX for Pancreatic Cancer

The initial phase II study of FOLFIRINOX for patients with PDAC enrolled 47 chemotherapy-naïve patients with metastatic disease and 46 were treated (33). The regimen included administration of oxaliplatin 85mg/m², irinotecan 180 mg/m², leucovorin 400 mg/m², 5-FU 400 mg/m² on day 1, then 5-FU 2400 mg/m² as a 46 hour continuous infusion. Confirmed response rate was 26% with 4% complete responses. Median time to progression was 8.2 months and median overall survival was 10.2 months. Grade 3/4 toxicities included neutropenia (52%), nausea (20%), vomiting (17%), diarrhea (15%), and neuropathy (15%). No toxic death occurred.

FOLFIRINOX then was tested in metastatic disease after failure of previous gemcitabine therapy (30). 13 patients were treated, with 9 evaluable for response. Six patients experienced stable disease with a mean time to progression of 6.6 months, and 3 patients had disease progression.

A randomized phase II/phase III study comparing gemcitabine to FOLFIRINOX as first line treatment of metastatic pancreatic cancer soon followed (31). 342 patients were accrued;

approximately 1/3 of patients had cancers of the head of the pancreas. Overall objective response rate was 32% versus 9.4% with gemcitabine. PFS was 6.4 months versus 3.4 months and overall survival 11.1 months versus 6.8 months, both in favor of FOLFIRINOX. Notable toxicities of at least grade III/IV, which were all worse with FOLFIRINOX, included neutropenia (45.7 vs 18.7%), febrile neutropenia (5.4 vs 0.6%), fatigue (23.7 vs 14.2%), vomiting (14.5 vs 4.7%) and diarrhea (12.7 vs 1.2%). Although the toxicities associated with this regimen are not insignificant, recent proposals have suggested that modifications to this regimen (omission of the bolus of 5FU, prophylactic administration of G-CSF and more intensive supportive care) may result in safer therapy with fewer grade III or IV events, while not compromising efficacy.

1.9 Postoperative Gemcitabine as Adjuvant Therapy for Resected Pancreatic Cancer

Gemcitabine is currently the standard of care for patients with resected PDAC in the postoperative setting (1) FOLFIRINOX has not been subjected to study in this setting as yet and would therefore add an undesirable extra dimension of complexity and uncertainty to the protocol. We also believe that it is a more toxic and therefore difficult regimen to administer in the postoperative setting where patients struggle to complete additional chemotherapy. Appropriate dose modification of gemcitabine as needed usually allows for successful delivery of treatment without the added cost and complexity of growth factors.

1.10 Correlative Study Rationale and Design

Pancreatic ductal adenocarcinoma has been largely left behind in the genomic revolution occurring in oncology today. This is in no small part due to the paucity of tissue collected and the difficulty inherent in working with pancreatic tumors with high stromal content/low cellularity. The correlative study in A021101 will compare alternative methods of tissue acquisition in PDA to one another with molecular analytes such as genomic DNA suitable for next generation sequencing as the endpoint. After DNA isolation, quantitative sequencing of the KRAS gene will be performed to estimate both DNA quality and cellularity.

The majority (>90%) of PDAs harbor activating mutations in KRAS. Thus, it is possible to estimate cellularity of a given PDA sample by using PCR to amplify all copies of the KRAS genes (in both stroma and tumor cells), and then to quantitatively sequence the PCR product. This results in a quantitative assessment of stromal contamination (32).

1.11 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of 5-FU, oxaliplatin, irinotecan, gemcitabine, or capecitabine treatment in subsets defined by race, gender, or ethnicity, and there is no reason to expect that such differences exist.

Accrual Targets					
Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	0	+	0	=	0
Not Hispanic or Latino	9	+	11	=	20
Ethnic Category: Total of all subjects	9	+	11	=	20
Racial Category					

American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	0	=	0
Black or African American	0	+	0	=	0
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	9	+	11	=	20
Racial Category: Total of all subjects	9	+	11	=	20

2.0 OBJECTIVES

2.1 Primary Objectives

- 2.1.1 To assess the accrual rate of this study.
- 2.1.2 To assess the rate of treatment-related toxicity and treatment delay during preoperative therapy.
- 2.1.3 To assess the rate of completion of all preoperative and operative therapy.

2.2 Secondary Objectives

- 2.2.1 To assess the macroscopic (R0/R1) resection rate.
- 2.2.2 To estimate the rate of radiographic and histopathologic response to preoperative therapy.
- 2.2.3 To estimate the time to locoregional and distant recurrence.
- 2.2.4 To assess overall survival (OS).
- 2.2.5 To retrieve nucleic acids from pretreatment pancreatic ductal adenocarcinoma biopsies and to assess the quality of these nucleic acids using a sequencing-based assessment of tumor DNA.

3.0 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 will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Documented psychiatric illness, which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral

contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).

- Inability to take oral medications.
- Biliary decompression should be performed if clinically warranted. Biliary decompression may be performed during the pre-registration phase and should be accomplished endoscopically, preferably with a short metallic stent.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the Alliance Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

4.1 Pre-registration Eligibility Criteria

4.1.1 Documentation of Disease and Radiographic Staging

- Cytologic or histologic proof of adenocarcinoma of the pancreatic head or uncinate process.
- Objective radiographic staging with a) contrast-enhanced, helical thin-cut CT/MRI scan of the abdomen and b) CT scan/MRI of the chest.

Note: Echoendoscopic staging will be permitted as an adjunctive modality, but all stage definitions below will be determined using CT/MRI as outlined below. In the event echoendoscopic stage and CT/MRI stage are discordant, the CT/MRI stage will be used. Significant discordance should be discussed with the study PI prior to enrollment.

- Borderline resectable primary tumor, defined by the presence of *any one or more* of the following on CT/MRI, and confirmed by central radiographic review ([see Section 6.4](#)):
 - An interface between the primary tumor and the superior mesenteric vein or portal vein (SMV-PV) measuring $\geq 180^\circ$ of the circumference of the vessel wall
 - Short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction
 - Short segment interface (of any degree) between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and reconstruction.
 - An interface between the tumor and SMA measuring $< 180^\circ$ of the circumference of the vessel wall.

No Potentially Resectable Disease Defined as Primary Tumors with *all* of the following:

- An interface between the primary tumor and the SMV-PV measuring $< 180^\circ$ of the circumference of the vessel wall
- No radiographic interface between the tumor and the SMA, hepatic artery or celiac axis
- No radiographic evidence of metastatic disease

No Metastatic Disease Defined as *any one or more* of the following:

- Suspicious lymphadenopathy outside the standard surgical field (i.e., aortocaval nodes, distant abdominal nodes)

- Radiographic evidence for metastatic disease in distant organs, such as masses in distant organs or ascites

No locally advanced and/or unresectable disease clearly defined by *any one or more* of the following by CT/MRI:

- An interface between the tumor and the SMA measuring $\geq 180^\circ$ of the circumference of the vessel wall.
- No interface between the tumor and the aorta.
- Occlusion of the SMV or portal vein without a sufficient cuff of normal vein above and below the level of obstruction with which to perform venous reconstruction.
- Long-segment interface (of any degree) between the tumor and the common hepatic artery or its major tributaries with insufficient artery proximal and distal to the interface to perform reconstruction.

4.1.2 No prior chemotherapy or chemoradiation for pancreatic cancer.

4.1.3 No patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for ≥ 3 years.

4.1.4 Baseline peripheral sensory neuropathy must be grade < 2 .

4.1.5 No patients with known Gilbert’s Syndrome or homozygosity for UGT1A1*28 polymorphism.

4.1.6 No history of pulmonary embolism in the past 6 months.

4.1.7 Age ≥ 18 years of age

4.1.8 ECOG/Zubrod Performance Status 0 – 1

4.1.9 Pregnancy/Nursing Status:

Non-pregnant and non-breast-feeding. Female participants of child-bearing potential must have a negative urine or serum pregnancy test prior to registration. Perimenopausal participants must be amenorrheic > 12 months to be considered not of childbearing potential.

4.1.10 Required Pre-registration Laboratory Values

Granulocytes	$\geq 2,000/\mu\text{l}$
Hemoglobin	> 9 g/dL
Platelets	$\geq 100,000/\mu\text{l}$
Albumin	> 3.0 g/dL
Creatinine	≤ 1.5 x ULN
AST (SGOT) & ALT (SGPT)	≤ 2.5 x ULN

4.2 Registration Eligibility Criteria

4.2.1 Confirmation of [Section 4.1.1](#) by the Alliance central radiographic review (see [Section 6.1.3](#)).

4.2.2 Required Registration Laboratory Value:

Bilirubin	≤2 mg/dl
CA19-9	<1000 U/ml (from timepoint when bilirubin is ≤2 mg/dl)

5.0 PRE-REGISTRATION AND REGISTRATION

Patients who meet the pre-registration eligibility criteria will be pre-registered. Once a patient is pre-registered the staging CT scans will be centrally reviewed to confirm the patient meets the radiographic criteria for borderline resectable pancreatic cancer. Once the site receives confirmation from the central imaging reviewers and the registration criteria have been met the patient can be registered.

5.1 OPEN Registration System Access Requirements

OPEN Access Requirements: All participating institutions will use the OPEN (Oncology Patient Enrollment Network) to enroll patients to this study. OPEN is a web-based registration system for patient enrollments onto NCI-sponsored cooperative group clinical trials. OPEN provides the ability to enroll patients 24 hours a day, 7 days a week.

OPEN may be accessed at <https://open.ctsu.org>, from the OPEN tab on the CTSU website at <https://www.ctsu.org>, or from the OPEN Registration tab on the ALLIANCE website.

To enroll a patient within OPEN, institution staff must have:

1. A valid and active CTEP-IAM account. This is the same user ID and password used for CTSU's website (for more information see https://www.ctsu.org/public/CTEP-IAM_Factsheet.pdf).
2. Enrollment of patients on ALLIANCE coordinated protocols requires a "Registrar" role in the ALLIANCE roster. Assignment of the "Registrar" role is managed through the ALLIANCE Central Office via submission of a roster update form signed by the Principal Investigator of the member network.

5.2 Pre-registration

Pre-registration Requirement: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form is required.

Patient Pre-registration Procedures

- Patients will be pre-registered to A021101 using the OPEN registration system. OPEN may be accessed at <https://open.ctsu.org>, from the OPEN tab on the CTSU website at <https://www.ctsu.org>, or from the OPEN Registration tab on the ALLIANCE website.
- The OPEN system will provide the registering site with a printable confirmation of pre-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923, or ctsucontact@westat.com.

After the patient has been pre-registered the staging scans should be sent to the Alliance Imaging Core Lab, per [Section 6.1](#). If, within 21 days of scan submission not all registration eligibility criteria are met, the patient should not be registered.

5.3 Registration

Registration Requirement: Patients must be evaluated by a medical oncologist, surgeon and radiation therapist prior to registration.

Registration Procedures: The Alliance Imaging Core Lab will notify the pre-registering site, within 3 business days of receipt, whether or not the patient is eligible based on the central imaging review. Patients will then be registered using the OPEN system (registration will occur within 21 days of scan submission). The CRA should enter the ID number obtained at pre-registration into the OPEN system to register the patients. The OPEN system will provide the institution with a printable confirmation of registration. Please print this confirmation for your records.

- Registration to Companion Study

The correlative science substudy must be offered to all patients enrolled on A021101. The substudy included with A021101 is: A021101-ST1, Correlative Science Study in A021101.

If the patient answers “yes” to “ I agree that my specimens may be used for the research described above” question #1 in the model consent, they have consented to participate in the substudy described in [Section 6.3](#). The patient should be registered to A021101-ST1 at the same time they are registered to the treatment trial (A021101). Samples should be submitted per [Section 6.3](#).

