Phase II Study of Preoperative FOLFIRINOX Followed by Accelerated Short Course Radiation Therapy for Borderline-Resectable Pancreatic Cancer

PROTOCOL 11-328

NCT01591733

Protocol Version Date: 5/19/16

Protocol Version Date: 5/19/16

Local Protocol #: 11-328

Title: Phase II Study of Preoperative FOLFIRINOX followed by Accelerated Short Course Radiation Therapy for Borderline-Resectable Pancreatic Cancer

Principal Investigator: Theodore S. Hong, MD (MGH)

Coordinating Center: N/A

Co-Investigators:
Janet E. Murphy, MD
Alec Kimmelman, M.D.
Harvey Mamon, MD, PhD (DFCI)
Lawrence Blaszkowsky, MD
Michael Blake, MD
Thomas DeLaney, MD
Jeffrey Clark, MD
Eunice Kwak, MD, PhD
David Ryan, MD
Andrew Zhu, MD, PhD
Jill Allen, MD
Jeffrey Meyerhardt, MD
Robert J Mayer, MD
Charles Fuchs, MD
Peter Enzinger, MD
Matthew Kulke, MD
Pankaj Bhargava, MD
Dushyant Sahani, MD
Jennifer Wo, MD
Lorraine Drapek, RN, FNP-BC
Ryan Nipp, MD
Theresa McDonnell, DNP, ACNP-BC
Ann Donnelly, NP
Rhaea Photopoulos, MS, ANP-BC
Caroline Kuhlman, MS, NP, AOCNP
Patricia Tammaro, NP
Emily Olson, NP

Statistician: Beow Yeap, ScD, MGH

Study Coordinator/Data Manager: [redacted]

Responsible Research Nurse: TBN

Agent(s): *5-Fluorouricil, Leucovorin calcium, Oxaliplatin, Irinotecan, Capecitabine, Proton or Photon Beam Irradiation, (no IND)*

Funding Support: **Federal Share of program income earned by Massachusetts General Hospital on C06 CA059267, Proton Therapy Research and Treatment Center**

Perioperative FOLFIRINOX with Short Course Radiation Therapy

in Borderline Resectable and High-Risk Cancer of the Pancreas

SCHEMA

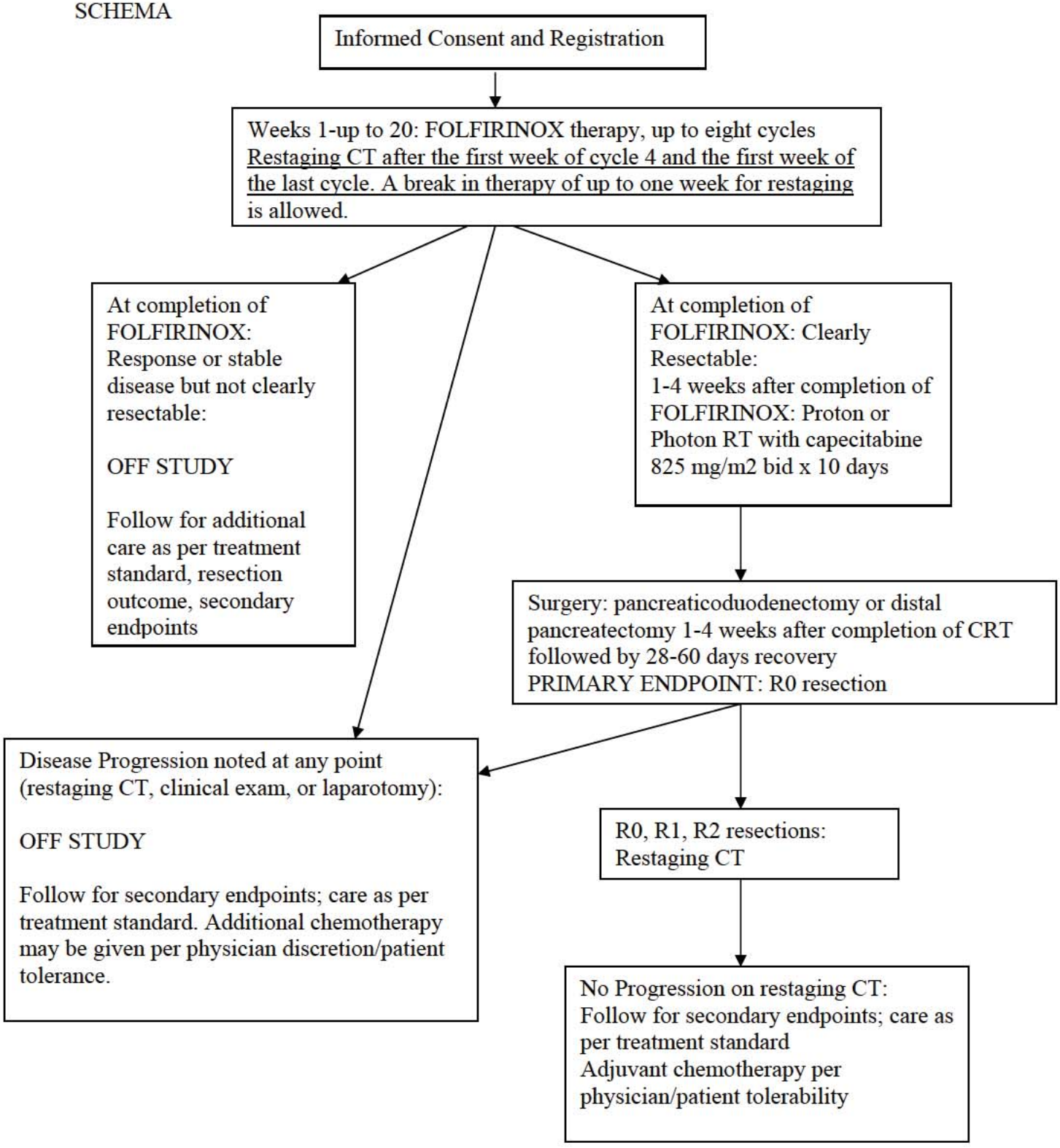


TABLE OF CONTENTS

1.1 Study Design 8

1.2 Primary Objective 8

1.3 Secondary Objectives 8

2 BACKGROUND 9

2.1 Study Agents 9

2.2 Disease Background 16

3 ELIGIBILITY CRITERIA 30

3.1 Inclusion Criteria: 30

3.2 Exclusion Criteria 32

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations 33

4 REGISTRATION PROCEDURES 33

4.1 General Guidelines for DF/HCC and DF/PCC Institutions 33

4.2 Registration Process for DF/HCC and DF/PCC Institutions 34

5 TREATMENT PLAN 34

5.1 Pre-Treatment Criteria 34

5.2 Agent Administration 35

5.3 General Concomitant Medication and Supportive Care Guidelines: 41

5.4 Duration of Therapy 41

5.5 Duration of Follow Up 41

5.6 Criteria for Removal from Study 42

6 EXPECTED TOXICITIES AND DOSING DELAYS/MODIFICATIONS 42

6.1 Anticipated Toxicities 42
6.2 Toxicity Management 44
6.3 Capecitabine and Proton Radiation 50
7 DRUG FORMULATION AND ADMINISTRATION 50
7.1 5-Fluorouracil (5-FU; fluorouracil; Adrucil") 50
7.2 Leucovorin Calcium (Folinic Acid). 51
7.3 Oxaliplatin [Eloxatin] 52
7.4 Irinotecan (CPT-11, CAMPTOSAR®) 54
7.5 Capecitabine 55
8 CORRELATIVE STUDIES 59
8.1 Correlative Studies: SNaPshot analysis 59
9 STUDY CALENDAR 61
10 MEASUREMENT OF EFFECT 64
10.1 Evaluation Of Response 64
10.2 Definitions 65
10.3 Disease Parameters 66
10.4 Methods for Evaluation of Measurable Disease 66
10.5 Response Criteria 67
10.6 Response Review 68
11 ADVERSE EVENT REPORTING REQUIREMENTS 68

11.1 Definitions....68
11.2 Procedures for AE and SAE Recording and Reporting....71
11.3 Reporting Requirements....71
11.4 Reporting to the Study Sponsor....72
11.5 Reporting to the Institutional Review Board (IRB)....73
11.6 Reporting to Hospital Risk Management....74
11.7 Monitoring of Adverse Events and Period of Observation....74

12 DATA AND SAFETY MONITORING....74
12.1 Data Reporting....74
12.2 Safety Meetings....76
12.3 Monitoring....76

13 REGULATORY CONSIDERATIONS....77
13.1 Protocol Review and Amendments....77
13.2 Informed Consent....77
13.3 Ethics and Good Clinical Practice (GCP)....78
13.4 Study Documentation....79
13.5 Records Retention....79

14 STATISTICAL CONSIDERATIONS....79
14.1 Study Design/Endpoints....79
14.2 Sample Size/Accrual Rate....80
14.3 Stratification Factors....80
14.4 Analysis of Secondary Endpoints....80
14.5 Reporting and Exclusions....82

15 PUBLICATION PLAN....82

16 REFERENCES 83

1. OBJECTIVES

1.1 Study Design

This is a single-arm Phase II study of the neoadjuvant administration of the FOLFIRINOX regimen and preoperative proton or photon RT followed by surgery in patients with borderline-resectable adenocarcinoma of the pancreas.

1.2 Primary Objective

1.2.1 To determine the rate of R0 resection of patients with borderline-resectable adenocarcinoma of the pancreas.

1.3 Secondary Objectives

1.3.1 To determine the progression-free survival of patients who receive preoperative FOLFIRINOX and preoperative short-course radiation therapy.

1.3.2 To determine overall survival in patients treated with preoperative FOLFIRINOX and short-course radiation therapy.

1.3.3 To determine the toxicity of FOLFIRINOX + short-course radiation therapy in patients with pancreatic cancer.

1.3.4 To determine the surgical morbidity in patients undergoing pancreaticoduodenectomy or distal pancreatectomy who received preoperative FOLFIRINOX and preoperative short-course radiation therapy.

1.3.5 To determine 30-day post-operative mortality after pancreaticoduodenectomy or distal pancreatectomy in patients who receive preoperative FOLFIRINOX and short-course radiation therapy.

1.3.6 To determine pathologic downstaging of FOLFIRINOX + short course radiation therapy.

1.3.7 To determine local control rates with FOLFIRINOX + preoperative short-course radiation therapy.

1.3.8 To correlate mutational analysis biomarkers (SNaPSHOT assay) with response to treatment.

1.3.9 To describe quality of life, symptom burden and mood in the study population

1.3.10 To measure utilization of health services (emergency room, hospital and intensive care unit) in the study population

2 BACKGROUND

2.1 Study Agents

2.1.1 5-Fluorouracil

5-Fluorouracil (5-FU) is a pyrimidine antagonist that interferes with nucleic acid biosynthesis. The deoxyribonucleotide of the drug inhibits thymidylate synthetase, thus inhibiting the formation of thymidylic acid from deoxyuridylic acid, thus interfering in the synthesis of DNA. It also interferes with RNA synthesis. It is systemically metabolized, with the enzyme dihydropyrimidine dehydrogenase (DPD) being rate-limiting. It forms the backbone of treatment for most gastrointestinal malignancies, and is a crucial component of the FOLFIRINOX regimen, in which it is administered as a 400 mg/m2 bolus, followed by a 2400 mg/m2 46 hour infusion. Neutropenia and diarrhea are the dose limiting toxicities of 5-fluorouracil. Nausea and vomiting with 5-fluorouracil tends to be mild but patients often become dehydrated due to diarrhea. Stomatitis is a common complication of 5-fluorouracil and typically occurs 5-8 days after initiating treatment. Ileus may occur as a result of 5-fluorouracil enteritis. Anemia and thrombocytopenia are also associated complications. Dermatologic side effects are common, and include dryness of skin, palmar-plantar erythrodysesthesias (Hand-Foot syndrome), alopecia, loss of nails/brittle nails and a maculopapular rash. Neurological complications are rare and consist of ataxia. Cardiotoxicity is another very rare complication of 5-fluorouracil, manifested as ischemia and sometimes asymptomatic S-T changes. Excessive lacrimation is common and less common is eye duct stenosis. 5-FU may also increase the INR in patients taking warfarin.

Initial dose of 5-FU may be reduced if necessary; then gradually increased to full dose if tolerated. All dose reductions are to be made at the discretion of the treating medical oncologist.

2.1.2 Oxaliplatin

Oxaliplatin is a platinum compound classified with the alkylating agents. Its mechanism of action is via intra-strand cross-linking, thereby inhibiting DNA replication and transcription. In the FOLFIRINOX regimen it is administered as an 85 mg/m2 infusion over 2 hours. Neurotoxicity is generally the dose-limiting toxicity of the drug, as it causes both immediate and delayed neuropathy manifesting as cold sensitivity (immediate) and parasthesias, numbness, and ataxia (incoordination, including abnormal gait) (delayed.) It is also associated with CNS complaints such as insomnia, mood alteration (depression, anxiety) neuropathy cranial (ptosis), vertigo, neuropathy sensory (including acute laryngeo-pharyngeal dysesthesias, L'Hermitte's sign, paresthesia). Oxaliplatin is associated with allergic and hypersensitivity reactions including chills, flushing, or anaphylaxis. It is associated with mild ototoxicity. Bone marrow suppression (particularly thrombocytopenia), cardiac arrythmia, and hepatic toxicity, specifically increased alkaline phosphatase, increased bilirubin, increased GGT (gamma-glutamyl-transpeptidase), hepatic enlargement, increased AST (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase) have been observed. It is associated with rare but serious pulmonary fibrosis. Initial dose of oxaliplatin may be reduced if necessary; then gradually increased to full dose if tolerated. All dose reductions are to be made at the discretion of the treating medical oncologist.