6.0 IMAGING REVIEW, PATHOLOGY REVIEW, CORRELATIVE SCIENCE SUBSTUDY, DATA SUBMISSION, AND SURGICAL QUALITY ASSURANCE

6.1 Imaging Review

6.1.1 Institutional Imaging Credentialing Procedures

Prior to the enrollment of patients on A021101, institutions must be credentialed by the Alliance Imaging Core Laboratory (ICL) at The Ohio State University Medical Center. If the site is already credentialed by the ICL to participate in imaging studies, the ICL will provide a brief A021101 protocol refresher prior to the site enrolling patients on this trial.

6.1.2 Imaging Guidelines

CT scans are preferred over MRI and should be used if possible (unless the patient is allergic to contrast or has renal insufficiency, for example). The same method of scanning must be used at baseline and for all subsequent evaluations.

CT Scan

Dual phase imaging

- Slice thickness: No thicker than 3mm images (however, a set of axial images 2-3 mm for review of each phase is needed). Thinner images, if obtained, should also be submitted (in case reconstructions are needed).
- Injection rate: Faster is preferable, but whatever the injection rate, the duration of the injection should be at least 30 seconds (in order to image during the pancreatic parenchymal phase, and given an average cardiac circulation time of 13-16 seconds). Injection rates should be 3-5cc/second (unless poor IV access requires slower injection times).

- Pancreatic parenchymal phase: Imaging of the abdomen (whether the entire abdomen, or just of the pancreas) should finish approximately 45-50 seconds after contrast injection terminating below the level of the horizontal course of the duodenum.
- Portal venous phase: Imaging of the entire abdomen, to begin 55-70 seconds after the start of contrast injection, to cover the liver, and pancreas to the level of the iliac crest.
- For both phases, coronal and sagittal reconstructions (2-3mm thick, every 2-3mm)

NOTE: Separate/dedicated CTs of chest/upper abdomen must be obtained at all required time points.

MRI Scan (Dynamic contrast enhanced MRI for preoperative staging of the pancreas)

Equipment: 1.5 Tesla or 3 Tesla with a dedicated surface coil capability and appropriate experiences. Patients need to be scanned on the same MR system for consistency between baseline and follow-up examinations.

Pre-contrast Imaging

- SSFSE/ HASTE T2 coronal scouts 5-8 mm thickness (with or without breath-hold, per institutional standards)
- In-Out phase T1 breath-hold T1 GRE (4-6 mm thickness) to cover liver and pancreas
- Out- phase T1 GRE with or without fat sat (4-5 mm thickness) for pancreas only
- Respiratory Triggered FSE T2 weighted images (4-6 mm thickness for liver and pancreas)
- 2D or 3D MRCP sequence for the pancreas as performed in your institution

Contrast Scanning

- Sequence- 3D or 2D VIBE or SPGR/ LAVA T1 GRE (2-6 mm thickness, not >7 mm for 2D sequence) acquired preferably in the coronal or axial plane. First acquire a non-contrast sequence for confirming the coverage and quality.
- Inject Gd-chelate MR contrast volume with weight-based dosing according to the product label @ 2cc/sec.
- Dynamic scanning using a 3D or 2D VIBE or SPGR/ LAVA T1 GRE (2-6 mm thickness) is then performed in the same plane as the pre-contrast scanning at 20/70/180 seconds delay after contrast medium injection.
- Axial and coronal T1 out-phase T1FS GRE/VIBE through the liver and pancreas (same thickness as dynamic above). If needed use two sequences to cover the anatomy.

Chest CT

Lung lesions should be excluded with either CT or MRI of the chest.

6.1.3 CT Submission Instructions

The following images will be collected digitally for centralized, real-time re-review:

- Baseline (prior to study treatment)
- Time of pre-surgical restaging

The complete CT/MRI scan in digital **DICOM** format will be submitted to Alliance Imaging Core Laboratory. BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the Imaging Core Laboratory. The Imaging Core Lab will notify site and Alliance A021101 imaging

committee within **2 business days** of the data receipt as well as within **3 business days** of the quality check report upon data receipt.

Sites need to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g., 112136) and protocol number (e.g., A021101), respectively.

For baseline staging and pre-surgical restaging CT/MR scans, imaging data must be submitted to the Imaging Core Lab **electronically** via Web-based data transfer and FTP data transfer approaches for real-time central review purposes. For CT and/or MR scans at other time points, CD/DVD Shipment is acceptable. All CT/MRI images will be collected digitally for archival purposes.

Web-based data transfer:

Any PCs with Internet access can be used to upload images to the Imaging Core Lab via this approach. The standard Web access information will be provided separately through the specific trial e-mail Alliance021101@ImagingCoreLab.com, per the request by participating sites before their first data submission.

FTP Transfer:

Any FTP software can be used to upload images to the secure FTP Server of the Imaging Core Laboratory. The standard FTP access information will be provided separately through the specific trial e-mail Alliance021101@ImagingCoreLab.com, per the request by participating sites before their first data submission.

Shipment/Mail Transfer:

If the electronic data transfer approaches cannot be achieved at sites, the de-identified digital images in DICOM format can be burned to CDs, labeled with Alliance A021101 patient ID (e.g., 112136), date of study and study period (e.g., baseline, D22-28), and mailed to the Imaging Core Lab at:

Alliance Imaging Core Lab
 Attn: Alliance A021101
 Wright Center of Innovation
 The Ohio State University
 Rm#414, 395 W. 12th Ave
 Columbus, Ohio, 43210
 Direct: (614) 293-2929 Office: (614) 293-2788
 Fax: (614) 293-9275

Send an e-mail notification to inform the Imaging Core Lab at Alliance021101@ImagingCoreLab.com of the imaging data submission once the data transfer is completed. Any questions or problems about the data transfer to the Imaging Core Lab, call the Core Lab IT group at 614-293-2630 or 614-366-4932 for help.

6.2 Pathology Review

6.2.1 Central Review of Resected Tumor following Surgery

All patients undergoing surgery will have a tissue block submitted for standardized central determination of treatment effect score and tumor grade following complete initial local histopathologic review. A tissue block from a representative section of resected tumor is required, along with the de-identified surgical pathology report, coded with the Alliance patient ID number.

The Alliance has instituted special considerations for the small percent (5%) of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage (4%) of

hospitals whose policies prohibit release of any block. Contact the Alliance Pathology Coordinating Office (Tel: 614-293-7073) with questions concerning the processing and storage of blocks as well as to obtain an alternative cutting schema for this protocol.

6.2.2 Submission of Pretreatment Cytology in Patients with a Pathologic Complete Response following Protocol Surgery

It is anticipated that the pretreatment diagnosis of pancreatic adenocarcinoma will be established by fine needle aspiration (FNA) cytology in most cases. Less commonly, core needle biopsy may have been performed for initial diagnosis. All patients will undergo local pathology review of the biopsy for confirmation of diagnosis.

Following protocol surgery, in the unlikely event that the surgical pathology report of the resected tumor demonstrates no pathologic evidence of malignancy (i.e., pathologic complete response; pCR) or an unexpected histology other than adenocarcinoma, the pretreatment diagnostic cytology/pathology specimens and representative slides of the resected post-treatment specimen will be requested and reviewed at the Alliance Pathology Coordinating Office. The following materials, derived from formalin fixed, paraffin embedded diagnostic and surgical pathology tissue blocks are required for central pathology review:

One stained representative slide of the FNA or core needle biopsy containing unequivocal adenocarcinoma is required. The de-identified surgical pathology report, coded with the Alliance patient ID number, must accompany all tissue sample submissions.

6.2.3 Sample Shipping Instructions

All submitted specimens must be labeled with the protocol number (A021101), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood). For tissue specimens the labeling should include institutional surgical pathology case number and block number.

Specimens for patients registered on this study must be logged and shipped using the online Alliance Specimen Tracking system. All institutions may access this system via the Alliance Web site, <http://www.calgb.org>. A copy of the Shipment Packing Slip produced by the ALLIANCE Specimen Tracking System must be printed and placed in the shipment with the specimens.

USE OF THE SPECIMEN TRACKING SYSTEM IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

For procedural help in logging and shipping specimens, please refer to the Specimen Tracking System User Guide, which can be accessed via the Help link within the Specimen Tracking System.

To report technical problems with the Alliance Specimen Tracking System, such as login issues or application errors, and/or for further assistance using the application, please contact the Alliance Help Desk at 877-442-2542 or calgb-support@calgb.duhs.duke.edu.

The paraffin blocks should be sent within 30 days of registration or surgery. The aliquoted, frozen plasma samples should be shipped within 30 days on dry ice by overnight express courier to:

Alliance Pathology Coordinating Office (PCO)
 Innovation Centre
 2001 Polaris Parkway
 Columbus, OH 43240
 Tel: 614-293-7073

Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary. Samples should be shipped Monday-Friday by overnight service. IF SHIPPING ON FRIDAY, FEDEX OR UPS MUST BE USED AND THE AIR BILL MUST BE MARKED "FOR SATURDAY DELIVERY." DO NOT SHIP SPECIMENS ON SATURDAYS.

6.3 Specimen Submission for Correlative Study

All participating institutions must ask patients for consent to participate in the correlative science study in A021101 (A021101-ST1), although patient participation is optional. The pre-treatment biopsy will be submitted to the PCO, see [Section 6.2.3](#) (sample shipping instructions) for information on where to submit the pre-registration biopsy.

6.4 Data Submission

This study will use Medidata Rave for remote data capture (RDC) of all study data. Access the RAVE system through the iMedidata portal at <https://login.imedidata.com>.

For additional information regarding account set up, training, technical questions or difficulties concerning Medidata RAVE go to <https://www.calgbapps.org/confluence/display/HELP/Rave+Help+Menu>.

For questions regarding forms completion and submission, please contact the Data Manager listed on the Protocol Resources page of the protocol.

6.5 Surgery

6.5.1 Surgical Protocol Quality Assurance Requirements

The Surgical Quality Data Sheet (SQA A021101 Surgical Quality Assurance Form) will be completed by the Surgical Study Chair within 30 days after surgery. Surgical data from this study will be reviewed at regular meetings of the Surgical Quality Assurance Committee (SQAC) of the Alliance. This committee meets quarterly to review ongoing Alliance protocols with surgical components.

Any deviations in surgical quality identified by the SQAC will be addressed by the surgical Co-Chair of this trial (Dr. Syed Ahmad).

All AE in the post-operative period will be documented to determine risk of complications related to neoadjuvant FOLFIRINOX therapy followed by chemoradiation and surgery.

6.5.2 Surgical Quality Assurance (Procedure)

Credentialing

This study will not require credentialing of the operating surgeon. However, this study is a limited access study designed for centers skilled at the multidisciplinary management of pancreas cancer. Enrolling centers will perform more than 12 pancreaticoduodenectomies per year. The operating surgeon will be skilled at vascular resection and reconstruction procedures or should partner with a vascular surgeon as necessary.

Deviations in Protocol Performance in Relationship to Surgery

Major Deviations

The following will be considered major protocol deviations:

- Surgery prior to 4 weeks or greater than 10 weeks after completion of radiation.
- Arterial resection excluding segmental hepatic artery (SMA or celiac trunk).

Minor Deviations

The following will be considered minor protocol deviations:

- Failure to perform a frozen section of bile duct or pancreatic neck margins at the time of surgery.
- Incomplete documentation and/or characterization of dissection of uncinata off of SMA.

7.0 REQUIRED DATA

Pre-Study Testing Intervals

To be completed within 16 DAYS before pre-registration:

- All bloodwork
- History and physical

To be completed within 28 DAYS before pre-registration:

- CT scan/MRI used for staging

	Prior to Pre-Reg*	Prior to Reg	Induction (Day 1 of each cycle)	Re-staging**	Combined ChemoRT (Day 1 of each cycle)*	Surgery*	Adjuvant Therapy (Day 1 of each cycle)*	Post Tx Follow-up***
Tests & Observations								
Physical (physician/PA/APN visit)	X		X		X		X	
Pulse, BP	X		X		X		X	X
Height	X							
Weight/BSA	X		X		X		X	X
Perf. Status	X		X		X		X	X
Drug Toxicity Assessment (can be non-physician)			Weekly		Weekly		X	
Laboratory Studies								
CBC, Differential, Platelets	X		X	X	X		X	X
AST/ALT, Alk phos	X		X	X	X		X	X
Total bilirubin		X	X	X	X		X	X
BUN, Creat, Na/K/CL, CO ²	X		X	X	X		X	
Pregnancy Test****	X							
PT/INR	X					X		
CA 19-9		B		X				X
Staging								
Staging CT Scan or MRI of chest/abdomen/pelvis	X			X	Restage**	Restage**		X
Radiographic Review	X			X	Restage**			
Histologic Review						A		
Substudy								
Pre-treatment Specimen								

* Pre-registration labs may be used for day 1 of cycle 1 tests if obtained within 7 days prior to day 1 of Cycle 1. For subsequent cycles labs may be obtained within 48 hours prior to day of treatment.

** Restaging will take place at 3 timepoints: After induction therapy, after combined chemoradiotherapy, and after surgery. During protocol therapy central radiology review is required after the combined chemoradiotherapy. The treating physician will discuss the surgical plans with the Alliance imaging reviewers and the Study Chair before surgery occurs.

All restaging laboratory studies can be used as day 1, cycle 1 labs if obtained within 14 days of treatment.

*** At least every 4 months for 3 years for all patients that have received surgery, then follow for survival. For those patients that discontinue therapy at any time prior to surgery, follow only for survival.

**** A pregnancy test is required in patients of child-bearing potential.

A All patients will have slides from their surgical specimens submitted for a central review. Those patients that have no pathologic evidence of malignancy at surgery will need to have their initial, pre-registration biopsy submitted to the PCO for evaluation.

B Required prior to registration only when bilirubin ≤ 2 .

C For patients that consented to the optional substudy, A021101-ST1, the pre-registration biopsy will be submitted to the PCO, as outlined in [Section 6.3](#).

8.0 TREATMENT PLAN

Protocol treatment is to begin within 7 days of registration. Questions regarding treatment should be directed to the Alliance Study Chair.

The following is a sequence of events for this trial:

- **mFOLFIRINOX:** Register and receive mFOLFIRINOX therapy within 7 days following registration.
- **Restage/Break/Real-time QARC RT review:** Following mFOLFIRINOX, patients will be given a 2-6 week break. Within 2 weeks of initiation of chemoradiation, all patients will be restaged. Submit the radiotherapy dose plan to QARC at least 7 days prior to the combined chemoradiation. The RT plan must be approved by QARC before proceeding to combined chemoradiation.
- **Combined Chemoradiation:** After the 2-6 week break, with RT plans reviewed/approved by QARC, treat patients with the combined chemoradiation.
- **Restage/Break/Real-time Imaging Review:** Following the combined chemoradiation patients will take a 4-10 week break before surgery. Within two weeks of the scheduled operation date, patients will be restaged. The restaging scans will be submitted for real-time review to the ICL. The ICL will then contact the site with information about the recommended treatment plan (surgery vs. no surgery, based on response).
- **Surgery:** Patients with resectable or borderline resectable tumors, as confirmed by the ICL, will proceed to surgery. Pancreaticoduodenectomy will occur 4-10 weeks after the last dose of capecitabine. Following surgery, a tissue block will be sent to the PCO for review. In the rare case that a patient will have no evidence of disease at surgery, a specimen from the pre-registration biopsy will also need to be submitted to the PCO to confirm the diagnosis.
- **Restaging/Break:** Following surgery patients will be restaged and will have a 6-8 week break prior to the start of gemcitabine.
- **Adjuvant therapy:** Patients will receive gemcitabine 6-8 weeks following surgery.

8.1 Induction Therapy (Chemotherapy)

mFOLFIRINOX (administered for 4 cycles pre-operatively; 1 cycle = 14 days)

- Oxaliplatin 85 mg/m² IV over 2 hours on Day 1, followed by
- Irinotecan 180 mg/m² IV over 90 minutes on Day 1, followed by
- Leucovorin* 400 mg/m² IV over 2 hours on Day 1, followed by
- 5FU** 2,400 mg/m² IV over 46 – 48 hours

* Alternatively, leucovorin may be administered concurrently with the last 30 minutes of oxaliplatin, and the entire 90 minutes of irinotecan

** 5FU is administered via infusion only; there is no bolus injection of 5FU

Initial Restaging - After completion of mFOLFIRINOX (Induction) Therapy

Evaluation should occur within 2 weeks prior to initiation of chemoradiation and should include assessments specified in the Required Data table. No central review of imaging will occur at this timepoint.

Based on the results of the initial restaging evaluation, the corresponding action below should be taken:

1. Radiographically responding or stable disease: Patients should proceed to chemoradiation per protocol.
2. Clinically significant local tumor progression that changes the stage of the primary tumor from borderline resectable to locally advanced: Patients should proceed to chemoradiation. **Please note that progression by RECIST criteria does not mean the patient discontinues protocol therapy.**
3. Evidence of obvious extra-pancreatic disease progression (to liver, peritoneum or other extra-pancreatic sites): Patients may be removed from protocol therapy and treated according to the local standard of care. Patients should be followed for survival only.
4. Decline in performance status without radiographic evidence for disease progression: Delay of chemoradiation should occur until performance status is recovered. If chemoradiation cannot be initiated within 6 weeks of completion of chemotherapy, patients may be removed from protocol therapy and treated according to the local standard of care. Patients will be followed for survival only.

8.2 Combined Chemoradiation (Capecitabine + Radiation Therapy)

Note: The dosimetric plan must be submitted at least 7 days prior to the start of treatment.

8.2.1 Capecitabine

Capecitabine 825 mg/m² PO twice daily Monday through Friday, beginning on day 1 of radiation and ending on day 28 of radiation (the final day). Capecitabine will be held during breaks in radiation for any reason (i.e. holidays, toxicity). Capecitabine dose should be rounded to the nearest 150mg.

8.2.2 Radiation Therapy

This protocol requires a “rapid review” PRIOR TO DELIVERY of radiation treatment. This rapid review is aimed at providing feedback from the Study Chairs on the institution’s contours and treatment plan. In order to accomplish this rapid review, plan data must be submitted digitally at least seven days prior to the start of radiotherapy. To

accomplish this, patients should be simulated and planned during the second cycle of chemotherapy.

Protocol radiation treatment must begin no sooner than 2 weeks and within 6 weeks after the last chemotherapy dose.

Credentialing

Either 3D conformal or intensity modulated radiation therapy (IMRT) planning techniques are allowed on this study. Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Conformal Benchmark; those treating with IMRT must complete the IMRT questionnaire and either the QARC Benchmark or irradiate the Radiological Physics Center's (RPCs) IMRT abdominal phantom. The benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) and must be submitted before patients on this protocol can be evaluated. Please contact the RPC (<http://rpc.mdanderson.org/rpc>) for information regarding their IMRT phantoms.

Technical Factors

Equipment: Photons of at least 6 MV will be used. IMRT is allowed, for which inverse-planning capable software is required. IMRT may be delivered either at fixed gantry angles with a multileaf collimator or in rotational mode using a multileaf collimator or tomotherapy. NOTE: Credentialing for IMRT is specific to the planning system and treatment mode that is used.

3D conformal plans must have a minimum of 3 or 4 fields with customized beam angles and weighting.

Localization, Simulation, and Immobilization

Treatment Planning Simulation

Treatment planning must be conducted after performing a restaging pancreatic protocol diagnostic CT. In order to optimize target delineation, the diagnostic images must be fused with the planning CT, or intravenous contrast must be used at the time of simulation unless there is renal insufficiency or iodine allergy. In case intravenous contrast is not used, an MRI scan should be obtained if possible and fused with the simulation images. Whether or not intravenous contrast is used, oral contrast (VoLumen is recommended) must be used at time of simulation. Patients will be simulated (and treated) supine with arms up. Immobilization is required. A thorax board is recommended. Planning scan slice thickness must be no greater than 3 mm.

In order to complete the rapid review process, plan data must be submitted digitally to the Quality Assurance Review Center (QARC) at least seven days prior to the start of radiation treatment. The treatment plan will be reviewed prior to the start of radiation therapy.

Set-Up Verification

Orthogonal images must be obtained on the first day of treatment for set-up verification and weekly thereafter. Either kilovoltage (kV) or megavoltage (MV) imagers may be used. IGRT techniques can be used and are recommended for daily imaging, but they will not be collected. Also, the use of IGRT cannot be used as a justification for the reduction of the margins. The patient should be aligned based on the vertebral bodies adjacent to the PTV.

Target Volumes

ICRU-50 and ICRU-62 prescription methods and nomenclature shall be utilized for this study.

Volume Definitions

- The GTV will include the primary tumor and regional adenopathy > 10 mm seen on the pre-chemotherapy protocol CT (scan obtained prior to FOLFIRINOX). There will be no intent to treat nodal regions prophylactically.
- The CTV is defined as the GTV plus a 10 mm expansion for microscopic extension in regions at risk (e.g., vertebral body to be excluded). Uninvolved regional nodes will NOT be included in the CTV.
- The PTV is defined as the CTV plus a 20 mm expansion in the cranial and caudal directions and a 10 mm expansion in the radial (lateral, anterior and posterior and oblique dimensions).

Dose Prescription

Dose Specification: Dose is to be prescribed to an isodose surface that encompasses the PTV and that satisfies the dose uniformity guidelines below.

Prescription Dose: The prescription dose will be 50.4Gy in 28 fractions (1.8 Gy per day).

Fractionation: Treatment shall be given 5 days per week.

Dose Uniformity: The minimum dose within the PTV must not fall below 97% of the prescribed dose. The maximum dose within the PTV must not exceed 110% of this dose.

Tissue Heterogeneity: Calculations shall take into account the effect of tissue heterogeneities.

Organs at Risk

- The normal structures to be contoured are: left and right kidneys, liver, stomach, duodenum, and spinal cord.
- Contour the kidneys, liver, stomach and duodenum in their entireties and any jejunum that is within 5 cm of the PTV.

(The structures listed in the table below must be contoured and the constraints listed can be used for treatment planning purposes.)

Structure	Constraints
Kidney (L & R)	Not more than 30% of the total volume can receive ≥ 18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥ 18 Gy.
Stomach, duodenum, jejunum	Max dose 55 Gy
Liver	Mean dose cannot exceed 30 Gy
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤ 45 Gy

Treatment Interruptions:

Treatment interruptions should be clearly documented in the patient's treatment record. If the sum total exceeds 10 break days, the treatment will be considered a major deviation. If any single break lasts over 21 days, the patient should be removed from protocol and treated per institutional standards.

Documentation Requirements

Quality Assurance Documentation

Digital Submission

Submission of treatment plans in digital format (either Dicom RT or RTOG format) is required. Digital data must include CT scans, structures, plan and dose files. Submission may be by either SFTP or CD. Instructions for data submission are on the QARC Web site at www.qarc.org. Any items on the list below that are not part of the digital submission may be included with the transmission of the digital RT data via sFTP.

- Prior to the start of radiotherapy, the following data shall be submitted for pre-treatment review:

External Beam Treatment Planning System

- a. RT treatment plans including CT, structures, dose and plan files. These items are included in the digital plan.
- b. Dose volume histograms (DVH) for the composite treatment plan for all target volumes and required organs at risk. A DVH shall be submitted for the organs at risk. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVHs are included in the digital plan.
- c. Digitally reconstructed radiographs (DRR) for each treatment field, showing the collimator and beam aperture. Please include two sets, one with and one without overlays of the target volumes and organs at risk. When using IMRT, orthogonal setup DRRs are sufficient.
- d. Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- a. All diagnostic imaging used to define the target volume.
- b. Prescription sheet for entire treatment.
- c. Documentation of an independent check of the calculated dose when IMRT is used.
- d. If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by QARC and the radiation oncology reviewers.