2.1.3 Irinotecan

Irinotecan is a camptothecin topoisomerase I inhibitor commonly used in gastrointestinal malignancies. In the FOLFIRINOX regimen it is delivered as a 180 mg/m2 infusion over 90 minutes on Day 1 of treatment. Diarrhea and neutropenia are the major dose-limiting toxicities of irinotecan. Diarrhea can occur either acutely (within the first 24 hours) and delayed (after 2-4 days.) Acute diarrhea is thought to be mediated by non-competitive inhibition of acetyl

cholinesterase activity by irinotecan, and is readily treatable with atropine, 0.25-1 mg, intravenously. Delayed diarrhea often manifests after the second or third weekly dose of irinotecan, and is thought to be secretory in nature, resulting from abnormal intestinal ion transport. Anti-diarrheal agents, such as loperamide, diphenoxylateatropine (Lomotil®), octreotide, scopolamine and bismuth are typically ineffective once grade IV diarrhea has occurred. The diarrhea usually lasts 5-7 days before resolving. Early recognition of diarrhea and prompt institution of an intensive and prolonged course of loperamide appears to be the most effective approach to this problem. Myelosuppression is manifested primarily as leukopenia and neutropenia. Other toxicities include nausea, vomiting, alopecia and cumulative fatigue or asthenia. Instances of possible drug related hepatic toxicity have occurred, but are rare. Initial dose of Irinotecan may be reduced if necessary; then gradually increased to full dose if tolerated. All dose reductions are to be made at the discretion of the treating medical oncologist.

2.1.4 Leucovorin

Leucovorin is a reduced folate which, when combined with 5FU, augments 5FU cytotoxicity by increasing the inhibition of TS by the 5FU active metabolite FdUMP. It is well-tolerated but can be associated with allergic reactions (rash, urticaria, anaphylaxis) and is contraindicated in patients with B12 deficiency and pernicious anemia.

2.1.5 Capecitabine

Capecitabine is a rationally designed oral fluoropyrimidine.[1, 2] Given its lack of a need for an implantable access device or portable infusion pump and patient convenience, it has become an attractive agent to be combined with radiation therapy. Capecitabine undergoes three steps of enzymatic activation before converting to the active drug. It is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxyesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase . Some human

carcinomas express this enzyme in higher concentrations than surrounding normal tissues. Capecitabine is rapidly and extensively absorbed with the peak plasma concentrations for the drug and its two main metabolites occurring shortly (0.5 - 1.5 hours) after administration. Then concentrations decline exponentially with a half-life of 0.5 - 1 hour. Plasma concentrations of the cytotoxic moiety 5-FU are very low.

Capecitabine is generally well tolerated. Major side effects include diarrhea, nausea, hand-and-foot syndrome, vomiting, fatigue, and stomatitis. The most frequent grade 3 or 4 laboratory abnormality was elevated total bilirubin and alkaline phosphatase, or abnormal liver function tests. Myelosuppression has been rarely reported (< 2%).

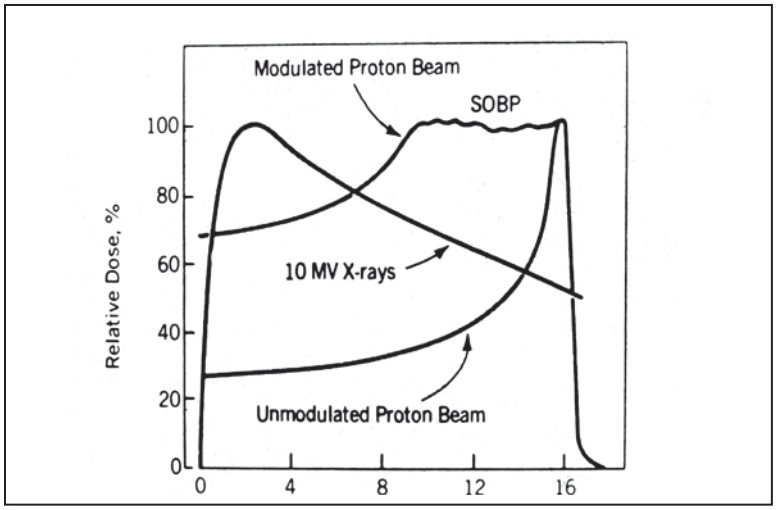
Its role as a radiosensitizer has been most studied in rectal cancer. Dunst et al reported the results of a phase I study using capecitabine in T3 and T4 rectal cancer.[3] Thirty-six patients with rectal cancer received treatment in the adjuvant, neoadjuvant, or palliative setting with a total radiation dose of 50.4 Gy. Capecitabine was administered at escalating doses from 250 to 1,250 mg/m^2 twice a day concurrently with radiation. They were able to escalate the capecitabine dose to 825 mg/m^2 twice a day. Dose-limiting grade 3 hand-and-foot syndrome was observed in two of six patients treated at 1,000 mg/m^2 bid. Other toxicities were generally rare and/or mild. One pathologic complete remission of a T3N1 tumor and nine partial remissions were observed in 10 patients treated in the neoadjuvant setting. In another study, capecitabine was administered concurrently with radiotherapy in locally advanced rectal cancer.[4] The treatment consisted of 2 cycles of 14-day oral capecitabine (825 mg/m^2 BID) and leucovorin (10 mg/m^2 BID), each of which was followed by a 7-day rest period. The overall downstaging rate, including both primary tumor and nodes, was 84%. A pathologic complete response was achieved in 31% of patients. Twenty-one patients had tumors located initially 5 cm or less from the anal verge; among the 18 treated with surgery, 72% received sphincter-preserving surgery. Grade 3 toxicities included hand-foot syndrome (7%), fatigue (4%), diarrhea (4%), and radiation dermatitis (2%). NSABP is planning a prospective randomized trial to compare capecitabine with infusional 5-FU in patients undergoing preoperative radiation therapy. Preliminary results from a trial combining capecitabine with radiation therapy in patients with locally advanced pancreatic cancer demonstrated the combination to be safe and tolerable at a dose of 825 mg/m2 twice daily.[5]

2.1.6 Proton Beam Radiation Therapy

There have been unprecedented efforts in radiation oncology to develop and use sophisticated, conformal photon techniques in order to improve the outcome for cancer patients. The aim of these new techniques is to concentrate the radiation dose distribution more completely on the disease target, thereby sparing critical normal tissues and increasing the target dose. Toward this end, many advances have been made and examples of new developments include tomotherapy and intensity modulated photon therapy. At the same time, heavy, charged-particle programs, particularly those for proton therapy, have been developed. Proton therapy dose distributions are superior to those of photon therapy and this provides the potential to further improve clinical outcomes. Several institutions have committed to build dedicated proton therapy centers such as the Francis H. Burr Proton Therapy Center (FHBPTC) at the Massachusetts General Hospital (MGH) and the Loma Linda University Medical Center proton therapy facility. Several more proton therapy centers are in the final planning stage.

2.1.6.1 The Advantages of Protons for Delivery of Conformal Therapy

Characteristics of Proton Beams



The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, the depth dose characteristics of the two beams are qualitatively different (see Figure 1). Protons lose their energy in tissue mostly by coulombic interactions with electrons in the constituent atoms; however, a small fraction of energy is transferred through nuclear collisions. The energy loss per unit path length is relatively small and constant as the proton traverses the tissue until near the end of the proton range where the residual energy is lost over a short distance (approximately 0.7 cm in width at 80% of the maximum dose) and the proton comes to rest, resulting in a distinctive sharp rise in the tissue absorbed dose (energy absorbed per unit mass) - known as the Bragg peak (see the curve labeled "unmodulated proton beam" in Figure 1). In physical terms, the magnitude of the transfer of

energy to tissue per unit path length traversed by the protons is inversely proportional to the square of the proton velocity. The low dose region between the entrance and the Bragg peak is called the plateau of the dose distribution and the dose there is 30-40 percent of the maximum dose.

The Bragg peak is too narrow in extent to irradiate any but the smallest of targets, ablation of the pituitary gland for example. For the irradiation of larger targets/tumors the beam energy is modulated - several beams of closely spaced energies (ranges) are superimposed to create a region of uniform dose over the depth of the target. These extended regions of uniform dose are called "spread-out Bragg peaks" (SOBP). This is shown in Figure 1 as the “modulated proton beam”.

For comparison, Figure 1 also shows the depth-dose curve for a 10 MV x-ray beam, an x-ray energy commonly used to treat deep seated tumors. Note that the x-ray beam dose rises to a maximum value at relatively shallow depths, then falls off exponentially to lower doses at the treatment depth. A clinical comparison of single-beam proton and photon beams is shown in Figure 2 where a single posterior beam is used for the treatment of the spinal axis in the treatment of medulloblastoma. Note that, for the photon treatment, the heart, mediastinum, esophagus, lung and spinal cord are irradiated by the treatment beam whereas for the proton treatment, the beam stops abruptly distal to the target volume and there is no irradiation of the tissues and organs distal to the target volume.

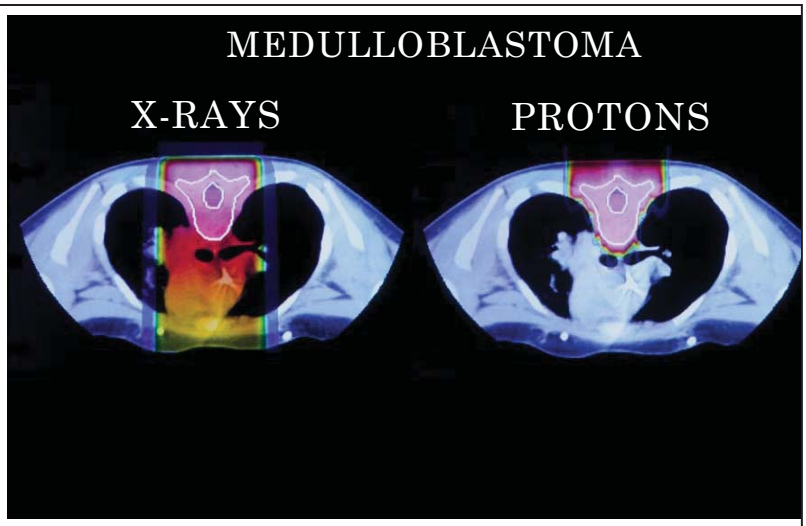


Figure 2. Posterior, single-beam treatment of the spinal axis.

In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments. However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams or complex beam arrangements. In modern proton therapy facilities, which have isocentric gantries and sophisticated beam delivery and control systems,

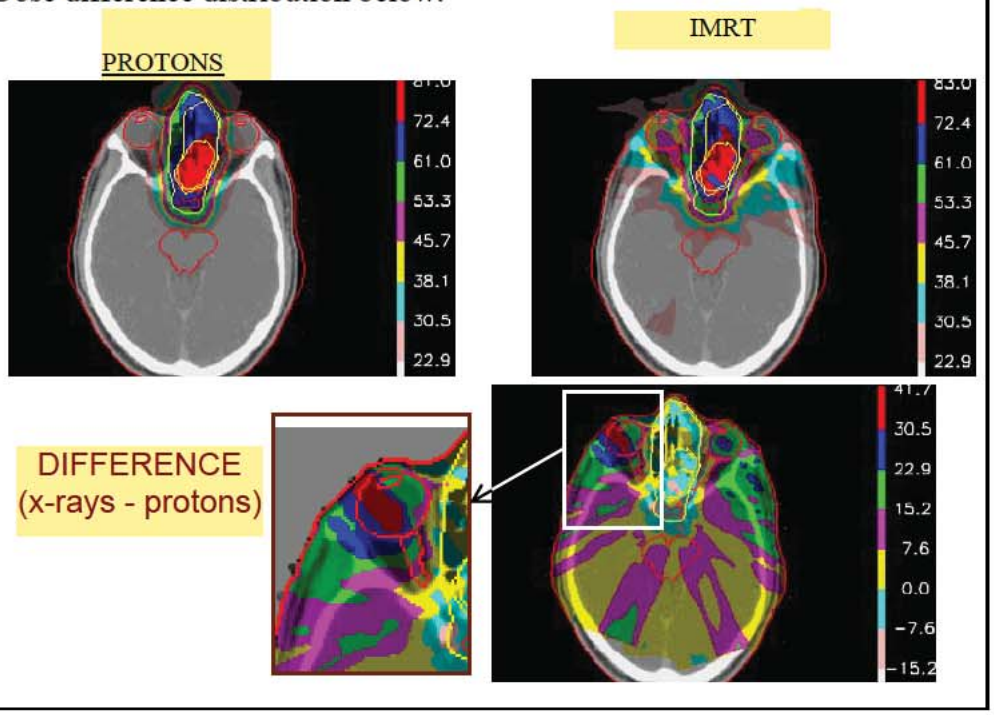
proton therapy capabilities are equivalent to those for state-of-the-art, conformal therapy using x-rays with respect to numbers of beams, beam directions and complex delivery techniques such as intensity modulation.

2.1.6.2 Intensity Modulated Radiation Therapy

Intensity-modulated x-ray therapy (IMXT) – the use of x-ray beams each of which is purposely made non-uniform over its cross-section – provides a new degree of freedom in treatment delivery and can lead to more conformal dose distributions. Protons, too, can be used in an intensity modulated mode (IMPT) similar to that for photons and, in an additional degree of freedom, are also made non-uniform in depth. The advantage that single beams of protons have over single beams of x-rays, which is maintained when multiple cross-firing beams of uniform intensity are employed, is similarly maintained when intensity modulation is employed.

In IMXT, the dose can be made to conform to the target volume while avoiding selected adjacent sensitive structures (although the dose uniformity within the target volume is strongly influenced by such selective avoidance and is often of undesirable magnitude). However, IMXT does not reduce the integrated dose delivered outside the target volume (as compared to standard conformal photon therapy); it only, in general, spreads that energy out over a larger volume. In our treatment planning intercomparisons (in nasopharynx, paranasal sinus, lung and Ewing's sarcoma) we have found that the integral dose for

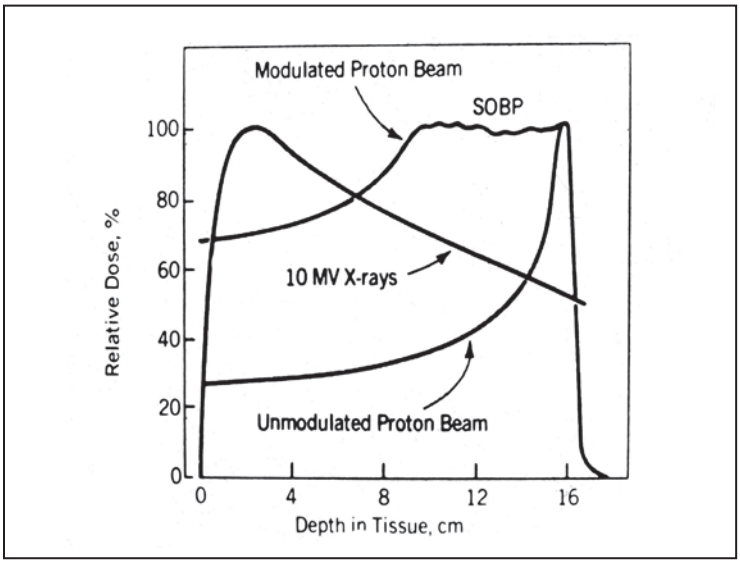
Figure 3: Paranasal sinus tumor treated with IMPT (left) and IMXT (right). Dose difference distribution below.