Forms

- RT-1/IMRT Dosimetry Summary

Within 1 week of the completion of radiotherapy, the following data shall be submitted for all patients:

- The RT-2 Radiotherapy Total Dose Record Form
- A copy of the patient's radiotherapy record including the prescription, and the daily and cumulative doses to all required areas, critical organs and reference points.
- Documentation listed above showing any modifications from the original submission.
- Supportive data and forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail (physics@qarc.org) or mailed to:

Quality Assurance Review Center
640 George Washington Hwy, Suite 201
Lincoln, RI 02865
Tel: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the completion of RT-1/IMRT Dosimetry Summary Form and RT-2 data forms, dose calculations or documentation should be directed to:

Protocol Dosimetrist
Quality Assurance Review Center
640 George Washington Hwy, Suite 201
Lincoln, RI 02865
Tel: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the radiotherapy section of this protocol, including treatment interruptions, should be directed to:

Dr. Joseph Herman
Johns Hopkins Hospital
Tel: 410-502-3823
Jherma15@jhmi.edu

Compliance Criteria

Prescription Dose

- Minor Deviation: The dose to the prescription isodose surface differs from that in the protocol by between 6% and 10%.
- Major Deviation: The dose to the prescription isodose surface differs from that in the protocol by more than 10%.

Dose Uniformity

- Minor Deviation: Minimum dose within the PTV is less than 97% of the prescribed dose, but does not fall below 93% of this dose or Maximum dose within the PTV is greater than 110% of the prescribed dose, but does not exceed 115% of this dose.
- Major Deviation: Minimum dose within the PTV is less than 93% of the prescribed dose or Maximum dose is greater than 115% of the prescribed dose.

Volume

- Major Deviation:
 - Incomplete contouring of the entire GTV or PTV;
 - Use of different margins than specified for the CTV and PTV;
 - Over-contouring of the GTV by >30cc (15cc if it results in inclusion of extra duodenum, small intestine or stomach);
 - Incorrect contouring of the duodenum, stomach or small intestine that results in >15 cc overlap of the PTV with the OAR.

Treatment Interruptions

- No Deviation: Treatment interruptions lasting up to 3 treatment days
- Minor Deviation: Treatment interruptions lasting 4 to 10 treatment days.
- Major Deviation: Treatment interruptions exceeding 10 treatment days.

Pre-operative Restaging - After completion of Combined Chemoradiation

Pre-operative evaluation should occur within 2 weeks prior to the planned surgery date and should include assessments specified in the Study Calendar. Real-time rapid central review of imaging by the Imaging Co-chair, Dr. Larry Schwartz, and Surgery Co-chair, Dr. Syed Ahmad, will occur. As soon as the re-staging scan results become available to the treating physician and prior to the initiation of any surgery or any non-protocol therapy, the re-staging CT or MRI scans of the abdomen must be submitted in digital format.

The treating physician will be contacted by telephone within 3 business days with information regarding the central re-review and recommended treatment plan. Based on the results of the pre-operative evaluation, including central review of the imaging, the corresponding action below will be taken:

1. Radiologically responding or stable disease: Patients should proceed to surgery per protocol.
3. Clinically significant local tumor progression that changes the stage of the primary tumor from borderline resectable to locally advanced: Patients should be removed from protocol therapy and treated according to the local standard of care. Patients will be followed for survival only.
2. Evidence of obvious extra-pancreatic disease progression (to liver, peritoneum or other extra-pancreatic sites): Patients should be removed from protocol and treated according to the local standard of care. Patients will be followed for survival only.
4. Decline in performance status without radiographic evidence for disease progression: Delay of surgery should occur until performance status is recovered. If surgery cannot be performed within 10 weeks from completion of chemoradiation, patients may be removed from protocol and treated according to the local standard of care. Patients will be followed for survival only.

8.3 Surgery

8.3.1 General Considerations

Pancreaticoduodenectomy should occur within 4-10 weeks after the last dose of preoperative chemoradiation. Staging laparoscopy may be performed at the time of planned laparotomy but is not required. Either standard or pylorus-preserving pancreaticoduodenectomy may be performed. Surgical drains and enteral tubes (e.g. gastrostomy and/or jejunostomy tubes) may be placed at the discretion of the operating surgeon.

8.3.2 Specific Considerations

Exploration of the peritoneal cavity should include evaluation for radiographically occult macroscopic peritoneal or hepatic metastases. Biopsy proof of liver or peritoneal metastatic disease (by frozen section assessment) should be considered criteria for abandoning planned pancreatectomy.

Lymph node sampling or frozen section lymph node biopsy is not required or recommended as part of the intraoperative assessment for extra-pancreatic disease, and is at the discretion of the surgeon.

The retroperitoneal dissection along the medial edge of the uncinate process and the right lateral border of the superior mesenteric artery is believed to be an important oncologic part of the operation. All soft tissue to the right of the superior mesenteric artery (SMA)

should be removed. This requires exposure and dissection along the right lateral border of the SMA.

Vascular resection and/or reconstruction of the superior mesenteric vein, portal vein, SMV/ Portal vein confluence, or hepatic artery will be done at the discretion of the operating surgeon. In general, vascular resection should be performed when necessary to achieve a R0 resection. The operating surgeon or a vascular surgeon consult can perform this reconstruction. The details of this operation should be delineated in the operative report.

8.3.3 Intraoperative Frozen Section Assessment of Surgical Margins

Frozen section evaluation of the pancreatic parenchymal and hepatic (or bile) duct margins should be performed. In the event of a positive frozen section margin at either of these loci, further resection in an effort to achieve microscopically negative margins should be performed if possible.

The superior mesenteric arterial (SMA) margin should be evaluated on permanent section only.

8.3.4 Specimen Orientation for Surgical Pathology

The surgeon should ensure that the specimen is oriented for the surgical pathologist. Any segment of resected vascular structure (e.g. superior mesenteric or portal vein) should be identified and marked. Relevant margins evaluated by intraoperative frozen section (i.e. the hepatic (bile) duct, and pancreatic parenchymal) should be identified. The SMA margin (the soft tissue immediately adjacent to the SMA) should be separately inked using the principles outlined in the 7th edition AJCC staging system for exocrine pancreatic cancer.

Note: The SMA margin cannot be identified accurately after the specimen has been fixed in formalin or after the specimen has been dissected for histopathologic analysis.

8.3.5 Operative Note Dictation and Editing: Resection Classification

The attending surgeon should dictate the operative note. The operative report should contain:

1. A section detailing the operative findings with respect to the extent of disease and the primary tumor anatomy.
2. A statement as to whether or not the surgeon believes there is residual macroscopic tumor.

The surgeon should integrate the operative findings with the microscopic surgical margins reported on the final pathology report in order to assign a resection classification prefix of R0, R1, or R2 (defined below). Whenever possible, this prefix should be added to the final operative note before finalizing the document. An example of the final procedure description for a patient who underwent macroscopically complete tumor removal with a positive SMA margin on permanent section final pathology is: "R1 pylorus-preserving pancreaticoduodenectomy."

The definitions for the resection classification that should be utilized in operative notes include:

- R0 – macroscopically complete tumor removal with negative microscopic surgical margins (bile duct, pancreatic parenchyma, and SMA margins)
- R1 – macroscopically complete tumor removal with any positive microscopic surgical margin (bile duct, pancreatic parenchyma, or SMA margins)

- R2 – macroscopically *incomplete* tumor removal with known or suspected residual gross disease

8.3.6 Surgical Pathology

A local pathologist experienced in the diagnosis of pancreatic adenocarcinoma should carry out pathological examination of the resected pancreatic tumor specimen. Following local review, a tissue block will be sent for central re-review.

Three primary margins (bile duct, pancreatic neck, and SMA) should be identified and inked by the surgeon and/or pathologist. Any segment of resected vascular structure (e.g. superior mesenteric or portal vein) should be identified and marked. The SMA margin (that tissue immediately adjacent to the SMA) should be separately inked according to the procedures and recommendations of the American Joint Commission on Cancer 7th edition staging system and the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). The tumor should be thoroughly sampled (at least one section per 1 mm of greatest tumor dimension, taken perpendicular to the inked SMA margin). The distance between the closest tumor cell and the inked SMA margin should be reported.

Frozen Section Assessment of Margins

Section assessment of bile duct and pancreatic neck margins should be performed by the local pathologist in all cases as requested by the surgeon (see [Section 8.3.3](#)).

Permanent Section Assessments and Final Pathology Report

The pathology report should contain all of the elements outlined in the College of American Pathologists guidelines for reporting of resected exocrine pancreatic cancer (2012). In particular, there should be specific comment on:

1. Histologic diagnosis with comment on the cell of origin (pancreatic vs. bile duct vs. ampulla)
2. Degree of differentiation (well, moderate, poor)
3. Total number of lymph nodes examined
4. Number of positive nodes
5. Final margins status for the bile duct, pancreatic parenchymal, and SMA margin
6. Distance (in mm) from the tumor to the inked SMA margin
7. Extent of tumor infiltration (if present) of the blood vessel wall for any resected major blood vessels including the maximum histologic depth of invasion (e.g., adventitia, media).

Central Re-Review of Resected Tumor Specimen

Representative slides should be sent for central re-review to standardize determination of both treatment effect score and tumor grade.

Treatment effect score will be determined using the following system:

Treatment Effect Score I- <5% residual tumor cells in the specimen

Treatment Effect Score II- ≥5% residual tumor cells in the specimen

8.3.7 Patients with Residual Gross Disease (R2 Resections)

In cases where the surgeon documents the presence of residual gross disease following surgery, patients may be removed from protocol therapy and treated at the discretion of the physician. The management of these patients should be done according to local practice standards for patients with residual gross disease or locally advanced disease.

8.3.8 Post-operative Restaging

Evaluation should occur within 2 weeks prior to initiation of postoperative chemotherapy and should include assessments specified in the Required Data table (Section 7.0). No central review of post-operative restaging will occur.

8.4 Adjuvant Chemotherapy (Gemcitabine)

Gemcitabine (administered for 2 cycles post-operatively):

Gemcitabine 1,000 mg/m² IV on days 1, 8 and 15 every 28 days.

9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

Dose levels for mFOLFIRINOX

Dose Level	5-FU Infusion (mg/m ²)	Leucovorin (mg/m ²)	Oxaliplatin (mg/m ²)	Irinotecan (mg/m ²)
0	2400	400	85	180
-1	1920	400	65	150
-2	1600	400	50	120
-3	1360	400	40	100

9.1 Dose Modifications during Induction Therapy (mFOLFIRINOX)

9.1.1 Hematologic toxicity

Note: mFOLFIRINOX dose modifications for hematologic toxicity are not based on CTCAE severity grades.

For ANC 1,000 – 1,200: Delay mFOLFIRINOX until ANC > 1,200, then resume mFOLFIRINOX at the same dose level.

Second or More Occurrence of ANC 1000 - 1200: Delay mFOLFIRINOX until ANC > 1,200, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. NOTE: the dose of leucovorin is not reduced.

For ANC < 1,000: Delay mFOLFIRINOX until ANC > 1,200, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. NOTE: the dose of leucovorin is not reduced.

For Febrile Neutropenia (defined as ANC < 1,000 and temperature ≥ 100.5°F): Delay mFOLFIRINOX until resolution of fever and ANC > 1,200, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

For Platelets 50,000 – 75,000: Delay mFOLFIRINOX until platelets > 75,000, then resume mFOLFIRINOX at the same dose level.

Second or More Occurrence of platelets 50,000 - 75,000: Delay mFOLFIRINOX until platelets > 75,000, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

For Platelets < 50,000: Delay mFOLFIRINOX until recovery to Plts > 75,000, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

9.1.2 Gastrointestinal Toxicity

Early Diarrhea: Lacrimation, rhinorrhea, miosis, diaphoresis, hot flashes, flushing, abdominal cramping, diarrhea, or other symptoms of early cholinergic syndrome may occur during or shortly after receiving irinotecan. Atropine, 0.25-1 mg IV or SC may be used to treat these symptoms. In patients with troublesome or recurrent symptoms, prophylactic administration of atropine shortly before irinotecan therapy may be considered. Additional antidiarrheal measures may be used at the discretion of the treating physician. Combination anticholinergic medications containing barbiturates or other agents (e.g., Donnatal®) should not be used because these may affect irinotecan metabolism. Anticholinergics should be used with caution in patients with potential contraindications (e.g., obstructive uropathy, glaucoma, tachycardia, etc.).

Late diarrhea (e.g., developing more than 24 hours after irinotecan infusion) should be managed with loperamide as described in Section 11.3. The following dose modifications are based on toxicity experienced at any time during a cycle.

Patients should be optimally managed with anti-diarrheal medications before dose modifications are made.

For Grade 2 Diarrhea (despite optimal medical management):

- First Occurrence: Delay mFOLFIRINOX until recovery to grade \leq 1 or baseline, then resume mFOLFIRINOX at the same dose level.
- Second or More Occurrence: Delay mFOLFIRINOX until recovery to grade \leq 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

For Grade 3 Diarrhea (despite optimal medical management):

- First Occurrence: Delay mFOLFIRINOX until recovery to grade \leq 1 or baseline, then resume 5-FU, leucovorin, and oxaliplatin, at the same dose level and irinotecan with one dose level reduction for all subsequent cycles.
- Second or More Occurrence: Delay mFOLFIRINOX until recovery to grade \leq 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

For Grade 4 diarrhea (despite optimal medical management): Delay mFOLFIRINOX until recovery to grade \leq 1 or baseline then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

Nausea/Vomiting

The following dose modifications are based on toxicity experienced during a cycle. Patients should be optimally managed with anti-emetic medications before dose modifications are made (See [Section 11.2](#)).

For Grade 3 Nausea/Vomiting (despite optimal medical management):

- First Occurrence: Delay mFOLFIRINOX until recovery to grade \leq 1 or baseline, then resume 5-FU and leucovorin, at the same dose level and oxaliplatin and irinotecan with one dose level reduction for all subsequent cycles.

- Second or More Occurrence: Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

For Grade 4 Nausea/Vomiting (despite optimal medical management):

Delay mFOLFIRINOX until recovery to grade ≤ 1 or baseline, then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

Mucositis

The following dose modifications are based on toxicity experienced at any time during a cycle.

Grade 3 Mucositis:

- First Occurrence: Delay mFOLFIRINOX until recovery to grade ≤ 1 , then resume irinotecan, oxaliplatin, and leucovorin at the same dose level and 5-FU with one dose level reduction for all subsequent cycles.
- For Second or More Occurrence: Delay mFOLFIRINOX until recovery to grade ≤ 1 , then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

Grade 4 Mucositis: Delay mFOLFIRINOX until recovery to grade ≤ 1 , then resume mFOLFIRINOX with one dose level reduction for all subsequent cycles. The dose of leucovorin is not reduced.

9.1.3 Peripheral Sensory Neuropathy

Note: Dose modifications for sensory neuropathy are not based on CTCAE severity grades.

For paresthesia/dysethesia interfering with function and persisting between treatments: Decrease oxaliplatin by one dose level for all subsequent cycles.

For painful paresthesia/dysethesia or symptoms that interfere with function and ADL, but improve (no longer painful or no longer interfering with ADL) between treatments: Decrease oxaliplatin by one dose level for all subsequent cycles.

For painful paresthesia/dysethesia or symptoms that interfere with function and ADL that persists between treatments: Discontinue oxaliplatin.

For persistent disabling or life-threatening paresthesia/dysethesia: Discontinue oxaliplatin.

For pharyngo-laryngeal dysethesia: Increase the duration of oxaliplatin infusion to 6 hours for subsequent cycles.

9.1.4 Venous Thromboembolic Events

For Grade 2 or 3 venous thromboembolic event: Continue mFOLFIRINOX at the same dose level. Do not use warfarin for therapeutic anticoagulation; use of low molecular weight heparin is allowed.

Grade 4 venous thromboembolic event: Discontinue mFOLFIRINOX.

9.1.5 Liver Function Tests

For Grade 2 Increased Blood Bilirubin: Skip irinotecan until bilirubin improves to \leq grade 1.

For hyperbilirubinemia considered at least possibly related to irinotecan, resume irinotecan with one dose level reduction for all subsequent cycles.

For hyperbilirubinemia considered unrelated to irinotecan, resume irinotecan at the previous dose level.

For Grade 3 or 4 Increased Blood Bilirubin: Delay mFOLFIRINOX until bilirubin improves to \leq grade 1. If bilirubin is thought to be due to a chemotherapy drug, then resume that drug at the next lower dose level and the other drugs at the same dose level when total bilirubin improves to \leq grade 1.

For hyperbilirubinemia considered unrelated to treatment (all drugs), resume mFOLFIRINOX at the previous dose levels.

9.1.6 Allergic Reactions

For grade 2 allergic reactions: Interrupt infusion(s). Manage reaction according to institutional policy. Restart the infusion(s) when symptoms resolve to \leq grade 1 and pre-treat before all subsequent doses.

For grade 3 or grade 4 allergic reactions: Discontinue infusion. Manage reaction according to institutional policy. Discontinue mFOLFIRINOX.

9.1.7 Oxaliplatin-induced pharyngolaryngeal dysesthesias

Should a patient develop oxaliplatin-induced pharyngolaryngeal dysesthesia, her/his oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent may be given and the patient observed in the clinic until the episode has resolved. Following resolution of symptoms, patients may continue/resume oxaliplatin if the reaction is NOT determined to be an allergic reaction.

A table comparing pharyngo-laryngodysesthesia to platinum hypersensitivity reactions is presented below.

Comparison of the Symptoms and Treatment of Pharyngolaryngodysesthesias and Platinum Hypersensitivity Reactions

Clinical Symptoms	Pharyngo-Laryngeal Dysesthesias	Platinum Hypersensitivity
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O ₂ saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritis	Absent	Present
Urticaria/rash	Absent	Present
cold-induced symptoms	Yes	No
Blood pressure	Normal or increased	Normal or decreased
Treatment	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

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9.1.8 Other non-hematologic toxicities

For all other grade 3 non-hematologic toxicities considered at least possibly related to mFOLFIRINOX: Skip the responsible drug(s) until toxicity improves to \leq grade 1, then resume the responsible drug(s) with one dose level reduction for all subsequent cycles.

For grade 4 non-hematologic toxicities considered at least possibly related to mFOLFIRINOX: Discontinue the responsible drug(s).

9.1.9 Dose Modifications 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 actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation.

9.2 Dose Modifications for Capecitabine

If capecitabine is interrupted but radiation continues, the missed doses of capecitabine are not made up.

9.2.1 Hematologic:

For grade ≥ 3 neutrophil count decreased, interrupt capecitabine until ANC improves to grade ≤ 2 , then resume capecitabine at a dose of 625 mg/m² twice daily for the remainder of chemoradiation.

For grade ≥ 2 platelet count decreased, interrupt capecitabine until platelets improve to \leq grade 1, then resume capecitabine at a dose of 625 mg/m² twice daily for the remainder of chemoradiation.

9.2.2 Dose Modifications for Renal Function

For grade 2 or 3 creatinine increased, decrease capecitabine to 625 mg/m² twice daily for the remainder of chemoradiation.

For grade 4 creatinine increased, discontinue capecitabine.

9.2.3 Dose Modifications for Bilirubin

For grade 3 or 4 increased blood bilirubin, interrupt capecitabine until bilirubin improves to \leq grade 2, then resume capecitabine at a dose of 625 mg/m² twice daily for the remainder of chemoradiation.

9.2.4 Dose Modifications for Diarrhea

For grade 3 or 4 diarrhea, interrupt capecitabine until diarrhea improves to \leq grade 2, then resume capecitabine at a dose of 625 mg/m² twice daily for the remainder of chemoradiation.

For recurrent grade 3 or 4 diarrhea, interrupt capecitabine until diarrhea improves to \leq grade 2, then resume capecitabine at a dose of 425 mg/m² twice daily for the remainder of chemoradiation.

9.2.5 Dose Modifications for Hand-foot Syndrome

For grade 2 hand-foot syndrome, interrupt capecitabine until hand-foot syndrome improves to \leq grade 1, then resume capecitabine at a dose of 625 mg/m² twice daily for the remainder of chemoradiations.

For grade 3 hand-foot syndrome, interrupt capecitabine until hand-foot syndrome improves to \leq grade 1, then resume capecitabine at a dose of 425 mg/m² twice daily for the remainder of chemoradiation.

9.2.6 Dose modifications for other non-hematologic toxicity

For grade 3 other non-hematologic toxicity considered at least possibly related to capecitabine, interrupt capecitabine until toxicity improves to \leq grade 1, then resume capecitabine at a dose of 625 mg/m² twice daily for the remainder of chemoradiation.

For grade 4 other non-hematologic toxicity considered at least possibly related to capecitabine, discontinue capecitabine.

9.3 Dose Modifications for Radiation

9.3.1 Dose Modifications for hematologic toxicity

For grade 4 neutrophil count decreased, hold RT until ANC improves to \leq grade 3, then resume chemoradiation.

For grade 3 platelet count decreased, hold RT until platelets improve to \leq grade 2, then resume chemoradiation.

9.3.2 Dose Modifications for diarrhea

For grade 3 or 4 diarrhea, hold RT until diarrhea improves to \leq grade 2, then resume combined chemoradiation.

9.3.3 Dose Modifications for hand-foot syndrome

For grade 3 hand-foot syndrome, hold RT until hand-foot syndrome improves to \leq grade 1, then resume chemoradiation.

9.3.4 Dose Modifications for other non-hematologic toxicity

For grade 3 or 4 other non-hematologic toxicity, hold RT until toxicity improves to \leq grade 2, then resume chemoradiation.

9.4 Dose Modifications during Adjuvant Chemotherapy (gemcitabine)

9.4.1 Dose modifications for hematologic toxicity:

For grade 4 neutrophil count decreased on day 1 of a cycle, delay gemcitabine until ANC improves to \leq grade 3.

For grade 3 neutrophil count decreased on day 1, 8, or 15 of a cycle, continue gemcitabine at a dose of 750 mg/m² for this and all subsequent doses.

For grade 4 neutrophil count decreased on day 8 or 15 of a cycle, skip gemcitabine. Skipped doses are not made up.

For grade \geq 3 platelet count decreased on day 1 of a cycle, delay gemcitabine until platelets improve to \leq grade 2.

For grade 2 platelet count decreased on day 1, 8, or 15 of a cycle, continue gemcitabine at a dose of 750 mg/m² for this and all subsequent cycles.

For grade ≥ 3 platelet count decreased on day 8 or 15 of a cycle, skip gemcitabine. Skipped doses are not made up.

Febrile neutropenia: For febrile neutropenia (defined as temperature $\geq 100.5\text{F}$ and ANC < 500), decrease gemcitabine to 750 mg/m^2 for all subsequent doses.

9.4.2 Dose modifications for bilirubin

For grade 3 increased blood bilirubin, decrease gemcitabine to 750 mg/m^2 for this and all subsequent doses.

For grade 4 increased blood bilirubin on day 1, delay gemcitabine until bilirubin improves to \leq grade 3, then resume gemcitabine at 750 mg/m^2 for this and all subsequent doses.

For grade 4 increased blood bilirubin on day 8 or 15, skip gemcitabine. Skipped doses are not made up.

9.4.3 Dose modifications for kidney function

For grade 3 or 4 creatinine increased, decrease gemcitabine to 750 mg/m^2 for this and all subsequent doses.

9.4.4 Dose modifications for other non-hematologic toxicity

For grade 3 other non-hematologic toxicity considered at least possibly related to gemcitabine, delay (day 1) or skip (day 8 or 15) gemcitabine until toxicity improves to grade ≤ 1 , then resume gemcitabine at a dose of 750 mg/m^2 for this and all subsequent doses.

For grade 4 other non-hematologic toxicity considered at least possibly related to gemcitabine, discontinue gemcitabine.