IMPT is a factor of two (on the average) less than for IMXT. Moreover, whatever improvement IMXT achieves over standard conformal x-ray therapy, a comparable improvement is achieved when IMPT is compared to standard conformal proton therapy.

Figure 3 demonstrates the above points. It is a comparison of two IMRT plans, one with x-rays and one with protons, designed to treat a paranasal sinus tumor (with three target volumes receiving 76, 66, and 56 Gy, respectively). The two plans were subject to identical dose constraints on normal tissues. The proton dose distribution (left) is clearly excellent; the photon distribution on the right is also very good. However, the presentation of the dose in the top panels does not adequately reveal the significant differences between the two distributions. The lower panels show the dose difference between the plans. X-rays deliver an additional "bath" of from 5 to 15 Gy throughout the brain and, in the region of the right eye (which is magnified in the lower left), up to 40 Gy more than the protons. (The constraint on the right eye's retina was 50 Gy; had it been reduced, x-rays could certainly have reduced the dose in that region – but at the price of increased dose elsewhere and, perhaps, of greater non-uniformity of dose in the target volumes.)

Pancreatic tumors also have a number of normal structures in close proximity that have limited radiation tolerance including kidneys, liver, spinal cord and stomach. The lack of exit dose from proton beam radiation can allow for reduced dose to these and other normal tissues.



2.2 Disease Background

2.2.1 Defining the study cohort

The optimal treatment sequence in the management of resectable pancreatic cancer is controversial, as is the role of chemotherapy versus chemoradiation in the pre- and postoperative setting. In borderline-resectable disease, the case for neoadjuvant treatment is more compelling but data for the definitive benefit is lacking, with case series rather than prospective clinical trials predominating the literature. The current trial

will enroll patients with borderline resectable disease,as defined by vascular criter (see inclusion criteria). Based on potential unresectability and/or micrometastatic spread at presentation, this group represents the opportune population to offer the combination of highly active systemic chemotherapy (the FOLFIRINOX regimen) with preoperative radiation therapy.

2.2.1.1 Borderline-resectable disease based on NCCN criteria.

The NCCN has adopted guidelines published by the Expert Consensus Report for Resectable and Borderline Resectable Pancreatic Cancer (2009) and now defines borderline-resectable pancreatic adenocarcinoma as:

- No distant metastases
- Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, either tumor thrombus or enacasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection or reconstruction
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.[6]

In addition to the above criteria dictated by the NCCN, the definition of "borderline-resectable" can be expanded to include tumor invasion into retroperitoneal structures that can be surgically removed (ie. kidney).

The clinical course and postoperative prognosis of patients with borderline resectable disease are difficult to delineate because patients are often considered alongside those with locally advanced, categorically unresectable, disease. Outcomes with neoadjuvant chemotherapy and chemoradiation in borderline-resectable disease will be discussed shortly.

2.2.2 Neoadjuvant photon chemoradiation in resectable pancreatic adenocarcinoma

In patients with resectable disease, prospective and retrospective data suggest that compared

with surgery alone, the combination of pancreaticoduodenectomy with postoperative fluorouracil (5-FU) and external-beam radiation therapy (EBRT) improves survival duration and local-regional control.[8,9] However, the morbidity and often prolonged recovery time associated with pancreaticoduodenectomy prevent the timely delivery of postoperative chemotherapy and EBRT in at least 20% of eligible patients.[10] The risk of delaying postoperative adjuvant chemoradiation has prompted investigators to assess the efficacy of chemotherapy and EBRT before pancreaticoduodenectomy in patients with potentially resectable adenocarcinoma of the pancreas.

The concept of neoadjuvant therapy is based on several principles.[11] First, it allows for management and potential sterilization of micrometastatic disease. Second, it delivers chemotherapy and radiation to an intact tumor with patent blood supply. Finally, it allows for biologic selection of patients with gross metastatic disease prior to highly morbid intervention such as laparotomy or pancreaticoduodenectomy. In practice, several additional considerations support the use of preoperative chemotherapy and EBRT. Positive gross or microscopic margins of resection along the right lateral border of superior mesenteric artery (SMA) are common following pancreaticoduodenectomy, suggesting that surgery alone may be an inadequate strategy for local tumor control.[12] Second, because chemoradiation is given before surgery, delayed postoperative recovery does not affect the delivery of multimodality therapy.

Studies from the MD Anderson Hospital first used a standard-fractionation treatment schema of preoperative chemoradiation and pancreaticoduodenectomy.[13-16] Radiation therapy was delivered 5 days/week over 5.5 weeks delivering a total dose of 50.4 Gy in 28 fractions. 5-FU was given concurrently by continuous infusion at a dosage of 300 mg/m2 per day, 5 days per week, through a central venous catheter. Thirty-eight patients were evaluable for analysis of patterns of treatment failure; 1 perioperative death occurred. Tumor recurrence was documented in 29 patients: 8 recurrences (21%) were local-regional (in the pancreatic bed and/or peritoneal cavity), and 30 (79%) were distant (in the lung, liver, and/or bone). The liver was the most frequent site of tumor recurrence, and liver metastases were a component of failure in 53% of patients (69% of all patients who had recurrences). Isolated local or peritoneal recurrences were documented in only 4 patients (11%). In contrast, previous reports of pancreaticoduodenectomy alone for adenocarcinoma of the pancreas documented local recurrence in 50 to 85% of patients.[17,18] The improvement in local-regional control with preoperative chemoradiation was

seen even though 14 of 38 evaluable patients had undergone laparotomy with tumor manipulation and biopsy prior to referral for chemoradiation and reoperation. Excluding these 14 patients, local or peritoneal recurrence was a component of treatment failure in only 2 patients (8%). However, this 5.5-week chemoradiation program was associated with gastrointestinal toxicity (nausea, vomiting, and dehydration) that required hospital admission of one third of patients. Moreover, in an ECOG trial evaluating preoperative chemoradiation for pancreatic cancer patients, 51% of patients required hospital admission for toxicity of treatment during or within 4 weeks after completing chemoradiation.[19]

These findings prompted a change in the delivery of preoperative chemoradiation at the MD Anderson in favor of short course EBRT. In a series of prospective trials, investigators at MD Anderson treated 60 patients with either preoperative standard course RT at a total dose of 50.4 Gy (1.8 Gy/Fraction, 28 fractions, 5 days/week), short course RT at a total dose of 30 Gy (3 Gy/fraction, 10 fractions, 5 days/week), or postoperative standard course RT at a total dose of 50.4 Gy.[20] 5-FU was given concurrently by continuous infusion 5-FU at a dosage of 300 mg/m2 per day, 5 days/week. This short course chemoradiation program was designed to avoid the gastrointestinal toxicity seen with standard-fractionation chemoradiation (5.5 weeks) while attempting to maintain the excellent local tumor control achieved with multimodality therapy. As with other neoadjuvant treatment schemas, restaging with chest radiography and abdominal CT was performed 4 weeks following completion of chemoradiation in preparation for pancreaticoduodenectomy. The short course RT was associated with fewer grades 3 toxicity than standard course RT (7% vs 19%). No difference in efficacy could be ascertained as no patient treated with preoperative chemoradiation who underwent R0 resection experienced a local recurrence.

More recently, data from 132 consecutive patients who received preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas also supported the use of rapid-fractionation chemoradiation.[21] Forty-four patients received standard fractionation (45-50 Gy, 1.8 Gy/fraction/day) EBRT and 88 patients received short course EBRT (30 Gy, 3 Gy/fraction per day). The median overall survival from the time of tissue diagnosis was 21 months. Survival duration was not influenced by the dose of preoperative EBRT and chemotherapy used. The data suggested that short course chemoradiation (30 Gy in 2 weeks)

combined with pancreaticoduodenectomy performed on accurately staged patients might be equivalent to standard-fractionation chemoradiation (45-50 Gy in 5-6 weeks).

2.2.3 Neoadjuvant photon chemoradiation in borderline resectable pancreatic adenocarcinoma

In addition to the rationale presented above for the potential benefit of neoadjuvant treatment in resectable pancreatic cancer, patients who present with borderline resectable disease have the added need for both upfront local control and timely systemic therapy. Local control aims to provide potential tumor downstaging to increase the chance of R0 resection. Systemic therapy aims to sterilize micrometastatic disease, as this population is at higher risk for micrometastatic extension at presentation (as high as 80%).[11]

The largest case series of neoadjuvant therapy in borderline resectable disease comes from MD Anderson.[22] One hundred sixty patients with borderline resectable disease (classified due to tumor abutment of the visceral arteries or short-segment occlusion of the SMV) were followed. Of these, 125 (78%) completed preoperative therapy and restaging. Preoperative therapy was generally administered off-protocol, but some patients were treated on protocols designed for patients with locally advanced disease. Chemoradiotherapy consisted of external beam radiation therapy (50.4Gy in 28 fractions or or 30 Gy in 10 fractions) with concomitant chemotherapy with 5-fluorouracil, paclitaxel, gemcitabine, or capecitabine at radiosensitizing doses. Systemic chemotherapy consisted of gemcitabine alone or in combination; some patients received targeted agents. In total, 82 patients had induction chemotherapy and 117 had chemoradiotherapy. After neoadjuvant therapy, 66 (41%) subsequently underwent pancreatectomy. Vascular resection was required in 18 (27%) of 66 patients, and 62 (94%) underwent a margin-negative pancreatectomy. A partial pathologic response to induction therapy (< 50% viable tumor) was seen in 37 (56%) of 66 patients. Median survival was 40 months for the 66 patients who completed all therapy and 13 months for the 94 patients who did not undergo pancreatectomy ($p < 0.001$).

A smaller, retrospective review of patients with borderline resectable pancreatic cancer treated with preoperative chemoradiation and chemotherapy at Fox Chase Cancer Center included 13 patients treated in the neoadjvuant setting with chemoradiation (radiosensitizer fluorouracil (5-FU) in 3 patients, gemcitabine in 9 patients, and capecitabine and bevacizumab in

1 patient administered with 50.4 Gy in 1.8-Gy fractions. [23] Patients received a median of 3 cycles of full-dose chemotherapy consisting of gemcitabine for 4 patients, gemcitabine and oxaliplatin for 3 patients, gemcitabine and erlotinib for 4 patients, gemcitabine and bevacizumab for 1 patient, and 5-FU and erlotinib for 1 patient. After neoadjuvant therapy, 12 of 13 patients subsequently had surgery, resulting in 2 R1 and 11 R0 resections. Nine patients were alive with a median follow-up of 20 months. Five patients recurred at a median of 4 months.

Finally, a recent series of 170 patients at University of Virginia included 40 patients with borderline resectable disease, and explored the benefit of shorter course radiation in the borderline setting. [24] Of the 40 borderline resectable patients enrolled, 34 (85%) completed neoadjuvant therapy consisting of 50 Gy of radiation in 28 fractions in 6 weeks (8 patients) or 50 Gy in 20 fractions in 4 weeks plus chronomodulated capecitabine (8 patients.) After restaging, pancreatic resection was completed in 16 patients (46%). An R0 resection was achieved in 12 of the 16 patients (75%). Notably, 5 patients (63%) treated in 20 fractions had >90% pathologic response versus 1 (13%) treated in 28 fractions ($P < .05$). Borderline resectable patients completing surgery had similar survival to patients with resectable disease who underwent surgery. Patients receiving accelerated fractionation radiation had improved survival compared with patients treated with standard fractionation protocol.

These case series demonstrate early promise for the neoadjuvant approach in pathologic downstaging to R0 resection. The Consensus statement for combined modality treatment of resectable and borderline resectable pancreas cancer states that at the present time, borderline resectable patients should ideally be enrolled in a clinical trial, and in its absence, “induction systemic chemotherapy followed by chemoradiation and CT assessment of resectability is the preferred approach.” [11]

2.2.4 The FOLFIRINOX regimen in advanced pancreatic cancer

In advanced pancreatic cancer (M1 disease), the standard of care of gemcitabine monotherapy was challenged in 2010 with the presentation of the final results of the Prodige 4 – ACCORD 11/04023 trial. This large Phase III trial arose from promising interim results from a randomized phase II trial comparing FOLFIRINOX to gemcitabine in which a 31.8% response rate was detected in the FOLFIRINOX arm, compared to an 11.4% response rate in the gemcitabine arm. [25]

In the Phase III trial, patients were randomized to FOLFIRINOX versus gemcitabine therapy, with CT assessment every two months and six months planned upfront therapy.[26] The FOLFIRINOX regimen was delivered as a 14-day cycle consisting of oxaliplatin 85 mg/m2 infused over two hours; 5FU 400 mg/m2 bolus with leucovorin 400 mg/m2, followed by infusional 5FU with 2400 mg/m2 delivered over 46 hour infusion; and irinotecan 180 mg/m2 delivered over 90 minutes. Gemcitabine was delivered in the standard fashion of 1000 mg/m2 over 30 minutes given weekly on weeks 7/8 and then weekly 3/4. [27]

Patients were stratified by center, performance status (0 versus 1), and site of primary tumor (head of the pancreas versus body and tail.) The study excluded patients with biliary obstruction, enrolling patients only with serum bilirubin values of 1.5x the upper limit of normal and lower. Notably, lesions in locations other than the head of the pancreas comprised the majority of the study population in both arms – 60.8% in the FOLFIRINOX arm and 63.2% in the gemcitabine arm. The primary endpoint of the study was overall survival, with the secondary endpoints of objective response rate (by RECIST), toxicity, progression-free survival, and quality of life measured on the EORTC QLQ-C30 v3.0 scale. One hundred seventy one patients were observed by intention-to-treat in each arm.