9.5 Dose Modifications 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 actual weight without any modification unless explicitly described in the protocol. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation

10.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

- 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.
- Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) 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.

10.1 Oxaliplatin

Please refer to the package insert for complete product information.

Availability

Oxaliplatin is commercially available a solution in vials containing 50 mg, 100 mg, and 200mg 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. According to the manufacturer, solutions diluted in D5W are stable for 6 hours at room temperature or 24 hours under refrigeration. Solutions diluted in D5W to a concentration of 0.7 mg/mL are reported to be stable (sterility not tested) for up to 30 days at room temperature or 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 chloride-containing 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 2 hours prior to irinotecan, and prior to or concurrent with leucovorin. Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia.

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, paresthesias, dysesthesias, and hypoesthesia of the hands, feet and perioral region. 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 in 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 hypoesthesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Various agents have been used in an attempt to minimize neurotoxicity of oxaliplatin (e.g. carbamazepine, Mg⁺, Ca⁺⁺). Calcium and magnesium infusions appear to be beneficial in preventing neurotoxicity. Contrary to preliminary findings described in 2007, calcium and magnesium do not appear to interfere with tumor response to FOLFOX. Calcium and magnesium infusions are generally given before and after oxaliplatin, and should not be prepared in the same infusion solution as FOLFOX or FOLFIRINOX components.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea. Grade 3 or 4 neutropenia was reported in 46% of patients receiving FOLFIRINOX, and grade 3 or 4 thrombocytopenia was reported in 9%.

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, dysphagia) 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.

10.2 5-Fluorouracil (5-FU)

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.

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 an IV infusion over 46 – 48 hours. There is no bolus injection of 5-FU in Alliance A021101.

Toxicity

GI: Nausea, diarrhea, vomiting (mild); stomatitis: 5-8 days after treatment initiation; Myelosuppression: neutropenia (9-14 days); thrombocytopenia (7-14 days);

Dermatologic: Alopecia; nails changes; vein pigmentation; photosensitivity; maculopapular rash; palmar-plantar erythrodysesthesias,

CNS effects: cerebral ataxia (rare);

Cardiotoxicity: MI, angina; asymptomatic S-T changes;

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.

10.3 Leucovorin Calcium (Folinic Acid)

(Calcium folinate; citrovorum factor; N 5-formyltetrahydrofolate; 5-formyl-FH₄; folinic acid)

Please refer to the package insert for complete product information.

Availability

Leucovorin calcium is commercially available in 50 mg, 100 mg, 200 mg, and 350 mg vials for reconstitution, and 50 mL vials of solution at a concentration of 10 mg/mL.

Storage and Stability

Intact vials of powder for reconstitution should be stored at room temperature and protected from light. Solutions reconstituted with bacteriostatic water for injection are stable for up to 7 days at room temperature. Solutions reconstituted with sterile water for injection should be used immediately.

Intact vials of solution should be stored under refrigeration and protected from light.

Solutions further diluted for infusion are stable for 24 hours at room temperature, and 4 days under refrigeration.

Preparation

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

Administration

Leucovorin will be administered as a 400 mg/m² IV infusion over 2 hours after, or concurrent with, oxaliplatin and irinotecan. For administration concurrent with oxaliplatin (30 minutes) and irinotecan (90 minutes), leucovorin is administered as a separate infusion (i.e., not in the same IV solution).

Toxicity

The only adverse reactions associated with leucovorin are allergic reactions. These are rare.

10.4 Irinotecan (CPT-11, CAMPTOSAR®)

Please refer to the package insert for complete product information.

Availability

Irinotecan is commercially available as a 20 mg/mL solution for injection in 2 mL and 5 mL vials.

Storage and Stability

Intact vials should be stored at controlled room temperature 59° to 86° F (15° to 30° C) and protected from light. Solutions diluted in D5W are reported to be stable for 24 hours at room temperature, or 48 hours under refrigeration and protected from light.

Preparation

Irinotecan is diluted in 5% dextrose (D5W) 500 mL to a final concentration of 0.12 – 2.8 mg/mL. Stability is improved in D5W as compared with NaCl.

Administration

In this study irinotecan will be administered as an IV infusion over 90 minutes, following oxaliplatin, and prior to, or concurrent with, leucovorin.

Toxicities

Neutropenia and/or late diarrhea (diarrhea occurring more than 24 hours after irinotecan administration) are frequently dose-limiting. Other commonly observed adverse events include nausea and vomiting, anorexia (irinotecan is considered moderately emetogenic), abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia. Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may experience 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. Elevations of bilirubin and alkaline phosphatase have been reported in up to 84% and 13% of patients, respectively. Sporadic cases of pulmonary toxicity, manifested as shortness of breath, nonproductive cough, and transient infiltrates on chest X-ray have been reported. Infrequent occurrences of mucositis or colitis (sometimes with gastrointestinal bleeding) have been observed. Irinotecan is metabolized to Sn-38, an active metabolite. SN-38 is conjugated by UGT1A1. Homozygosity for the UGT1A1*28 allele increases the risk of severe neutropenia with irinotecan, and known homozygotes are not eligible for this trial.

Further information regarding irinotecan may be obtained from the package insert.

10.5 Gemcitabine

(2'-deoxy-2',2'-difluorocytidine; dFDC; difluorodeoxycytidine; gemcitabine hydrochloride; Gemzar®)

Please refer to the FDA-approved package insert for gemcitabine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Gemcitabine is a nucleoside analogue in the pyrimidine antimetabolite class, which is S-phase specific. Its phosphorylated product is incorporated into DNA and interferes with DNA synthesis. Gemcitabine also exhibits self-potential by causing anenzymatically-mediated reduction in the intracellular nucleotide pool.

Availability

Gemcitabine is commercially supplied as a powder for reconstitution in 200 and 1 gram vials.

Storage and Stability

Intact vials containing sterile powder are stored at room temperature. When prepared as directed, reconstituted vials are reportedly stable for 35 days at room temperature and protected from light. Further diluted solutions of gemcitabine are stable for up to 7 days at room temperature when protected from light. However, the manufacturer recommends that solutions be used within 24 hours. The diluted solution should be clear and colorless to light straw-colored solution.

Preparation

Reconstitute the 200 mg vial with 5 mL 0.9% NaCl and the 1 g vial with 25 mL 0.9% NaCl. The resulting solution is approximately 38 mg/mL, but the concentration varies. It is suggested that when the desired dose is less than the entire vial, the entire volume be drawn up into a syringe in order to determine the actual concentration. Then the desired amount should be measured and diluted in 0.9% NaCl for infusion.

Administration

In this study, gemcitabine will be given intravenously over 30 minutes in an appropriate volume of 0.9% NaCl.

Toxicities:

Flu-like syndrome: Flu-like syndrome is manifested by fever, fatigue, myalgias, headache, and cough.

Myelosuppression: Myelosuppression is the usual dose-limiting toxicity. Infusions longer than 1 hour are associated with increased myelosuppression.

Hepatotoxicity: Mild elevations in hepatic transaminase levels occur in as many as two-thirds of patients, but are reversible.

Dyspnea: Dyspnea occurs in 10-23% of patients and is usually associated with a drug-induced pneumonitis. More often, dyspnea is likely associated with the underlying malignancy.

Gastrointestinal: Nausea, vomiting, and anorexia are common but usually of mild to moderate severity. Stomatitis and diarrhea or constipation occurs less often.

Nephrotoxicity: Proteinuria and hematuria are usually asymptomatic though they occur frequently. A serious hemolytic-uremic syndrome occurs in less than 1% of patients.

Nervous system: Parasthesias and peripheral neuropathies occur in 2-10% of patients.

Hypersensitivity reactions: Allergic reactions including bronchospasm have been reported in 4% of patients.

Dermatologic: Minimal alopecia (15%) and macular or maculopapular rashes have been reported.

10.6 Capecitabine

(Xeloda®, 5'-deoxy-5-fluoro-N-[(pentylloxy)carbonyl]-cytidine)

Please refer to the FDA-approved package insert for capecitabine for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Capecitabine is a prodrug that is readily absorbed from the gastrointestinal tract. Activation occurs through a 3-step enzymatic process. In the liver, a carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). Thymidine phosphorylase then hydrolyzes 5'-DFUR to the active drug 5-FU. The inactive

ingredients in the tablets include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

Availability

Capecitabine is commercially available as 150mg tablets or 500 mg tablets.

Rounding Suggestions

Calculated Dose in Mg	Actual Dose
1500-1575	1500
1576-1725	1650

Storage and stability

Capecitabine tablets should be stored at room temperature (25°C or 77°F).

Administration

Capecitabine is to be taken within 30 minutes of food consumption.

Toxicity

Carcinogenesis, mutagenesis and impairment of fertility: Long term studies in animals to evaluate carcinogenicity have not been performed. Capecitabine was not mutagenic in vitro to bacteria or mammalian cells. 5-fluorouracil does cause mutations in bacteria and yeast. Capecitabine did alter estrus in mice and caused a reversible decrease in fertility as well as degenerative changes in the testes.

Cardiac: Cardiotoxicity has been associated with fluorinated pyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These events may be more common in patients with a prior history of coronary disease.

Dermatologic: Capecitabine can cause hand-and-foot syndrome (palmar-plantar erythrodysesthesia) characterized by: numbness, dysesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering and severe pain. If grade 2 or 3 hand-and-foot syndrome occurs while taking capecitabine, therapy should be interrupted until the toxicity resolves to grade 0-1. Radiation recall, increased sweating and photosensitivity have been reported.

Gastrointestinal: Diarrhea, sometimes severe can be caused by capecitabine. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. The median time to first occurrence of grade 2-4 diarrhea was 31 days. Patients \geq 80 years old may experience a greater incidence of GI grade 3 or 4 adverse events. Nausea and vomiting can occur but generally is <grade 3 in severity (only 3-4% of patients experienced grade 3 nausea or vomiting with no grade 4 events). Necrotizing enterocolitis has been reported.

Hepatobiliary: 17% of 570 patients with colorectal or breast cancer (many with liver metastases) have experienced grade 3 or 4 increases in bilirubin (with 76% of these patients having a concurrent elevation in alkaline phosphatase and/or transaminases – 6% grade 3 or 4) which resolved when therapy was interrupted.

Hematologic: generally less than 5 % of patients receiving capecitabine as a single agent experience grade 3 or 4 hematologic toxicity.

Pregnancy: Capecitabine may cause fetal harm when given to pregnant women. Teratogenic malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. There are no adequate and well-controlled studies in pregnant women using capecitabine. If the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving capecitabine.

Stomatitis: 4-7% of patients have been reported with grade 3 stomatitis.

Vascular: Hypotension, hypertension, venous phlebitis, deep venous thrombosis, lymphedema, pulmonary embolism and cerebrovascular accidents have been reported.

11.0 ANCILLARY THERAPY

11.1 Hematopoietic Growth Factor Support

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

In accordance with accepted guidelines, erythropoiesis stimulating agents should not be used.

11.2 Anti-emetics

Patients should be premedicated prior to each treatment cycle of FOLFIRINOX with an HT-3 antagonist and dexamethasone. The addition of aprepitant (Emend) is strongly encouraged. Other anti-emetics, such as lorazepam may also be provided as clinically necessary.

Patients should be premedicated for the gemcitabine with either compazine or an HT-3 antagonist. Additional agents may be added if needed.

11.3 Anti-diarrheals

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

11.4 Antibiotics

Prophylactic oral antibiotic therapy will not be given at the start of study treatment. However, antibiotics (e.g. oral fluoroquinolones, Augmentin, or other agent(s) at investigator discretion) should be initiated at investigator discretion for patients in the following instances: those who have (a) endobiliary stents with an ANC that falls below 500; (b) endobiliary stents who develop a fever above 38.5C; (c) diarrhea persisting for more than 48 hours despite

loperamide; (d) fever with diarrhea, regardless of ANC. Administration of long-term prophylactic antibiotics following the first occurrence of any of the above scenarios may be considered only following discussions with the PI or one of the co-PIs.