The hematologic adverse event profile of the FOLFIRNOX regimen was significantly greater compared to gemcitabine. Rates of Grade 3/4 neutropenia (45.7% versus 21.0%), febrile neutropenia (5.4 versus 1.2%), and thrombocytopenia (9.1 versus 3.6%) were significantly higher. This resulted in 42.5% of patients in the FOLFIRINOX arm requiring G-CSF injection, versus 5.3% in the gemcitabine arm (per 2010 ASCO presentation of the trial results). Nonhematologic Grade 3/4 toxicities were also more prevalent, with peripheral neuropathy, vomiting, fatigue, diarrhea, and alopecia all occurring in the FOLFIRINOX arm at a significantly greater rate.

Despite greater toxicity, the FOLFIRINOX regimen outperformed gemcitabine in all outcomes measures. The partial response rate was 31% [24.7-39.1, 95% CI] versus 9.4% [5.9 – 15.4%, 95% CI] in the gemcitabine arm. Stable disease rates were more comparable, with 38.6% SD rate in the FOLFIRINOX arm and 41.5% in the gemcitabine arm. Overall this led to superior disease control rates (CR+PR+SD) for FOLFIRINOX versus gemcitabine, 70.2% and 50.9%, respectively. With a median follow-up of 26.6 months [95% CI: 20.5 – 44.9], progression-free survival of patients in the FOLFIRINOX arm was 6.4 months, versus 3.3 months in the gemcitabine arm (HR 0.47, 95% CI [0.37-0.59].) This translated to a median overall survival of 11.1 months in the FOLFIRINOX arm versus 6.8 months in the gemcitabine arm (HR 0.57, $p<0.0001$), with a 48.4% one-year survival rate (versus 20.6% one-year survival in the gemcitabine arm.)

The compelling features of the Prodige-4/ACCORD results that mandate moving the regimen into the neoadjuvant setting are twofold: first, its demonstrated superiority in systemic disease control, and second, its superior objective response rates. In the setting of high-risk or borderline resectable disease, the goal of providing chemotherapy to potentially downstage to surgical respectability while controlling local spread is paramount. FOLFIRINOX has compelling study to suggest it is more active in the preoperative setting than the current standard of gemcitabine-based therapy. As the current study plans to enroll patients with lesions in the body and tail in greater numbers than are representative of the clinic volume, it will potentially mirror the study population of the Prodige-4 trial as well.

2.2.5 Proton-based Short Course Radiation Therapy for pancreatic cancer: MGH Experience

The safety and efficacy of a one-week course of preoperative proton beam therapy and capecitabine followed by early pancreaticoduodenectomy (PD) was explored in a prior study in our institution in a different study population. Patients with radiographically resectable, biopsy-proven pancreatic cancer of the head of the pancreas were enrolled from May 2007-March 2010 on this IRB-approved, NCI-sponsored clinical trial. Eligibility included no CT involvement of the SMA or celiac arteries; adequate renal, hepatic and hematopoetic function; and ECOG Performance Status 0/1. Dose level 1 consisted of Proton Beam Therapy delivered 3 Gy x 10 Monday to Friday. Pateints in subsequent dose levels received 5 Gy x 5 in progressively shortened schedules: level 2 (week 1 Monday, Wednesday, Friday, week 2 Tuesday, Thursday),

level 3 (week 1 Monday, Tuesday, Thursday, Friday, week 2 Monday), level 4 (week 1 Monday-Friday). Proton beam therapy was targeted at pancreatic mass with elective nodal coverage. Patients received Capecitabine 825 mg/m2 BID weeks 1 and 2 Monday-Friday. Surgery was performed 1-6 weeks after completion of chemotherapy. Patients were recommended to receive 6 months of gemcitabine after surgery. 31 patients were enrolled on study. 27 patients are eligible for this analysis. Three patients were treated at each of dose levels 1-3. Six patients were at dose level 4, which was selected as the MTD. No dose limiting toxicities were observed. There were no unexpected 30-day post-op complications noted in comparison to historical controls. Four of 21 resected patients had positive margins. 17/21 had positive nodes. Median follow up is 10 months. There have been 2 local failures/progression in ALL patients, both with synchronous metastatic disease (at 10 months and 17 months). Metastatic failure has occurred in 15 out of 27 patients (56%). In summary, we found pre-operative Chemo Radiation Therapy with 1 week of Proton Beam Therapy and capecitabine followed by early surgery feasible and associated with satisfactory local control.

In summary, we hypothesize that preoperative FOLFIRINOX therapy will optimize the neoadjuvant treatment of patients with borderline pancreatic adenocarcinoma based on its superior response rate demonstrated in the Prodige-4/ACCORD trial. We anticipate that this benefit will be further potentiated by preoperative proton or photon radiation therapy. The combination allows for high-efficacy therapy to be delivered expeditiously and with manageable tolerable toxicity prior to pancreaticoduodenectomy or distal pancreatectomy.

2.2.6 Equivalence of Proposed Radiation Schedules

2.2.6.1 Clinical Efficacy

The role of neoadjuvant and adjuvant radiation therapy for resectable pancreatic cancer it to improve locoregional control by sterilizing microscopic disease that may not be removed with surgery. Hence, there may not be a clear benefit to higher doses of radiation therapy in this setting. The table below shows the biological and normalized equivalence among a conventional radiation schedule and the two proposed dose arms in this study.

Efficacy Comparison of Conventional and proposed radiation schedules:

Schedule	Dose per fraction	# Tx	Total Dose	*B.E.D (Gy) (no time correction)	**N.T.D (Gy) (no time correction)	*B.E.D. (Gy) (time correction)	**N.T.D. (Gy) (time correction)
Conventional	1.8 Gy	28	50.4	50.4	59.5	46.8	39
MDACC	3 Gy	10	30	39	32.5	39	32.5
MGH Proton	5 Gy (RBE)	5	25	37.5	31.3	37.5	31.3

*B.E.D. – Biologically equivalent dose
**N.T.D. – Normalized Total Dose, or equivalent physical dose if delivered in 2 Gy fractions.
RBE – Relative Biological Equivalent, assuming a Relative Biological Effectiveness of 1.1.

No repopulation (no time correction):
$B.E.D = nd(1+d/\alpha/\beta)$

With repopulation (time correction):
$B.E.D = nd(1+d/\alpha/\beta) - (T-T_k)(\ln 2/(\alpha\tilde{}\ T_{pot}))$

Where:
n = number of fractions
d = dose per fraction
nd = total dose
T = total time of treatment in days
T_k = time after start of treatment repopulation begins
T_{pot} = potential doubling time

Assuming:
$\alpha/\beta = 10$
$\alpha = 0.35$ T = assuming treatment starts on a Monday with no breaks during treatment
T_k = 28 d
T_{pot} = 5 days

$N.T.D. = B.E.D./ (1+2/\alpha/\beta)$

As demonstrated in the above Table, the reason for similar clinical outcomes between a conventional schedule and the MD Anderson 30 Gy short course may be due to both the larger fraction size and shorter treatment time. Similarly, in looking at the 25 Gy schedule, one would expect very similar clinical efficacy.

2.2.6.2 Clinical Toxicity

With alteration of a radiation schedule, there is always concern that the toxicity of treatment may increase. However, when investigators at MD Anderson moved from a conventional schedule to a short course, the clinical tolerability in fact improved. Furthermore, with larger fraction sizes, there is also a concern for increased late effects. Using linear-quadratic formulation, the risk for late effects appears to be lower for late effects than with a conventional schedule.

Late Effect Comparison of conventional, MD Anderson Short Course, and proposed schedule ($\alpha/\beta = 3$):

Schedule	Dose/fraction	# Tx	Total Dose	B.E.D (Gy)	**N.T.D. (Gy)
Conventional	1.8 Gy	28	50.4	80.6	48.4
MDACC	3 Gy	10	30	60	36
MGH Proton	5 CGE	5	25	66.7	40

In a randomized trial for low-lying rectal cancers comparing conventional fraction with 5 Gy x 5, an analysis of perioperative complications was also performed[28]. There were no differences in the rates of complications or in severe complications. These results suggest that there should not be an increase in surgical complications with this either of the proposed radiation schedules in this study.

Recommended dose limits for both acute and late effects can be adjusted for the accelerated schedule. However, the fewer number of fractions render the constraints significantly more stringent.

2.2.7 Correlative Science Background

2.2.7.1 Correlative Laboratory Studies

Preclinical and clinical work in the Steele Lab and elsewhere has identified the stromal-derived factor 1 alpha (SDF1α) as an attractive candidate for biomarkers of resistance to various therapies, but its role after proton beam radiation therapy is unknown. Based on findings from preliminary studies, we propose here to evaluate the changes in blood circulating SDF1α and circulating myeloid cells to explore potential associations between the changes in these biomarkers and resistance to treatment. These biomarkers will be monitored from baseline throughout FOLFIRNOX therapy, before and after a one-week schedule of proton beam radiation therapy (or a two-week schedule of photon radiation), after pancreaticoduodenectomy, and at time of disease progression. In exploratory studies, we will evaluate several other cytokines using multiplex protein array (Meso-Scale Discovery, Inc.).

Circulating cell populations will be evaluated by fluorescence-based flow cytometry. Protein concentration in plasma will be measured using ELISA kits for SDF1˜ and MSD multiplex kits for cytokines (IL-1, IL-6, IL-8 and TNF-˜) vascular growth factors (VEGF, sVEGFR1, PlGF

and bFGF). These techniques have been used in the Steele Lab for over 8 years to evaluate patients' samples.

2.2.7.1 Patient Reported Outcomes (PRO) background

There are few published studies measuring patient-reported symptoms and quality of life (QOL) outcomes in patients with pancreatic cancer. Most of the existing studies assessing QOL in patients with pancreatic cancer are focused on individuals with advanced disease.[6, 7] The few studies that have included patients with operable pancreatic cancer included small sample sizes in heterogeneous patients.[8, 9] Despite the fact that depression is a frequently reported symptom in patients with pancreatic cancer, the prevalence among different stages of disease has not been thoroughly investigated.[10] A more detailed and comprehensive understanding of the burdens faced by patients with locally advanced pancreatic cancer will identify areas for clinicians to enhance their supportive care efforts.

Studying patients' symptom burden and QOL while they are participating in a clinical trial provides an opportunity to better understand their disease- and treatment-related outcomes. Patients' symptom burden and QOL are better indicators of their treatment tolerability than clinician-reported toxicity monitoring. Combining objective endpoints, such as response rate, with subjective patient-reported outcomes has become increasingly important in determining efficacy, toxicity, and safety and for allowing comparisons across treatment arms.[11] Additionally, evaluating patient-reported measures may help highlight patients' difficulties with treatment adherence by demonstrating additional side effects and toxicities of therapy.[12] Increased attention to patients' symptom burden and QOL while they are participating in a clinical trial provides an opportunity to improve their quality of care.[13, 14] Thus, we aim to describe QOL, symptom burden and mood in this study population to help us better identify the side effects and challenges faced by patients with borderline resectable pancreatic cancer.

A randomized trial comparing the efficacy of gemcitabine and FOLFIRINOX in metastatic pancreatic cancer also assessed QOL, using the European Organization for the Research and Treatment of Cancer QOL Questionnaire C30 (EORTC QLQ-C30).[7] The authors demonstrated that FOLFIRINOX not only prolonged survival, but also significantly reduced QOL impairment compared to gemcitabine for patients with metastatic cancer. Thus, in addition to the utility of describing the symptom burden and QOL in patients with borderline resectable pancreatic cancer, it will also be useful to compare these outcomes in patients receiving different chemotherapy regimens.

We will use the EORTC QLQ-C30, a validated instrument designed for prospective clinical trials that evaluates five functions (physical, role, cognitive, emotional, and social), and nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties) to measure QOL.[15] We will use the Edmonton Symptom Assessment System-revised (ESAS-r) to measure symptoms, which has been previously validated in patients with advanced cancer.[16] The ESAS-r consists of ten items assessing pain, fatigue, drowsiness, nausea, anorexia, dyspnea, depression, anxiety, well-being, and a free-response item. We will include constipation as the free-response item. The ten items are scored

on a scale of 0-10 (0 reflecting no reported presence of the symptom and 10 reflecting the worst possible severity of the symptom). We will instruct patients that items are to be rated based on the previous 24-hour period. We will use the Hospital Anxiety and Depression Scale (HADS) to assess symptoms of depression and anxiety.[17] The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week. The questionnaire consists of a four-point item response format that quantifies the degree to which participants experience a particular emotion. Scores on each subscale range from 0 to 21, with a cutoff of 8 or greater denoting clinically significant depression or anxiety symptoms.

2.2.7.2 Health Care Utilization background

As oncologists strive to improve care quality and lower health care costs, their focus has turned to reducing avoidable admissions and decreasing hospital length of stay (LOS) for patients with cancer.[18, 19] Patients with pancreatic cancer often experience symptoms related to the cancer itselt or the therapies used to treat it.[8] Symptom management for these patients may necessitate frequent clinic visits, surgical interventions, and ultimately admissions to the hospital. Avoiding unnecessary hospitalizations is an area needing improvement for patients with cancer, but a better understanding of health care utilization is necessary in order to develop future interventions.[20] Thus, we propose to collect data on study participants' health care utilization including hospital admissions, intensive care unit stays and emergency room visits. Similar to measuring patient-reported outcomes, assessing health care utilization will help us better understand study patients' experience with their cancer treatment.

2.2.7.3 SNaPshot analysis

Tumor mutational analysis by SNaPshot technology. In pancreas cancer, mutations of interest do not occur randomly, but rather a relatively small number of well-characterized mutations compromise the vast majority of activating mutations. Other genes of interest already mentioned include APC, CTNNB1 (β-catenin), Braf, PTEN, and PIK3CA. Our institution has recently begun using an adaptation of SNaPSHOT (Applied Biosystems) as our clinical method of determining KRAS mutational status in tumors, as described by Dias-Santagata et al. [28] This testing is routinely done on all newly diagnosed GI cancer patients. Table 1 below shows the list of mutations tested in our tumor SNaPSHOT platform.

Table 1:

Gene	AA Mutation	CDS Mutation	Gene	AA Mutation	CDS Mutation
1. APC	R1114*(nonsense)	3340C>T	***9. NOTCH1***	L1575P	4724T>C
	Q1338*(nonsense)	4012C>T		L1601P	4802T>C
	R1450*(nonsense)	4348C>T			
	T1556fs*3 ins	4666_4667insA	***10. NRAS***	G12S/C/R	34G>A/T/C
				G12D/V/A	35G>A/T/C
2. CTNNB1 (β-catenin)	D32Y/N/H	94G>T/A/C		G13R/C/S	37G>C/T/A
	D32G/V/A	95A>G/T/C		G13D/V/A	38G>A/T/C
	S33C/F/Y	98C>G/T/A		Q61K/E	181C>A/G
	Gly34Glu/Val	101G>A/T		Q61R/L/P	182A>G/T/C
	S37A/P/T	109T>G/C/A		Q61H	183A>T/C
	S37F/C/Y	110C>T/G/A			
	T41A/S/P	121A>G/T/C	***11. PIK3CA***	R88Q	263G>A
	T41I/N/S	122C>T/A/G		E542K/Q	1624G>A/C
	S45P/A	133T>C/G		E545K	1633G>A
	S45F/Y/C	134C>T/A/G		Q546K/E	1636C>A/G
				Q546R/P/L	1637A>G/C/T
3. BRAF	V600M/K/R	1798G>A		H1047Y	3139C>T
	V600E/G/A/K/R	1799T>A/G/C		H1047R/L	3140A>G/T
				G1049S/R	3145G>A/C
4. EGFR	G719S/C	2155G>A/T			
	T790M	2369C>T	***12. PTEN***	R130*(nonsense)/G	388C>T/G
	L858R	2573T>G		R173C	517C>T
	E746_A750 del	2235_2249del15$_{(F+R)}$		R233*(nonsense)	697C>T
	E746_A750 del	2236_2250del15$_{(F+R)}$		K267fs*9 del	800 delA
5. FLT3	D835Y	2503G>T	***13. TP53***	R175H/L	524G>A/T
				G245S/C/R	733G>A/T/C
6. JAK2	V617F	1849G>T		R248W/G	742C>T/G
				R248Q/L/P	743G>A/T/C
7. KIT	D816V	2447A>T		R273C	817C>T
				R273H/L	818G>A/T
8. KRAS	G12C/S/R	34G>T/A/C		R306*(nonsense)	916C>T
			14.CDKN2A	DELETION	
	G12D/V/A	35G>A/T/C		ANALYSIS	
	G13C/S/R	37G>T/A/C			

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria:

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Cytologic or histologic proof pancreatic ductal carcinoma is required prior to study entry. Diagnosis must be confirmed by the MGH pathology department.

3.1.2 No evidence of metastatic disease as determined by chest CT scan, abdomen/pelvis CT scan (or MRI with gadolinium and/or manganese) within six weeks of study entry. All patients must be staged with a physical exam, chest CT, abdominal CT with intravenous contrast (or Abd MRI with gadolinium and/or manganese).

3.1.3 Staging laparoscopy is <u>not</u> required at the outset of the trial, including in patients who might otherwise receive staging laparoscopy per NCCN guidelines (high-risk body and tail lesions), because patients will receive systemic chemotherapy at equivalent dose to patients who have documented Stage IV disease.

3.1.4 Patients who are deemed 'borderline resectable' will be included. Borderline resectable is defined by the NCCN as tumors with venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, either tumor thrombus or enacasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection or reconstruction; gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; or tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall. Tumors involving retroperitoneal structures that can be surgically removed (ie. kidney), will also be included.

3.1.5 Patients must be 18 years old or older. There will be no upper age restriction.

3.1.6 Patients with ECOG-Performance Status of 0 or 1 are eligible.

3.1.7 Life expectancy of greater than 3 months.

3.1.8 Lab Values within one week of study entry:

ANC ≥ 1000 cells/mm3

Platelet count at least 100,000 cells/mm3.

AST and ALT ≤ 2.5 x upper limit of normal, OR two consecutive downtrending values for patients who have undergone biliary stenting.

Total Bilirubin ≤ 1.5 x upper limit of normal,

OR, for patients who have undergone biliary stenting, Total bilirubin ≤2.0 OR two downtrending values

Serum Creatinine ≤ 1.5 mg/dl

Creatinine Clearance ≥ 30ml/min *(as estimated by Cockroft Gault Equation):*

Creatinine clearance for males =

$$\frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

3.1.9 The effects of radiation on the developing human fetus are known to be teratogenic. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation plus 30 days from the last date of study drug adminsitration. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 The mutational analysis (SNaPSHOT panel) requires a paraffin-embedded block or ten unstained slides from the untreated biopsy specimen obtained at the time of upper endoscopy or initial diagnostic biopsy. Patients without sufficient material for SNaPSHOT will NOT be excluded from the study as this constitutes a secondary, exploratory aim of the study.

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

3.2 Exclusion Criteria

Patients who fulfill any of the following criteria will be excluded:

3.2.1 Serious concomitant systemic disorders incompatible with the study (at the discretion of the investigator), such as significant cardiac or pulmonary morbidity e.g. congestive heart failure, symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication) or myocardial infarction within the last 12 months, ongoing infection as manifested by fever.

3.2.2 Pregnant or lactating women. Women of childbearing potential with either a positive or no pregnancy test (serum or urine) at baseline. (Postmenopausal woman must have been amenorrheic for at least 12 months to be considered of non-childbearing potential).

3.2.3 Any prior chemotherapy, targeted/biologic therapy, or radiation for treatment of the patient's pancreatic tumor.

3.2.4 Treatment of other invasive carcinomas within the last five years with greater than 5% risk of recurrence at time of eligibility screening. Carcinoma in-situ and basal cell carcinoma/squamous cell carcinoma of the skin are allowed.

3.2.5 Other serious uncontrolled medical conditions that the investigator feels might compromise study participation.

3.2.6 Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome.

3.2.7 Known, existing uncontrolled coagulopathy.

3.2.8 Prior systemic fluoropyrimidine therapy (unless given in an adjuvant setting and ted at least 6 months earlier). Prior topical flouropyrimidine use is allowed. Prior unanticipated severe reaction to fluoropyrimidine therapy, or known hypersensitivity to 5-fluorouracil or known DPD deficiency.

3.2.9 Participation in any investigational drug study within 4 weeks preceding the start of study treatment.

3.2.10 History of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant, precluding informed consent, or interfering with compliance or oral drug intake.

3.2.11 Major surgery, excluding laparoscopy, within 4 weeks of the start of study treatment, without complete recovery.

3.2.12 Patients should not be on cimetidine as it can decrease the clearance of 5-FU. Another H2-blocker or proton pump inhibitor may be substituted before study entry.

3.2.13 Participants may not be receiving any other study agents.

3.2.14 History of allergic reactions attributed to compounds of similar chemical or biologic composition to 5-fluorouricil, irinotecan, or oxaliplatin.

3.3 Inclusion of Women, Minorities and Other Under Represented Populations

We do not expect the inclusion and exclusion criteria to either over or under represent women, minorities, or under represented populations.

4 REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the ODQ in the Clinical Trials Management System (CTMS) OnCore. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5 TREATMENT PLAN

Treatment will be administered on an outpatient basis and will include administration of the FOLFIRINOX regimen followed by Proton or Photon Radiation Therapy with capecitabine. Expected toxicities and potential risks as well as dose modifications for FOLFIRINOX and Radiation are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.1 Pre-Treatment Criteria

Prior to study enrollment patients must undergo the following evaluations:
Within 42 days of enrollment: Chest CT and Abdominal-pelvic CT (or MRI). If available, Paraffin-embedded block or ten unstained slides will be used from the untreated biopsy specimen obtained at the time of upper endoscopy or initial diagnostic biopsy for SNaPSHOT analysis.
Within 7 days of enrollment: Physical exam, Lab studies (CBC with diff, Na, K, BUN, Cr, Glucose, Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase, CA19-9, CEA, and a urine or serum HCG for women of childbearing potential).

If a patient has undergone biliary stent placement, the following eligibility guidelines will apply. If ALT and AST are elevated beyond 2.5 x the upper limit of normal at time of study enrollment, but demonstrate two consecutive down-trending values, the patient should begin treatment without Irinotecan, or with dose-reduced Irinotecan if clinically indicated. The agents 5-FU and Oxaliplatin may be given during Cycle 1 with Irinotecan incorporated as laboratory values permit. If total bilirubin is elevated above 2.0 mg/dl at time of enrollment, the patient may begin Cycle 1 with full dose 5-FU and Oxaliplatin, with Irinotecan incorporated as laboratory values permit. If total bilirubin is elevated between the upper limit of normal and 2.0 mg/dl at time of enrollment, the patient may receive full dose 5-FU and Oxaliplatin, with dose-reduced Irinotecan. Irinotecan may be increased to full dose in the first or second cycle if laboratory values permit.

Evaluations obtained to confirm study eligibility may be used as pre-treatment evaluations provided they are done within the above timeframes.

5.2 Agent Administration

Study participants will receive up to 8 cycles of FOLFIRINOX as indicated in the study schema. All treatments shall be administered according to institutional standard of care.

5.2.1 5-Fluorouricil: 5-FU will be administered at a dose of 400 mg/m2 push per institutional standard on day one, followed by a 1200 mg/M^2/d by continuous

infusion via an ambulatory infusion pump for the subsequent two days. 5-Fluorouracil is not a vesicant or irritant. Initial dose of 5-FU may be reduced if necessary; then gradually increased to full dose if tolerated. All dose adjustments are to be made at the discretion of the treating medical oncologist.

5.2.2 Oxaliplatin: Oxaliplatin will be administered as a dose of 85 mg/m2 by intravenous infusion over 120 minutes . Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia. Oxaliplatin is unstable in the presence of chloride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or other chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration. Initial dose of Oxaliplatin may be reduced if necessary; then gradually increased to full dose if tolerated. All dose adjustments are to be made at the discretion of the treating medical oncologist.

5.2.3 Leucovorin: Leucovorin (400 mg/m2) will be diluted with 5% dextrose and administered concurrently (in separate containers using a Y-type administration set) by IV infusion over 2 hours.

5.2.4 Irinotecan: In this study irinotecan will be administered as a dose of 180 mg/m2 by intravenous infusion over 90 minutes . Initial dose of Irinotecan may be reduced if necessary; then gradually increased to full dose if tolerated. All dose adjustments are to be made at the discretion of the treating medical oncologist.

5.2.5 Capecitabine: The dose of capecitabine will be given orally 825 mg/m2 BID (total 1650 mg/m^2 per day) for a total of 10 days M-F during the week of, and the week after, proton beam radiation; or the two weeks of photon radiation. The dose of capecitabine will be fixed unless there are dose level reductions. The daily dose will be administered in two divided doses approximately 12 hours apart. The medication should be given

within 30 minutes after the end of a meal or snack and swallowed with about 8 oz. of water. The dose of capecitabine will be calculated on the basis of milligrams of drug per square meter of body surface area (BSA).Doses will be rounded to the nearest multiple of whole tablets. Capecitabine tablets are either 150 or 500 mg in size, so the dose given will be rounded to the nearest 150 mg tablet. The BSA will be rounded to the nearest tenth and the investigator will prescribe capecitabine according to the following chart. The dose of capecitabine will not exceed 2000mg po bid. All dose adjustments will be at the discretion of the treating investigator.

Table 1: Capecitabine Dosing

BSA (m^2)	Dose BID (Total mg per dose)	500 mg tabs	150 mg tabs
1.0	800	1	2
1.1	1000	2	0
1.2	1000	2	0
1.3	1000	2	0
1.4	1150	2	1
1.5	1300	2	2
1.6	1300	2	2
1.7	1500	3	0
1.8	1500	3	0
1.9	1500	3	0
2.0	1650	3	1
2.1	1800	3	2
2.2	1800	3	2
2.3	2000	4	0
2.4	2000	4	0
2.5	2000	4	0

If vomiting occurs around the time of capecitabine ingestion or if doses of capecitabine are missed, additional ("make-up") doses of capecitabine should not be administered. A drug diary will be provided to document appropriate administration.

5.2.6 Radiation Therapy

5.2.6.1 Simulation and Planning

Tumor volume will be defined on the basis of CT and MRI imaging findings and operative notes and findings. The primary tumor and any clinically enlarged lymph nodes will be treated with a margin of 2 cm to include peripancreatic nodes. The porta hepatis, celiac axis, superior mesenteric artery (SMA) root, and the pancreaticoduodenal nodes will also be treated.

Total dose will be prescribed to the 95 to 100% isodose line based on coverage and will be 25 CGE protons in 5 fractions (5 Gy/day) or 30 Gy photons in 10 fractions (3 Gy/day) with multifield techniques. A dose painted boost to involved vasculature is permitted to a total dose of 30 Gy. Radiation treatment assignment will be based on resource availability at the time of radiation planning.

Patients will be simulated supine. Intravenous and oral contrast will be administered per standard department protocol. 4-D planning CT will be obtained for treatment planning to ascertain the extent of tumor motion.

The Gross Tumor Volume (GTV) is defined as the gross primary tumor and any lymph nodes enlarged over 1 cm during simulation using contrast given during CT or MRI. The clinical target volume (CTV) will also include the following at-risk nodal basins: porta hepatis, celiac axis, superior mesenteric artery, and pancreaticoduodenal nodes as defined by the inner-third of the duodenum. Planning target volume (PTV): PTV will be customized based on 4D CT scan. Generally 0.5 cm expansion will be used, except for superiorly/inferiorly 0.7 cm will be used.

Computerized dosimetry is required if more than two fields are used. All fields must be simulated using a machine that duplicates the geometry of the actual treatment machine. Patient contours and isodose plots are required. Isodose plots must account for the effect of all treated fields, including any blocking used.

5.2.6.2 Treatment

All radiation treatment will be given with the patient at the Francis H. Burr Proton Therapy Center or the Clark Center for Radiation Oncology at MGH. Film or digital images will be taken prior to each treatment in accordance with the Department of Radiation Oncology's standard practice for all patients. These images are used to verify the position of the patient and the aperture. These digital images are permanently stored electronically for each patient.

Radiation treatment must start on a Monday-Wednesday. If the proton center is unexpectedly not functioning for 1-2 days, these fractions may be made up the following week. However, if the proton center is not functioning longer than 2 days, patients may receive photon radiation for the remaining fractions. If radiation therapy start is delayed beyond 4 weeks after completion of FOLFIRINOX due to toxicity, the patient will proceed to radiation therapy on study at the discretion of the treating investigator.

5.2.6.3 Normal tissue volume and dose considerations

Normal tissue guidelines are as outlined below.