11.5 Anti-cholinergics

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

11.6 Guidelines for Management of Hyperglycemia

Dietary counseling should be provided. Consider referral to nutritionist/ dietician. Generally, treatment of hyperglycemia should be pursued as per local institutional guidelines. Intensification of a current anti-hyperglycemic regimen can be pursued as indicated. Initiation of metformin can be considered as a first-line agent for management of hyperglycemia, among patients not current on an anti-hyperglycemic regimen.

11.7 Low Molecular Weight Heparin

Low molecular weight heparin (e.g., enoxaparin) may be used at any time during therapy at the discretion of the treating physician.

11.8 Guidelines for Management of Jaundice and/or Cholangitis

It is anticipated that many patients enrolled in this study will have an indwelling plastic or metal endobiliary stent placed prior to therapy. Signs or symptoms of extrahepatic biliary obstruction may develop at any point during therapy as a consequence of stent occlusion in this group. Biliary obstruction may also occur in patients who did not undergo stenting prior to initiation of treatment. Generally, biliary obstruction should be treated on an urgent clinical basis, preferably by endoscopic means. In cases where this is not possible, percutaneous transhepatic biliary drainage is also acceptable. Antibiotics may also be administered at the discretion of the treating physician, particularly when evidence of infection exists (temperature > 38.5C, chills, sweats).

Following biliary decompression, treatment may resume once the total bilirubin is ≤ 3 , other laboratory studies have normalized to acceptable levels based on the eligibility criteria outlined in Section 4.11, and the patient is considered to be clinically stable per the treating oncologist.

12.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

Note: Radiographic response will be determined by central re-review using the criteria below but will not be used to determine each patient's progress through therapy.

12.1 Radiographic Determination of Treatment Response (RECIST)

Radiographic response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guidelines.

12.1.1 Measurable Disease

1. The primary tumor or any other non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 1.0 cm with CT scan or MRI, or ≥ 2.0 cm with chest x-ray.

2. A lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan.

12.1.2 Non-measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including lymph nodes (those with a short axis ≥ 1.0 to <1.5 cm), bone lesions, leptomeningeal disease, ascites, and pleural/pericardial effusions.

12.1.3 Guidelines for Evaluation of Measurable Disease

Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same radiographic method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

Acceptable Modalities for Measurable Disease: CT scan, MRI, chest x-ray. CT scans are preferred and should be used if possible (unless the patient is allergic to contrast or has renal insufficiency, for example). PET CTs are not allowed.

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

12.1.4 Measurement of Effect

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

Target Lesions & Target Lymph Nodes

- The primary pancreatic tumor is the only target non-nodal lesion at baseline. It is measured at baseline and followed at restaging with the longest diameter of the tumor.
- Baseline Sum of Dimensions (BSD): The longest diameter for the primary pancreatic target lesion will be reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- Post-Baseline Sum of the Dimensions (PBSD): The longest diameter for the primary pancreatic target lesion will be reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion, that should be recorded, even if it is below 0.5 cm. If the target lesion

is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion has likely disappeared, the measurement should be recorded as 0 cm.

- The minimum sum of the dimensions (MSD) is the minimum of the BSD and the PBSD.

12.2 Response Criteria

Radiographic response is determined by central review of the pretreatment and preoperative studies as described in Section 12.1.1. A change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of the primary pancreatic target lesion.

Partial Response (PR): At least a 30% decrease in PBSD (the longest diameter of the primary pancreatic target lesion) taking as reference the BSD.

Progression (PD) – At least one of the following must be true:

- At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
- At least a 20% increase in PBSD (the longest diameter of the primary pancreatic target lesion) taking as reference the MSD. In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

12.3 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on primary pancreatic target lesion, and new disease as defined in the following tables:

Note: Only disease in the liver, lung, ascites, local region observed at restaging will be counted as new site of disease.

Target Lesions & Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	No	CR
PR	No	PR
SD	No	SD
Not all Evaluated	No	Not Evaluated (NE)
PD	Yes or No	PD
ANY	Yes	PD

12.4 Histopathologic Determination of Treatment Response

Histopathologic response to preoperative therapy will be determined by analysis of the resected surgical specimen by the pathologist (see [Section 6.2.1](#)). The following grades will be used to semi-quantitatively characterize treatment response:

- I- <5% residual tumor cells in the specimen
- II- $\geq 5\%$ residual tumor cells in the specimen

12.5 Histopathologic Determination of R-status

12.5.1 “Macroscopic disease” is assessed by surgeon and “microscopic disease” is assessed by the histopathologist.

12.5.2 Margins to be assessed in this trial include 1) common bile duct, 2) SMA margin, 3) pancreatic neck as described in pathology section:

- R0- Macroscopically complete tumor removal with negative microscopic surgical margins.
- R1- Macroscopically complete tumor removal with positive microscopic margins (any or all).
- R2- Macroscopically incomplete tumor removal with known or suspected residual gross disease.

12.6 Treatment Evaluation After Completion of Surgery and Post-operative Chemotherapy

12.6.1 The term “recurrence” is used if cancer returns following R0 or R1 resection.

12.6.2 Recurrence is determined radiographically and biopsy need not be performed except as detailed below or when CT findings are equivocal in the determination of the enrolling physician.

- Local recurrence: identified by a new soft-tissue mass around the mesenteric vasculature or regional lymph nodes
- Distant recurrence: identified by a new hypodensity in the liver or nodule(s) in the lungs or peritoneum. Other sites of distant recurrence (adrenal, brain) may require biopsy confirmation. New ascites will require aspiration and cytology if it is an isolated finding and should not necessarily be taken to indicate carcinomatosis.

13.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

In the absence of treatment delays due to adverse events, treatment will be completed unless the patient experiences any one of the following:

- A change from borderline resectable to locally advanced at the pre-surgical restaging;
- A change from borderline resectable to metastatic at any point in the protocol;
- Decline in PS in the absence of radiographic evidence for disease progression if PS cannot be recovered;
- R2 surgical resection;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Patient decides to withdraw from the study; or
- General or specific changes in the patient’s condition that render the patient unacceptable for further treatment in the judgment of the investigator.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Overview

This pilot study is designed to assess the feasibility of conducting neoadjuvant clinical trials in borderline resectable PDAC patients receiving neoadjuvant FOLFIRINOX chemotherapy followed by concurrent chemoradiation and surgery and subsequent gemcitabine. The feasibility demonstration will establish the infrastructure for future randomized phase II clinical trials in a multi-center setting. Twenty patients with borderline resectable PDAC, confirmed by central radiologic review, will be enrolled and treated. The central review will be conducted before patient enrollment through a pre-registration process. The decision regarding whether this study demonstrates sufficient feasibility to support a randomized phase II study testing novel regimens in this disease population will be based on three key considerations:

- a. The study can meet the accrual goal.
- b. The proposed preoperative chemotherapy and chemo/RT will result in no more toxicity than has been established previously in the advanced setting by evaluating the prevalence of grade 3+ toxicities (excluding non-febrile neutropenia) and treatment delay rate (> 4 weeks).
- c. The completion rate of preoperative and operative therapy meets the goals.

14.2 Sample Size and Accrual Time

14.2.1 Sample Size

A maximum of 20 patients will be enrolled if the trial completes accrual.

14.2.2 Accrual time

The anticipated monthly accrual rate is approximately 2 patients per month. With start-up of 4 months for sites to obtain IRB approvals and required credentials, the trial is expected to accrue in approximately 15 months.

14.3 Statistical Design for Primary Endpoints

14.3.1 Primary Endpoints

The primary endpoints include 1) accrual rate, 2) rate and degree of treatment-related toxicity during preoperative therapy, and the rate of treatment delay (>4 weeks) during preoperative therapy, and 3) completion rate of all preoperative and operative therapy. All patients meeting the eligibility criteria, with confirmation of borderline resectable PDAC status by central radiology review, providing consent and having begun treatment will be considered evaluable for the primary endpoints.

14.3.2 Study Design and Decision Rules

The purpose of this study is to demonstrate the feasibility of conducting a study assessing the proposed regimen. The sample size of twenty patients with confirmed borderline resectable PDAC is selected based on financial and logistic considerations. However, we still propose decision rules based on testable hypotheses whenever possible. If, at the conclusion of the trial, none of the following stopping rules has been crossed, we will conclude that the proposed regimen and trial design warrants further randomized phase II study for assessing novel neoadjuvant chemotherapy/radiochemotherapy followed by surgery and subsequent chemotherapy in this disease population:

Accrual Stopping Rules

After study activation, every effort will be made to obtain local IRB approval in at least 5 sites (anticipated to take 4 months). The accrual stopping rules are specified as the following:

- If, 3 months following the date IRB approval is obtained and the study is opened at the fifth site, 5 or less than 5 patients have been accrued, we will conclude the study does not demonstrate sufficient feasibility.
- Thereafter, the accrual rate will be monitored bi-monthly. If at any evaluation time point, the accrual rate is less than 2 per month, we will conclude the study does not demonstrate sufficient feasibility. The accrual rate will be calculated by total number of patients accrued divided by number of months from the date the study is opened at the fifth site to the evaluation date.

Toxicity Stopping Rules

The toxicity feasibility stopping rules are specified as the following:

- The toxicity rate is defined as the proportion of treated patients with confirmed borderline resectable PDAC who experience at least one grade 3+ adverse event, excluding non-febrile neutropenia, and is considered at least possibly related to the preoperative treatment (i.e. an adverse event with attribute specified as “possibly,” “probably,” or “definitely” related to either mFOLFIRINOX or chemoradiation). The toxicity rate will be evaluated when the first 10, the first 15 and then 20 patients are enrolled and the toxicity data are available. The Lan-DeMets, O’Brien Fleming alpha spending function was applied to control overall alpha.
 - When toxicity data are available on the first 10 evaluable patients, if the toxicity rate is greater than 0.54 (> 5 patients experienced defined AEs), we will conclude the study does not demonstrate sufficient feasibility. Otherwise, continue accrual.
 - When toxicity data are available on the first 15 evaluable patients, if the toxicity rate is greater than 0.46 (> 6 patients experience defined AEs), we will conclude the study does not demonstrate sufficient feasibility. Otherwise, continue accrual.
 - When toxicity data are available on all 20 evaluable patients, if the toxicity rate is greater than 0.42 (>8 patients experience defined AEs), we will conclude the study does not demonstrate sufficient feasibility.
- This decision rule based on a sample size of 20 patients provides 79% power to test the null hypothesis that the toxicity rate is $\leq 30\%$ vs. the alternative hypothesis that the toxicity rate is $\geq 50\%$ based on a one-sided test at significant level of 0.16 (EAST v5)
- If 4 or more patients in the first 10 or after 10 patients 40% or more treated patients with confirmed borderline resectable PDAC experience treatment delay (> 4 weeks), we will conclude the study does not demonstrate sufficient feasibility.

Completion of Therapy Stopping Rules

The completion of therapy stopping rules are specified as the following:

- If at least 6 patients among 20 evaluable patients complete all preoperative and operative therapy including R0/R1 resection, we will conclude the

study warrants further randomized phase II study, provided that none of the other feasibility stopping rules are crossed at any time.

- If 5 or less than 5 patients among 20 evaluable patients complete all preoperative and operative therapy we will conclude that the study does not demonstrate sufficient feasibility.
- This decision rule based on a sample size of 20 patients provides 87.5% power to test the null hypothesis that the R0/R1 resection rate is $\leq 20\%$ vs. the alternative hypothesis that the R0/R1 resection rate is $\geq 40\%$ based on a one-sided test at significant level of 0.197 (EAST v5).

14.3.3 Analysis Plan

All AE and the maximum grade for each type of adverse events (including all adverse events and those that are possibly, probably or definitely related to study treatments) will be recorded for each patient. The frequency tables will be reviewed to determine the patterns. Point estimate and confidence interval will be reported for binary endpoints.

14.4 Supplementary Analysis Plans (Secondary Endpoints)

All patients meeting the eligibility criteria and confirmed by central review who have signed a consent form and have begun any dose of treatment will be evaluable for the following secondary endpoints, unless otherwise specified.