Table 2: Planning Goals - Normal tissue constraints

Organ	Normalized Total Dose **(2 Gy equivalents)**	Threshold Dose- **5 fraction schedule (CGE)**	**% Above threshold**
Liver	23.0 Gy_2	17.5	30%
Kidney	14.8 Gy_3	13	30%
Spinal Cord	40.6 Gy_2	24	0%
Stomach	38 Gy_{10}	7	10%

Assumed α/β in subscripts

- * If possible - Stomach dose threshold is to prevent nausea, an acute effect. No established guidelines exist. However, in the preliminary MGH IMRT experience, the above dose threshold is associated with ~ 10% rate of ANY anti-emetic use. The daily NTD of the conventional schedule is 1.36 Gy. This means that that the threshold dose (NTD) for a five fraction schedule is 6.8 Gy (2 Gy equivalents) and correlates with the listed dose threshold.

Treatment planning should be adjusted for decreased renal function based on an elevated serum creatinine, a history of unilateral or bilateral renal disease, and abnormalities in baseline laboratory or radiographic studies. Additional studies to assess renal function will be performed as needed. For protons, passively scattered protons and pencil beam protons are both permitted. For photons, 3D photons and IMRT are both permitted.

5.2.7 Other Modalities and Procedures

5.2.7.1 Surgery: Surgery will be performed one to four weeks after completion of capecitabine therapy. If surgery is delayed beyond four weeks after completion of capecitabine, the patient will be taken off study. At laparotomy, the liver and pancreas will be examined by palpation and inspection. In the absence of metastases, tumor mobilization and surgical resection will be performed. A pancreaticoduodenectomy (Whipple procedure) or distal pancreatectomy with standard lymphadenectomy will be done. This involves dissection up to the superior mesenteric artery, with skeletonization of the right lateral and anterior aspects of the vessels. Feeding jejunostomy and gastrostomy tubes may be placed at the discretion of the operating surgeon.

5.2.7.2 Pathology: Processing the specimen and pathology will be reported according to the AJCC Cancer Staging Manual, 6th Edition. Pancreatic transection margin, and the bile duct margin will be evaluated on frozen section. Recorded on permanent section will be: tumor size, degree of differentiation (well, moderate, poor), lymph node status, and margin status.

5.2.7.3 Chemotherapy: Patients may receive adjuvant chemotherapy afterat the discretion of the treating investigator. If adjuvant chemotherapy is administered, at minimum, administration of FOLFIRINOX therapy will be contingent on patients meeting original inclusion criteria (lab parameters and performance status). Physicians may opt to provide FOLFOX or FOLFIRI in the postoperative setting, with the full FOLFIRINOX regimen administered only when the patient is able to tolerate this therapy. If there is evidence of progression, patients will be withdrawn

from the study and as per NCCN guidelines, proceed to second-line therapy (likely gemcitabine-based chemotherapy.) Appropriate dose reductions and modifications can be made at the discretion of the treating physician.

5.3 General Concomitant Medication and Supportive Care Guidelines:

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, etc. when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets. Erythropoietin is allowed. As the Myeloid growth factors should not be used prophylactically but may be utilized to treat grade 3-4 neutropenia rate experienced in the ACCORD trial was 79.9% (see Section 6.1), the study will mandate prophylactic administration of GM-CSF (Neulasta(ANC < 1000) with each cycle of therapy. This should be administered 24-48 hours after discontinuation of infusional 5-fluorouracil.or without fever. Patients may receive all concomitant therapy deemed necessary to provide adequate support. No other cytotoxic therapy or radiotherapy may be used during therapy.

5.4 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

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

5.5 Duration of Follow Up

Study participants will be in active follow up after completion of neoadjuvant treatment and surgery per study guidelines, as outlined above, except in the case of documented progression, at which time they will be followed for survival only. Participants removed from study for

unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Theodore S. Hong, M.D. at [redacted]

6 EXPECTED TOXICITIES AND DOSING DELAYS/MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

6.1.1 FOLFIRINOX Therapy

6.1.1.1 Anticipated Hematologic adverse events

Below is the table of adverse events associated with the FOLFIRINOX regimen in the Prodige-4/ACCORD trial in patients with advanced pancreatic adenocarcinoma.

AE, % per patient	**Folfirinox N=171 (from NEJM 2011)**	
	All	**Grade 3/4**
Neutropenia	**79.9**	**45.7**
Febrile Neutropenia	**5.4**	
Anemia	**90.4**	**7.8**
Thrombocytopenia	**75.2**	**9.1**

6.1.1.2 Anticipated Non-Hematologic adverse events

Below is the table of adverse events associated with the FOLFIRINOX regimen in the Prodige-4/ACCORD trial in patients with advanced pancreatic adenocarcinoma.

AE, % per patient	**Folfirinox N=168 (from ASCO 2010)**	
	All	**Grade 3/4**
Infection without neutropenia	**6**	**1.2**
Peripheral neuropathy	**70.5**	**9**
Vomiting	**61.4**	**14.5**

Fatigue	**87.3**	**23.2**
Diarrhea	**73.3**	**12.7**
Alopecia (grade 2)	**32.5**	**(11.4)**
ALT	**64.8**	**7.3**

6.1.2 Radiation Therapy

The most common toxicities of radiation therapy are fatigue, nausea, abdominal pain, diarrhea, indigestion, vomiting, weight loss and anorexia. Other toxicities may include radiation fibrosis if surgery is delayed too long. Much less common toxicities could include liver damage, kidney damage, delayed wound healing, and late second malignancies.

6.1.3 Capecitabine

The most common toxicities of capecitabine are diarrhea, indigestion, nausea, vomiting, weight loss, anorexia, and hand-foot syndrome (skin changes and tenderness of hands and feet, especially fingers and toes). Other toxicities may include neutropenia, thrombocytopenia, anemia, cutaneous eruptions, alopecia, fever, and fatigue or general malaise. Much less common toxicities could include allergic reactions and coronary vasospasm.

6.2 Toxicity Management

6.2.1 FOLFIRINOX therapy

"One cycle" will constitute one administration of FOLFIRINOX therapy, administered on Day 1-3. Each cycle will be 14 days long, and will be repeated every 14 days, unless further dose delay is warranted by toxicities. Cycle adjustments of +3/-1 days may be made at the discretion of the treating physician. A break in therapy of up to one week for restaging is allowed.

The table below indicates potential dose levels for each of the agents for which dose modifications will be allowed. Dose adjustments of each agent may be made independently based on the specific types of toxicities observed. Only those agents specified in the sections below should be dose-reduced.

Patients who require multiple dose reductions during a cycle for grade 2 toxicity may, at the physician's discretion, begin the following cycle at one dose level higher than the current dose reduction. If dose reduction beyond –3 for any agent is required, that agent should be discontinued.

Agent*	Oxaliplatin	Irinotecan	5-FU Bolus	5-FU Infusion
Initial Dose	85 mg/m2	180 mg/m2	400 mg/m2	2400 mg/m2 per 46-48 hours
Level –1	65 mg/m2	150 mg/m2	320 mg/m2	1920 mg/m2 per 46-48 hrs
Level –2	50 mg/m2	120 mg/m2	270 mg/m2	1600 mg/m2 per 46-48 hrs
Level –3	40 mg/m2	100 mg/m2	230 mg/m2	1360 mg/m2 per 46-48 hrs

Leucovorin dose is always 400 mg/m2, IV given prior to the infusion of 5-FU. If any infusion of 5-FU is to be skipped, leucovorin must also be skipped. Initial doses may be reduced, if necessary, at the physician's discretion.

If a patient has undergone biliary stent placement prior to enrollment, the following treatment guidelines will apply for Cycles 1 and 2. If ALT and AST are elevated beyond 2.5 x the upper limit of normal at time of study enrollment, but demonstrate two consecutive down-trending values, the patient should begin treatment without Irinotecan, or with dose-reduced Irinotecan if clinically indicated. The agents 5-FU and Oxaliplatin may be given during Cycle 1 with Irinotecan incorporated as laboratory values permit. If total bilirubin is elevated above 2.0 mg/dl at time of enrollment, the patient may begin Cycle 1 with full dose 5-FU and Oxaliplatin, with Irinotecan incorporated as laboratory values permit. If total bilirubin is elevated between the upper limit of normal and 2.0 mg/dl at time of enrollment, the patient

may receive full dose 5-FU and Oxaliplatin, with dose-reduced Irinotecan. Irinotecan may be increased to full dose in the first or second cycle if laboratory values permit.

6.2.1.1 Hematologic toxicities

The following dose modifications are based on toxicity demonstrated during a mid-cycle visit and/or at the time of laboratory assessment for planned administration of the next cycle of therapy (for example on the planned day of administration of Cycle 2 Day 1 after completing the 14-day period constituting Cycle 1.) As the Grade 2-4 neutropenia rate in the PRODIGE-ACCORD trial was 79.9%, in this trial prophylactic GM-CSF (Neulasta) will be administered 24-48 hours after discontinuation of continuous infusion 5-FU.

Dose Reduction Table for Hematologic Toxicity

(Note: DR = Dose Reduction)

Hematologic Toxicity on the Day of Treatment (D1)	**Action**	**Oxaliplatin**	**Irinotecan**	**5-FU Bolus (Leucovorin follows protocol for 5FU bolus)**	**5-FU Continuous Infusion**
Neutropenia G2 (ANC 1500-1000) – all patients should have Neulasta support per institutional guidelines	HOLD ALL THERAPY	Hold until ANC >=1500, resume without dose reduction	Hold until ANC >=1500, resume without dose reduction	Hold until ANC >=1500, resume without dose reduction	Hold until ANC >=1500, resume without dose reduction
Neutropenia G3-4, Febrile neutropenia (ANC 1000-500, <500)	HOLD ALL THERAPY, Supportive care and antibiotics per institutional guidelines	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved	Hold until ANC >=1500, resume @ permanent DL-1 level once resolved
Thrombocytopenia G1 (LLN – 75K)	Treat with DR Oxaliplatin	Treat at permanent DL -1	No reduction	No reduction	No reduction

Thrombocytopenia G2 (75K – 50K)	HOLD ALL THERAPY	Hold until resolved to >100K, resume at permanent DL-1	Hold until resolved to >100K, no reduction	Hold until resolved to >100K, No reduction	Hold until resolved to >100K, No reduction
Thrombocytopenia G3-4 (50K – 25K, <25K)	HOLD ALL THERAPY	Hold until resolved to >100K. Resume @ permanent DL-1 if resolved in 1 wk, permanent DL -2 if >1 wk to resolve	Hold until resolved to >100K. Resume @ permanent DL-1.	Hold until resolved to >100K	Hold until resolved to >100K

6.2.1.2 Gastrointestinal toxicities:

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, 0.25-1.0 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. 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) should be managed with loperamide. The following dose modifications are based on toxicity experienced during a cycle (i.e., after Day 1 of any cycle):

The following dose modifications are based the grade of mucositis seen on the day of treatment for any day after Day 1 in any cycle.

Dose Reduction Table for Non-Hematologic Toxicity (Except Neuropathy)

(Note: DR = Dose Reduction)

Non-hematologic Toxicity on the Day of Treatment (D1)	**Action**	**Oxaliplatin**	**Irinotecan**	**5-FU Bolus (Leucovorin DR follows protocol for 5FU bolus DR)**	**5-FU Continuous Infusion**
Diarrhea G2	DR Irinotecan Bolus 5FU, and CI 5FU	No reduction	Treat at permanent DL -1	Treat at permanent DL -1	Treat at permanent DL -1
Diarrhea G 3-4	DR Irinotecan and CI 5FU and eliminate Bolus 5FU	No reduction	Treat at permanent DL -1	Permanently eliminate bolus	Treat at permanent DL -1
Mucositis G2	DR Bolus and CI 5FU	No reduction	No reduction	Treat at permanent DL -1	Treat at permanent DL -1
Mucositis G3-4	DR Irinotecan and CI 5FU, eliminate Bolus 5FU	No reduction	Treat at permanent DL -1	Permanently eliminate bolus	Treat at permanent DL -1
Nausea/Vomiting G3-4	HOLD ALL THERAPY	Maximal antiemetic therapy. Hold until resolved to G2 or less, resume @ permanent DL-1	Maximal antiemetic therapy. Hold until resolved to G2 or less, resume @ permanent DL-1	Maximal antiemetic therapy. Hold until resolved to G2 or less, resume @ permanent DL-1	Maximal antiemetic therapy. Hold until resolved to G2 or less, resume @ permanent DL-1

6.2.1.3 Neurotoxicity

Toxicity Scale for the Sensory Neuropathies Associated with Oxaliplatin Symptoms:

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

* May be cold induced

For **grade 2 neurotoxicity** persisting between treatments: Reduce oxaliplatin by one dose level for the next cycle and for all subsequent cycles.

For **grade 3 neurotoxicity** resolving to grade 2 between treatments: Reduce oxaliplatin by one dose level for the next cycle and for all subsequent cycles.

For **recurrent grade 3 neurotoxicity** resolving to grade 2 between treatments: Reduce oxaliplatin by one additional dose level for the next cycle and for subsequent cycles. Oxaliplatin will not be reduced beyond level –3. If further dose reduction is required for neurotoxicity, oxaliplatin will be discontinued. Patients should continue to receive other protocol therapy.

For **grade 3 neurotoxicity** persisting between treatments: Discontinue oxaliplatin. Patients should continue to receive other protocol therapy.

For **grade 4 neurotoxicity**: Discontinue oxaliplatin. Patients should continue to receive other protocol therapy.

For **pharyngo-laryngeal dysesthesia**: Increase the duration of oxaliplatin infusion to 6 hours for all subsequent treatments.

6.2.1.4 Extravasation

Extravasation of oxaliplatin has been associated with necrosis; if extravasation is suspected, the infusion should be stopped and the drug administered at another site. Extravasation may be treated according to institutional guidelines.

6.3 Capecitabine and Radiation

Hematologic and Non-Hematologic Toxicity

Capecitabine will be held for any Grade 3 or 4 toxicity. After toxicity resolves to ≤ grade 1, capecitabine will be resumed at 600 mg/m2 BID to complete the 10 weekdays of therapy. Capecitabine can be held a maximum of 7 days. If further grade 3 or 4 toxicity is noted at the reduced dose level, after toxicity resolves to ≤ grade 1, capecitabine will be resumed at 500 mg/m2 BID to complete two weeks of therapy. If the second dose reduction is not tolerated, capecitabine will be stopped. Patients will keep a capecitabine diary and will record the number of capecitabine tablets and the time that they take the tablets.