14.4.1 The macroscopic (R0/R1) resection rate is defined as number of patients achieved R0 or R1 resection during surgery divided by number of evaluable patients. Point estimate and confidence interval of the rate will be reported.

14.4.2 The radiographic response rate is defined as number of patients achieved CR or PR determined according to RECIST criteria version 1.1 during pre-operative chemo or radiochemo therapy divided by number of evaluable patients. Point estimate and confidence interval of the rate will be reported.

14.4.3 The histopathologic response rate is defined as number of patients achieved CR or PR determined according to histopathologic examination during pre-operative chemo or radiochemo therapy divided by number of evaluable patients. Point estimate and confidence interval of the rate will be reported.

14.4.4 Time to locoregional recurrence is defined as time from the date of registration to the date of the first documented locoregional recurrence. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).

14.4.5 Time to distant recurrence is defined as time from the date of registration to the date of the first documented distant recurrence. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).

14.4.6 Overall survival is defined as time from the date of registration to the date of the death due to all cause. The Kaplan-Meier methods will be used to estimate the median time, and event-free rate at specific time points (6 month, 12 month, etc.).

14.4.7 Correlative Science Endpoint

These endpoints include quality measures of nucleic acids retrieved from pre-treatment pancreatic ductal adenocarcinoma biopsies, using a sequencing based assessment of tumor

DNA. Due to the small sample size, statistical analysis will be mainly descriptive. Mean, median, standard deviation, and range will be reported for continuous biomarker variables (or changes between timepoints) overall and within relevant patient group(s). Frequency and percentage will be reported for categorical biomarker variable overall and within relevant patient group(s). Comparisons of biomarkers between groups will be kept in the exploratory fashion for hypothesis generating purposes. Parametric or nonparametric statistical tests will be selected based on the distribution examinations of the biomarker variables.

14.5 Safety Stopping Rules

In addition to toxicity feasibility stopping rules, accrual will be temporarily suspended to the study, if at any time, we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible,” “probably,” or “definite”) that meet the following:

- The rate of treatment-related deaths during treatment, or within the first 60 days following completion of treatment, exceeds 2 or more in the first 10 patients or after 10 patients 20% or more of all treated patients.

We will also review grade IV and V adverse events deemed “unrelated” or “unlikely to be related” to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event

14.6 Study Monitoring

14.6.1 Clinical Data Update System (CDUS)

This study will be monitored by the Cancer Therapy Evaluation Program via CDUS. CDUS data will be electronically submitted quarterly to the CTEP until all patients are off-study at which time a final report is submitted. Quarterly reports are due January 31, April 30, July 31, and October 31.

14.6.2 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the “ClinicalTrials.gov” website. The Primary and Secondary Endpoints (i.e., “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 24 months after the study opens to accrual, including 15 months to accrual, 6 month for the last patient enrolled to finish protocol treatment, and 3 months for data cleaning and analysis. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time that all registered patient have been off treatment

15.0 EXPEDITED ADVERSE EVENT REPORTING

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the, the Alliance Central Protocol Operations Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All such events must be reported in an expedited manner using the NCI Adverse Event Expedited Reporting System (AdEERS). The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for reporting. All treatment areas should have access to a copy of the CTEP Active Version of CTCAE. All reactions determined to be “reportable” in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS).

15.1 A021101 Commercial Agent Study

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND trial within 30 Days of the Last Administration of a Commercial Imaging Agent ¹

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for \geq 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization \geq 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization \geq 24 hrs	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- “24-Hour; 5 Calendar Days” - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of commercial agent require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs that are at least possibly related to treatment

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, and that are at least possibly related to treatment

Grade 3 adverse events that are at least possibly related to treatment

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via AdEERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

15.2 Additional Instructions or Exclusions to AdEERS Expedited Reporting Requirements for Commercial Agents in a non-IND trial

- All adverse events reported via AdEERS (i.e, serious adverse events) should also be forwarded to your local IRB.
- Treatment expected adverse events include those listed in [Section 10.0](#) and in the package inserts for fluorouracil, leucovorin, irinotecan, oxaliplatin, capecitabine, and gemcitabine.
- Grade 3 or 4 myelosuppression and hospitalization resulting from such do not require AdEERS, but should be submitted as part of study results.
- Other grade 1- 4 events that are expected do not require AdEERS expedited reporting, even if they result in hospitalization.
- Grade 4 events that are unexpected and that are at least possibly related to treatment must be reported via AdEERS within 10 calendar days.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of results of clinical trial, e.g., cooperative group data reporting.
- All new malignancies should be reported through AdEERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome (MDS)/acute myelogenous leukemia (AML), and *in situ* tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasm other, malignant (grade 3 or 4). Whenever possible, the AdEERS reports for new malignancies should include, tumor pathology, history of prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- All pregnancies and suspected pregnancies occurring in female patients or in the partner of a male patient during therapy or within 28 days after completion of treatment on A021101 must be reporting via AdEERS. In CTCAE version 4.0, use the event term, “*pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade 4)*”.
- AdEERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
- The AdEERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via AdEERS.

16.0 REFERENCES

- 1) Oettle, H., S. Post, et al. (2007). "Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial." *JAMA* 297(3): 267-77. 17227978.
2. Conroy, T., F. Desseigne, et al. (2011). "FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer." *The New England journal of medicine* 364(19): 1817-25. 21561347.
3. Brown, K. M., V. Siripurapu, et al. (2008). "Chemoradiation followed by chemotherapy before resection for borderline pancreatic adenocarcinoma." *Am J Surg* 195(3): 318-21. 18308038.
4. Chun, Y. S., B. N. Milestone, et al. (2010). "Defining venous involvement in borderline resectable pancreatic cancer." *Annals of surgical oncology* 17(11): 2832-8. 20725860.
5. Katz, M. H., P. W. Pisters, et al. (2008). "Borderline resectable pancreatic cancer: the importance of this emerging stage of disease." *J Am Coll Surg* 206(5): 833-46; discussion 846-8. 18471707.
6. Stokes, J. B., N. J. Nolan, et al. (2011). "Preoperative capecitabine and concurrent radiation for borderline resectable pancreatic cancer." *Annals of surgical oncology* 18(3): 619-27. 21213060.
7. Landry, J., P. J. Catalano, et al. (2010). "Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma." *J Surg Oncol* 101(7): 587-92. 20461765.
8. Katz, M. H., P. W. Pisters, et al. (2011b). "Borderline resectable pancreatic cancer: what have we learned and where do we go from here?" *Annals of surgical oncology* 18(3): 608-10. 21136179.
9. Abrams, R. A., A. M. Lowy, et al. (2009). "Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement." *Ann Surg Oncol* 16(7): 1751-6. 19390900.
10. Callery, M. P., K. J. Chang, et al. (2009). "Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement." *Ann Surg Oncol* 16(7): 1727-33. 19396496.
11. Katz, M. H., N. B. Merchant, et al. (2011a). "Standardization of Surgical and Pathologic Variables is Needed in Multicenter Trials of Adjuvant Therapy for Pancreatic Cancer: Results from the ACOSOG Z5031 Trial." *Ann Surg Oncol* 18(2): 337-344. 20811779.
12. Lu 1997 (need reference)
13. Katz, M. H., Wang, H., et al. (2011c). "Effect of neoadjuvant chemoradiation and surgical technique on recurrence of localized pancreatic cancer." *Journal of Gastrointestinal Surgery* in press.
14. McClaine, R. J., A. M. Lowy, et al. (2010). "Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer." *HPB : the official journal of the International Hepato Pancreato Biliary Association* 12(1): 73-9. 20495649.

15. Evans, D. B., G. R. Varadhachary, et al. (2008). "Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head." *J Clin Oncol* 26(21): 3496-502. 18640930.
16. Varadhachary, G. R., R. A. Wolff, et al. (2008). "Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head." *J Clin Oncol* 26(21): 3487-95. 18640929.
17. Meszoely, I. M., H. Wang, et al. (2004). "Preoperative chemoradiation therapy for adenocarcinoma of the pancreas: The Fox Chase Cancer Center experience, 1986-2003." *Surgical oncology clinics of North America* 13(4): 685-96, x. 15350942.
18. Small, W., Jr., J. Berlin, et al. (2008). "Full-dose gemcitabine with concurrent radiation therapy in patients with nonmetastatic pancreatic cancer: a multicenter phase II trial." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 26(6): 942-7. 18281668.
19. Gillen, S., T. Schuster, et al. (2010). "Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages." *PLoS medicine* 7(4): e1000267. 20422030.
20. Sahora, K., I. Kuehrer, et al. (2011). "NeoGemOx: Gemcitabine and oxaliplatin as neoadjuvant treatment for locally advanced, nonmetastasized pancreatic cancer." *Surgery* 149(3): 311-20. 20817204.
21. Reni, M., S. Cereda, et al. (2009). "Outcome of upfront combination chemotherapy followed by chemoradiation for locally advanced pancreatic adenocarcinoma." *Cancer chemotherapy and pharmacology* 64(6): 1253-9. 19381632.
22. Ohigashi, H., O. Ishikawa, et al. (2009). "Feasibility and efficacy of combination therapy with preoperative full-dose gemcitabine, concurrent three-dimensional conformal radiation, surgery, and postoperative liver perfusion chemotherapy for T3-pancreatic cancer." *Annals of surgery* 250(1): 88-95. 19561477.
23. Morganti, A. G., M. Massacesi, et al. (2010). "A systematic review of resectability and survival after concurrent chemoradiation in primarily unresectable pancreatic cancer." *Ann Surg Oncol* 17(1): 194-205. 19856029.
24. Moertel, C. G., S. Frytak, et al. (1981). "Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group." *Cancer* 48(8): 1705-10. 7284971.
25. Gastrointestinal Tumor Study Group (1988). "Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group." *Journal of the National Cancer Institute* 80(10): 751-5. 2898536.
26. Boz, G., A. De Paoli, et al. (2001). "Radiotherapy and continuous infusion 5-fluorouracil in patients with nonresectable pancreatic carcinoma." *Int J Radiat Oncol Biol Phys* 51(3): 736-40. 11597816.
27. Crane, C. H., J. L. Abbruzzese, et al. (2002). "Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer?" *Int J Radiat Oncol Biol Phys* 52(5): 1293-302. 11955742.

28. Mehta, V. K., J. C. Poen, et al. (2001). "Protracted venous infusion 5-fluorouracil with concomitant radiotherapy compared with bolus 5-fluorouracil for unresectable pancreatic cancer." *Am J Clin Oncol* 24(2): 155-9. 11319291.
29. Huguet, F., T. Andre, et al. (2007). "Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 25(3): 326-31. 17235048.
30. Breysacher, G., O. Kaatz, et al. (2010). Safety and efficacy of FOLFIRINOX in metastatic pancreatic cancer after first line chemotherapy. *GI ASCO*.
31. Conroy, T., B. Paillot, et al. (2005). "Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study." *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 23(6): 1228-36. 15718320.
32. Song, S, Nones, K, et al. qpure: A tool to estimate tumor cellularity from genome-wide single-nucleotide polymorphism profiles. *PLoS One*, 2012; 7(9):e45835.
33. Conroy T Et al. 2005 "Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer- a groupe tumeurs digestives of the federation nationale des centres de lute contre le cancer study: *J CLin Oncol* 23(6): 1228-36.

APPENDIX I

Staging Reference (Adapted from AJCC Manual, 7th Edition, 2010)

Definitions			
Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma <i>in situ</i>		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional Lymph Nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
Distant Metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping (TNM)			
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1
Histologic Grade			
GX	Grade cannot be assessed		
G1	Well differentiated		
G2	Moderately differentiated		
G3	Poorly differentiated		
G4	Undifferentiated		
Residual Tumor (R)			
RX	Presence of residual tumor cannot be assessed		
R0	No residual tumor		
R1	Microscopic residual tumor		
R2	Macroscopic residual tumor		