Grade 3 or 4 toxicities that are due to biliary ductal dilatation and resolved with placement of a biliary stent or with biliary stent change will not require a dose reduction of capecitabine or radiation therapy after stent placement. Therapy may be withheld for procedures like ERCP and biliary stenting, and restarted at the treating physician's discretion.

Radiation therapy will be held for Grade 3 or 4 nausea that is not well controlled with anti-emetic support, until nausea resolves to Grade 2 or less. It will then be resumed at same dose.

7 DRUG FORMULATION AND ADMINISTRATION

7.1 5-Fluorouracil (5-FU; fluorouracil; “Adrucil”)

Please refer to the package insert for complete product information.

Availability

5-FU is commercially available as a 50 mg/mL solution for injection in 10 mL, 20 mL, 50 mL and 100 mL vials.

Preparation

Inspect for precipitate; if found, agitate or gently heat in water bath. Bolus injections are prepared using undiluted drug. 46-48 hour infusion of 5-FU should be prepared for administration via ambulatory infusion pump according to the individual institution's standards. These solutions may be prepared in D5W or 0.9% NaCl. 5-FU should not be mixed in the same solution with most parenteral antiemetics.

Storage and Stability

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

Administration

In this study, 5-FU is administered as a 400 mg/m2 IV bolus followed by 2400 mg/m2 by IV infusion over 46 to 48 hours.

Toxicity

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

Drug Interactions

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

7.2 Leucovorin Calcium (Folinic Acid) Leucovorin Calcium (calcium folinate; citrovorumfactor; 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, 350 mg vials for reconstitution.

Storage and Stability

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

Preparation

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

Administration

Leucovorin will be administered as a 400 mg/m2 IV infusion over 2 hours (+/- 10 minutes) after oxaliplatin/irinotecan administration. Leucovorin may also be administered concurrently with oxaliplatin/irinotecan as a separate IV infusion.

Toxicity

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

7.3 Oxaliplatin [Eloxatin]

Availability

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

Storage and Stability

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

Preparation

The calculated dose of oxaliplatin should be diluted for infusion with 250 mL to 500 mL D5W. Oxaliplatin should not be diluted with a sodium chloride solution. Needles, syringes, catheters or

IV administration sets containing aluminum should not be used with oxaliplatin. As with other platinum compounds, contact with aluminum may result in a black precipitate.

Administration

Oxaliplatin will be administered by intravenous infusion over 120 minutes (+/- 10 minutes). Infusion time may be prolonged (up to 6 hours) in patients experiencing pharyngolaryngeal dysesthesia. Oxaliplatin is unstable in the presence of chloride or alkaline solutions. Do NOT mix or administer oxaliplatin with saline or other chloride-containing solutions. Do NOT administer other drugs or solutions in the same infusion line. Flush IV lines/catheters with Dextrose 5% in Water both before and after oxaliplatin administration.

Toxicity

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include, paresthesias, dysesthesias, and hypothesia of the hands, feet and perioral region. Jaw spasm, abnormal tongue sensation, dyarthria, 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 hypothesia. Abnormalities in momioception 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. Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea. Neutropenia is reported in 73% of patients receiving oxaliplatin with

5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination. Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis. Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, 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 hepato-megaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5-FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients. For more information on toxicities associated with oxaliplatin, please see the package insert.

7.4 Irinotecan (CPT-11, CAMPTOSAR®)

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 when protected from light. Solutions diluted in D5W are reported to be stable for 48 hours under refrigeration and protected from light. Irinotecan solutions should not be frozen as the drug may precipitate.

Preparation

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

Administration

In this study irinotecan will be administered as an IV infusion over 90 minutes (+/- 10 minutes).

Toxicities

Virtually all phase I and II studies of irinotecan have reported neutropenia and/or late diarrhea (diarrhea occurring more than 24 hours after irinotecan administration) as the dose-limiting toxicities (depending upon the schedule). Other commonly observed adverse events include nausea and vomiting, anorexia, abdominal cramping, alopecia, asthenia, lymphocytopenia, and anemia. Dehydration has occurred as a consequence of diarrhea, particularly when associated with severe vomiting. Patients may have an acute syndrome of lacrimation, diaphoresis, abdominal cramping, and diarrhea (early diarrhea) during or shortly after irinotecan administration; this syndrome is thought to be cholinergically mediated and may be treated and subsequently prevented with atropine. Sporadic cases of pulmonary toxicity, manifested as shortness of breath, 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. Occasionally, abnormalities of serum creatinine, hepatic enzymes, or thrombocytopenia have been observed. Further information regarding irinotecan may be obtained from the package insert.

7.5 Leucovorin

Storage

For stability of leucovorin, please refer to the leucovorin (e.g., WELLCOVORIN) Package Insert or Summary of Product Characteristics.

7.6 Capecitabine

Description: Capecitabine (Xeloda) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) that is converted to 5-fluorouracil.

Form: Capecitabine is supplied as a biconvex, oblong film-coat tablets for oral administration. Each light-peach colored tablet contains 150 mg capecitabine, and each peach colored tablet contains 500 mg capecitabine.

Storage and Stability: Store at 25^{o} C (77^{o} F); excursions permitted to 15^{o} to 30^{o} C (59^{o} to 86^{o} F), keep bottles or storage devices tightly closed.

Compatability: Capecitabine and some of its metabolites are converted principally by liver enzymes (carboxylesterase and cytidine deaminase and TP in tumor tissues). At present, it is unknown whether this metabolism is likely to be influenced by other treatments or alcohol, which either induce or inhibit certain liver enzymes.

Allopurinol: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

Sorivudine and Brivudine: A metabolite of the above two investigational antiviral agents, 5-bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Patients should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine. If a patient has received prior sorivudine or brivudine, then at least four weeks must elapse before the patient receives capecitabine therapy

Anticoagulants: See Warnings and Precautions Section 6.9 In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin: Increased phenytoin plasma concentrations have been reported during concomitant use of Xeloda® with phenytoin, suggesting a potential interaction. Patients taking phenytoin concomitantly with Xeloda® should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Laxatives: The use of drugs with laxative properties should be avoided.

Warnings and Precautions:

Renal Insufficiency: Patients with moderate renal impairment as measured by serum creatinine (> 1.3) at baseline require dose reduction. Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse events. Prompt interruption of therapy with subsequent dose adjustments will be made if a patient develops a grade 2 to 4 adverse event. Capecitabine is contraindicated in patients with a calculated creatinine clearance of < 30 ml/min. Creatinine level will be checked and creatinine clearance calculated on Study Day 8 for all subjects to ensure safety of continued administration of capecitabine.

Pregnancy/Nursing: Capecitabine may cause fetal harm when given to a pregnant woman. If the drug is used during pregnancy, or 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 treatment with capecitabine. Because of the potential for serious adverse reactions in nursing infants from capecitabine, the patient will be instructed that nursing must be discontinued when receiving capecitabine therapy.

Coagulopathy: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important Capecitabine-Warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time capecitabine was introduced. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. Age greater

than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

Cardiotoxicity: The cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse events may be more common in patients with a prior history of coronary artery disease.

This treatment is foreseen as a self-administered out-patient treatment, and in certain circumstances adverse events that could occur, such as diarrhea, or hand-foot syndrome can rapidly become serious. In the case where a patient experiences any toxicity between scheduled visits, the patient will be instructed to contact the clinic as soon as possible, for further directions, discontinuation of study medication, and/or treatment.

Handling: Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of capecitabine in a self-contained and protective environment.

Availability: Capecitabine is commercially available and will not be provided free of charge by the study. It is expected that the study participants or their insurers will be responsible for the cost of Capecitabine.

Preparation

N/A- Capecitabine comes in tablet formulation

Administration

Tablets should be swallowed with water 30 minutes after the end of a meal (breakfast and dinner). If necessary, tablets may be crushed.

Ordering

Capecitabine will be prescribed by the treating medical oncologist; prescriptions will be filled by the study participants at their pharmacy of choice.

Accountability

N/A drug is not study supplied.

Destruction and Return

N/A drug is not study supplied.

8 CORRELATIVE STUDIES

8.1 Correlative Studies: Circulating Biomarkers

Based on findings from preliminary studies, we propose here to evaluate the changes in blood circulating SDF1α and circulating myeloid cells throughout the treatment course to explore potential associations between the changes in these biomarkers and resistance to treatment. In exploratory studies, we will evaluate several other cytokines using multiplex protein array (Meso-Scale Discovery, Inc.).

8.1 Experimental Design

Blood will be drawn by venipuncture, and the first 7-10 ml blood will be excluded or used for other analysis. The following 8 ml will be collected in an EDTA tube. The EDTA tube with the blood sample will be shipped in wet ice within 2 hours of drawing for further processing at Steele Laboratory at MGH. We will analyze the correlation between plasma SDF1α and circulating myeloid cells with multiple measures of outcome (ORR, TTP, OS) in patients with borderline resectable pancreatic cancer before, during, and after treatment.

8.2 Collection

To this end we will measure circulating biomarkers at the following stages:

(i) Pretreatment
(ii) At beginning and end of FOLFIRINOX therapy
(iii) After radiation therapy
(iv) One month post-operatively
(v) At the time of disease progression

Samples will be collected at the following timepoints:

a. Prior to the start of therapy
b. Day 8 of Cycle 1 of FOLFIRINOX
c. After Cycle 4 (and Cycle 8 if received) of FOLFIRINOX
d. After chemoradiation OR pre-operatively
e.. 1 month after completion of therapy.
f. 1 month after pancreaticoduodenectomy (Whipple procedure)

g. Within 2 weeks after radiologic progression

8.3 Shipping Instructions

The tube containing the blood should be shipped with the following information

1. Study Number at the DF/HCC
2. Patient number on the study
3. Patient's initials
4. Treating physician's name
5. Date of collection
6. Date of shipping

The tube of blood should be placed in a sealable container and placed in a box with the necessary information. The box should be marked Biohazard.

The blood will be shipped to:

[redacted]

8.2 Patient Reported Outcomes

QOL (EORTC QLQ-C30, version 3.0), symptoms (ESAS-r), and mood (HADS) will be assessed at time of informed consent prior to neoadjuvant therapy; at weeks 3, 7, 11, and 15 of neoadjuvant chemotherapy; at week 2 of capecitabine chemoradiotherapy; and during active follow up. All PRO administrations have a window of +/- 2 weeks from the assigned assessment timepoint.

Pretreatment	**FOLFIRINOX**	**ChemoRT**	**Post-op**
At time of informed consent	**Day 1 of cycles 2,4,6,8 [Week 3, 7, 11, 15]**	**Week 2, day1**	**At 3 month follow up, then every 6months for the first 2 years of follow up, then yearly until completion of year 5**
EORTC QLQ-C30	EORTC QLQ-C30	EORTC QLQ-C30	EORTC QLQ-C30
ESAS-r	ESAS-r	ESAS-r	ESAS-r
HADS	HADS	HADS	HADS

8.3 Correlative Studies: SNaPshot analysis

Mutational analysis will be performed by tumor SNaPSHOT for the mutations listed in section 2.2.6.1. Paraffin-embedded block or ten unstained slides will be used from the untreated biopsy specimen obtained at the time of upper endoscopy or initial diagnostic biopsy. Analysis will be performed as described by Dias-Santagata (47) at the Translational Research Laboratory at MGH.

9 STUDY CALENDAR

Baseline laboratory evaluations are to be conducted within seven days prior to study entry. Non-laboratory evaluations (imaging, etc) must be done $\leq$42 days (6 weeks) prior to the start of therapy.

All pre-study assessments must be performed prior to administration of any study medication, unless otherwise noted. All study assessments and medications should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted. All follow up assessments may be performed +/- 21 days of the protocol-specified date.

Required Data Table

Tests and Observation	Prior to Study	Day 1 of each cycle of FOLFIRINOX and at Restaging	During ChemoRT	Post-op F/U(2)
Signed informed consent and registration	X			

History	X			
Physical Examination	X	X	X weekly	X
Vital Signs and performance status	X		X weekly	X
Height/Weight/Surface Area	X		X at start of ChemoRT	
Toxicity Assessment		X	X weekly	X
Laboratory (1):				
CBC/plts/diff	X	X	X Days 1, 8 and 15	X
Serum chemistries (Na, K, BUN, Cr, Glucose, Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase)	X	X	X Days 1, 8 and 15	X
Creatinine clearance calculation (Cockroft Gault)	X	X (day 1 of cycles 1, 3, 5, and 7 only)	X Days 1, 8 and 15	
CA19-9	X	X (at restaging visits only)	X, Days 1 and 15	X
CEA	X	X (at restaging visits only)	X Days 1 and 15	X
Pregnancy test*	X			
Staging:				

Chest CT Abd-pelvic CT (or MRI)	X	X after first week of cycle 4 and first week of last cycle of FOLFIRINOX		X
Tumor SNaPshot (3)	X			X
Nutritional Assessment	X(4)	X(4)	X(4)	
Correlative Studies	X(5)	X(5)	X(5)	X(5)
PROs (EORTC QLQ, ESAS-r, HADS) (details in section 8.2)	X	X	X	X

Notes

(1) Pre-study Laboratory values need to be obtained within 7 days of study entry.

(2) Post-op follow up schedule is as follows. For years 1 and 2 follow up will be visit and labs at least every three months, scans at least every 6 months, For year 3, visit and labs will be at least every 3 months and scans will be at least every 12 months. For years 4 and 5 visit and labs will be at least every 6 months and scans will be at least every 12 months. For patients with R0, R1 and R2 resections, the first post-op CT scan, visit and labs are 3-8 weeks postoperatively. All follow up assessments may be performed +/-21 days of the protocol-specified date.

(3) Tumor SHaPshot will be done once for each participant, either on the pre-treatment biopsy specimen (if available) or on the resected tumor specimen.

(4) Nutritional assessment will include meeting with an oncology nutritionist for evaluation and education at the beginning of treatment. The patient will then track dietary protein intake throughout treatment until time of surgery. The patient's logged protein intake will be reviewed in post-op follow up by the treatment team. Both the nutritionist evaluation and protein tracking are optional resources available to patients and are not required by the protocol.

(5) Peripheral blood for correlative studies will be obtained with clinical labs at pretreatment, day 8 of Cycle 1 FOLFIRINOX, at restaging visits, after proton beam radiation therapy/pre-operatively, 1 month after completion of therapy, 1 month post-operatively, and within two weeks of radiographic progression (these blood draws are optional).

10 MEASUREMENT OF EFFECT

10.1 Evaluation Of Response

10.1.1 Imaging Response

Response to therapy and/or progression after induction chemotherapy with FOLFIRINOX will be evaluated in this study using the international criteria proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. In the event that CT staging cannot be utilized, restaging MRI will be the substitute modality.

10.1.2 Pathological Response

All patients will undergo a full pathological review of their pancreaticoduodenectomy specimen according to the AJCC Staging Classification, 6th. Initial gross evaluation and identification of resection margins will be performed jointly by the surgeon and the pathologist. Pathological complete response will be defined as the absence of any viable tumor cells within the pathologic specimen.

10.1.3 Progression-free survival

Progression-free survival will be defined as the time from date of protocol entry to first objective documentation of progressive disease (distant or local) or death. Patients who die without a reported prior progression will be considered to have progressed on the day of their death.

10.1.4 Time to death

Time to death will be calculated as the time from date of protocol entry to date of death

10.1.5 Time to local recurrence

A local recurrence will be defined as any evidence of tumor recurrence within the radiation field. The time to local recurrence will be calculated from the date of protocol entry to the first objective documentation of a local recurrence.

10.2 Definitions

10.2.1 Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

10.2.2 Evaluable for objective response. Only those participants who have measurable disease present at baseline, have completed at least 4 cycles of induction chemotherapy, and have had their disease re-evaluated will be considered

evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of induction chemotherapy will also be considered evaluable.)

10.3 Disease Parameters

10.3.1 Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or ≥10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

10.3.2 Target lesions: The primary tumor is the target lesion.

10.4 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

10.4.1 Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

10.4.2 Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen,

and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

10.4.3 Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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

10.5 Response Criteria

10.5.1 Evaluation of Target Lesions

10.5.1.1 Complete Response (CR): Disappearance of all target lesion.

10.5.1.2 Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesion, taking as reference the baseline sum LD.

10.5.1.3 Progressive Disease (PD): At least a 20% increase in the sum of the longest diameter (LD) of target lesion, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (new lesions must be > slice thickness).

10.5.1.4 Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

10.5.1.5 Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

10.6 Response Review

Central radiology review is not planned, as most patients will proceed to chemoradiation and surgery after restaging.

11 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more sever form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures

- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care
- grade 4 lipase and lymphocytes

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study ` agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.

- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.2 Procedures for AE and SAE Recording and Reporting

Reporting Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected AND not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or

her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Theodore S. Hong, M.D.
[redacted]

Within the following 48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites should report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to:

Theodore S. Hong, M.D.
[redacted]

The DF/HCC Principal Investigator will submit SAE reports from outside institutions to the DFCI Office for Human Research Studies (OHRS) according to DFCI IRB policies and procedures in reporting adverse events.

11.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.7 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12 DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Lab Form	Within 14 days of registration; and within 14 days of protocol defined laboratory assessment
Tumor Measurement/Staging Form	Within 14 days of registration; and within 14 days of protocol defined restaging assessment
Chemotherapy Treatment Form	Within 10 days of the last day of the cycle of neoadjuvant FOLFIRINOX; within 10 days of the last cycle of adjuvant chemotherapy, if any
Chemoradiation Treatment Form	Within 10 days of completion of neoadjuvant combined capecitabine and proton radiation
Toxicity/Adverse Event Report Form	Every two weeks during neoadjuvant FOLFIRINOX; weekly during chemoradiation; and within 14 days of protocol defined follow up visit
PRO's	Within 14 days of completion
Surgery/Pathology Form	Within 14 days of surgery
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason

Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet as required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol,

institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13 REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and

dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- E6 Good Clinical Practice: Consolidated Guidance
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129515.pdf
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14 STATISTICAL CONSIDERATIONS

14.1 Study Design/Endpoints

This is a single-arm, phase II study to investigate the preoperative administration of FOLFIRINOX chemotherapy and accelerated short-course radiation therapy in patients with borderline-resectable adenocaricoma of the pancreas.

The primary endpoint of this study is R0 resection rate determined by final pathology of the surgical specimen. The previously studied approach involved four months of induction gemcitabine followed by six weeks of neoadjuvant 5-FU-based chemoradiation (50.4 Gy). Our internal data support a historical R0 resection rate of 20% for patients with resectable

disease who received induction chemoradiation (CRT) (8 of 40) or induction chemotherapy followed by chemoradiation (C-CRT) (6 of 30). In a retrospective surgical series at MGH, median tumor size was 29 mm for the CRT group and 35 mm for C-CRT group. Among patients considered 'borderline resectable' upfront (n = 24), 5 of 24 = 21% had eventual margin-negative resection (or 7 of 24 = 29%, if < 1 mm is considered as a negative margin / R0 resection).

14.2 Sample Size/Accrual Rate

The accrual goal of 50 patients is projected to be enrolled over a total period of 4 years based on the observed rate of accrual during the first two years since the protocol was open to patient entry.

The preoperative protocol regimen will have demonstrated an improvement in efficacy if an R0 resection were achieved in at least 16 of 50 patients. The decision rule is associated with 90% power if preoperative FOLFIRINOX and short-course radiation were able to improve the R0 resection rate to 40%. In contrast, the probability of type 1 error is only 3% if the underlying rate of R0 resection were truly the same as the historical data of 20%. All protocol patients who begin the preoperative regimen will be included in the denominator for analysis of the R0 resection rate, including those who do not undergo surgery due to progression or other reasons.

14.3 Stratification Factors

Not applicable.

14.4 Analysis of Secondary Endpoints

***Progression-free survival*:** All patients who start the protocol therapy will be analyzed based on the definition in Section 10.1.3. The Kaplan-Meier method will be used to estimate progression-free survival with 90% confidence intervals constructed by Greenwood's formula.

***Overall survival*:** Overall survival will be defined as the duration between the dates of protocol enrollment and death. The survival time of patients who are not known to have died will be censored at the date they were last known to be alive.

***Toxicity*:** All patients who begin protocol treatment will be included in the toxicity profile. Toxicity summaries will include the frequency and proportion of patients experiencing each type of toxicity, as well as summaries by toxicity category and grade.

***Surgical morbidity*:** Analysis will be based on the patients who undergo pancreaticoduodenectomy or distal pancreatectomy. The surgical morbidity rate will be calculated as the proportion of patients who experience peri- and post-operative complications within 30 days of surgery. A 90% confidence interval will be obtained using the exact binomial distribution.

***30-day post-operative mortality rate*:** Analysis will be based on the patients who undergo pancreaticoduodenectomy or distal pancreatectomy. The 30-day post-operative mortality rate will be calculated as the number of patients who die within 30 days of surgery. A 90% confidence interval will be obtained using the exact binomial distribution.

Pathologic downstaging: Analysis will be based on the patients who undergo pancreaticoduodenectomy or distal pancreatectomy. The pathologic downstaging rate will be calculated as the proportion of patients with the primary tumor and nodes downstaged based on final pathology of the surgical specimen.

***Local control rate*:** Local control will be defined as the time from protocol enrollment to the first objective documentation of local failure. Patients who have not experienced a local failure will be censored at the last date they were known to have local control. Kaplan-Meier methodology will be used to estimate the local control rate.

***Mutational analysis*:** The frequency of genetic mutations characterized by the SNaPshot platform (sections 2.6.1 and 8.1) will be summarized. A sample size of 50 patients will provide 90% confidence intervals of maximal width $\pm$12%, but the interval widths will be narrower in practice as the mutation rates are typically quite low. We shall analyze PFS differences by mutational status if 5 failure events have been observed within each mutational subgroup. However, the analysis will be purely exploratory due to the limited numbers expected per mutation subgroup.

***Circulating biomarkers*:** The association between plasma SDF1α and circulating myeloid cells with outcome measures will be examined by logistic regression for ORR or by Cox regression for TTP and OS. Pretreatment levels as well as the changes during and after treatment from baseline will be analyzed. Biomarker levels are typically log-transformed

for analysis, but we shall also consider other approaches such as categorizing based on the observed distribution or dichotomizing at the median.

Patient-reported outcomes: We will use descriptive statistics to describe QOL (EORTC QLQ-C30), symptom burden (ESAS-r) and mood (HADS) for the entire study cohort. Mean values and standard deviations will be used to describe QOL and symptom burden (T-test or Wilcoxon as appropriate). We will score the HADS subscales for depressive and anxiety symptoms categorically, using a cut-off of >7 to describe the proportion of patients with these symptoms. We will use Chi-square or Fisher's Exact Test, as appropriate, to analyze the categorical variables.

Health care utilization: We will use descriptive statistics to describe hospitalizations, ICU stays, ED visits and palliative care use for the entire study cohort. Mean values and standard deviations will be used to describe continuous variables (T-test and Wilcoxon rank sum, as appropriate). We will use Chi-square or Fisher's Exact Test, as appropriate, to analyze the categorical variables.

14.5 Reporting and Exclusions

All patients who begin protocol treatment will be included in the analysis of all the primary and secondary endpoints, except for the surgical outcomes as noted in 14.4.

15 PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection. A report may be published in a peer reviewed journal, or an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes will be made public no later than three (3) years after the end of data collection.

REFERENCES

1. Ninomiya I, Terada I, Yoshizumi T, et al. Anti-metastatic effect of capecitabine on human colon cancer xenografts in nude mouse rectum. Int J Cancer 2004;112(1):135-42.
2. Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer 1998;34(8):1274-81.
3. Dunst J, Reese T, Sutter T, et al. Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. J Clin Oncol 2002;20(19):3983-91.
4. Kim JS, Kim JS, Cho MJ, Song KS, Yoon WH. Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2002;54(2):403-8.
5. Ben-Josef E, Shields AF, Vaishampayan U, et al. Intensity-modulated radiotherapy (IMRT) and concurrent capecitabine for pancreatic cancer. Int J Radiat Oncol Biol Phys 2004;59(2):454-9.
6. NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. V.2.2010 (www.nccn.org)
7. Sohn TA, Yeo CJ, Cameron JL, Koniaris L, Kaushal S, Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas – 616 patients: results, outcomes, and prognostic indicators. J. Gastrointest Surg. 2000; 4(6) 567-79.
8. Kalser MH, Ellenberg SS. Pancreatic Cancer. Adjuvant Combined Radiation and Chemotherapy Following Curative Resection [Published Erratum Appears in Arch Surg 1986 Sep;121(9):1045]. Arch Surg 1985;120(8):899-903.
9. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg 2003;237(1):74-85.
10. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230(6):776-82; discussion 82-4.
11. Abrams RA, Lowy AM, O'Reilly EM, Wolff RA, Picozzi VJ, MMM, Pisters PWT.

Combined Modality Treatment of Resectable and Borderline Resectable Pancrease Cancer: Expert Consensus Statement. Ann Surg Oncol 2009 16: 1751-56.

12. Willett CG, Lewandrowski K, Warshaw AL, Efird J, Compton CC. Resection margins in carcinoma of the head of the pancreas. Implications for radiation therapy. Ann Surg 1993;217(2):144-8.
13. Rich TA, Evans DB, Curley SA, Ajani JA. Adjuvant radiotherapy and chemotherapy for biliary and pancreatic cancer. Ann Oncol 1994;5(Suppl 3):75-80.
14. Staley CA, Lee JE, Cleary KR, et al. Preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for adenocarcinoma of the pancreatic head. Am J Surg 1996;171(1):118-24; discussion 24-5.
15. Evans D, Abbruzzese J, Lee J, Cleary K, Rich T. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas (Meeting abstract). Proc Annu Meet Am Soc Clin Oncol 1994;13:A692.
16. Evans DB, Pisters PW. Preoperative chemoradiation therapy for pancreatic cancer. Surg Clin North Am 2001;81(3):709-13.
17. Tepper JE. Adjuvant Irradiation of Gastrointestinal Malignancies: Impact On Local Control and Tumor Cure. Int J Radiat Oncol Biol Phys 1986;12(4):667-71.
18. Whittington R, Bryer MP, Haller DG, Solin LJ, Rosato EF. Adjuvant Therapy of Resected Adenocarcinoma of the Pancreas. Int J Radiat Oncol Biol Phys 1991;21(5):1137-43.
19. Hoffman JP, Lipsitz S, Pisansky T, Weese JL, Solin L, Benson AB, 3rd. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1998;16(1):317-23.
20. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol 1997;15(3):928-37.
21. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol 2001;8(2):123-32.
22. Katz MH, Pisters PW, Evans DB, Sun CC, Lee JE, Fleming JB, Vauthey JN, Abdalla

EK, Crane CH, Wolff RA, Varadhachary GR, Hwang RF. Borderline Resectable Pancreatic Cancer: The Importance of This Emerging Stage of Disease. Ann Surg Oncol 2009; 16:1727–1733

23. Brown KM, Siripurapu V, Davidson M, Cohen SJ, Konski A, Watson JC, Li T, Ciocca V, Cooper H, Hoffman JP. Chemoradiation followed by chemotherapy before resection for borderline pancreatic adenocarcinoma. The American Journal of Surgery 2008;195: 318–321
24. Stokes JB, Nolan NJ, Stelow EB, Walters DM, Weiss GR, de Lange EE, Rich TA, Adams RB, Bauer TW. Preoperative Capecitabine and Concurrent Radiation for Borderline Resectable Pancreatic Cancer. Ann Surg Oncol. 2011 Jan 7. [Epub ahead of print]
25. Conroy T *et al.* J Clin Oncol 2005;23:1228-36 or Ychou M *et al.* J Clin Oncol 007;25:18S:201s
26. Conroy T, Desseigne F, Ychou M, Bouché O, et al. FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. N Engl J Med 2011; 364:1817-1825
27. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15(6):2403-13.
28. Dias-Santagata D, Ahkavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. EMBO Mol Med 2010;2:1-13.

APPENDICES

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined	40	Disabled, requires special care and assistance.

	to bed or chair more than 50% of waking hours.	30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Alberta Health Services

Covenant Health

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Drowsiness
No Nausea	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Nausea
No Lack of Appetite	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Lack of Appetite
No Shortness of Breath	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	Worst Possible _____

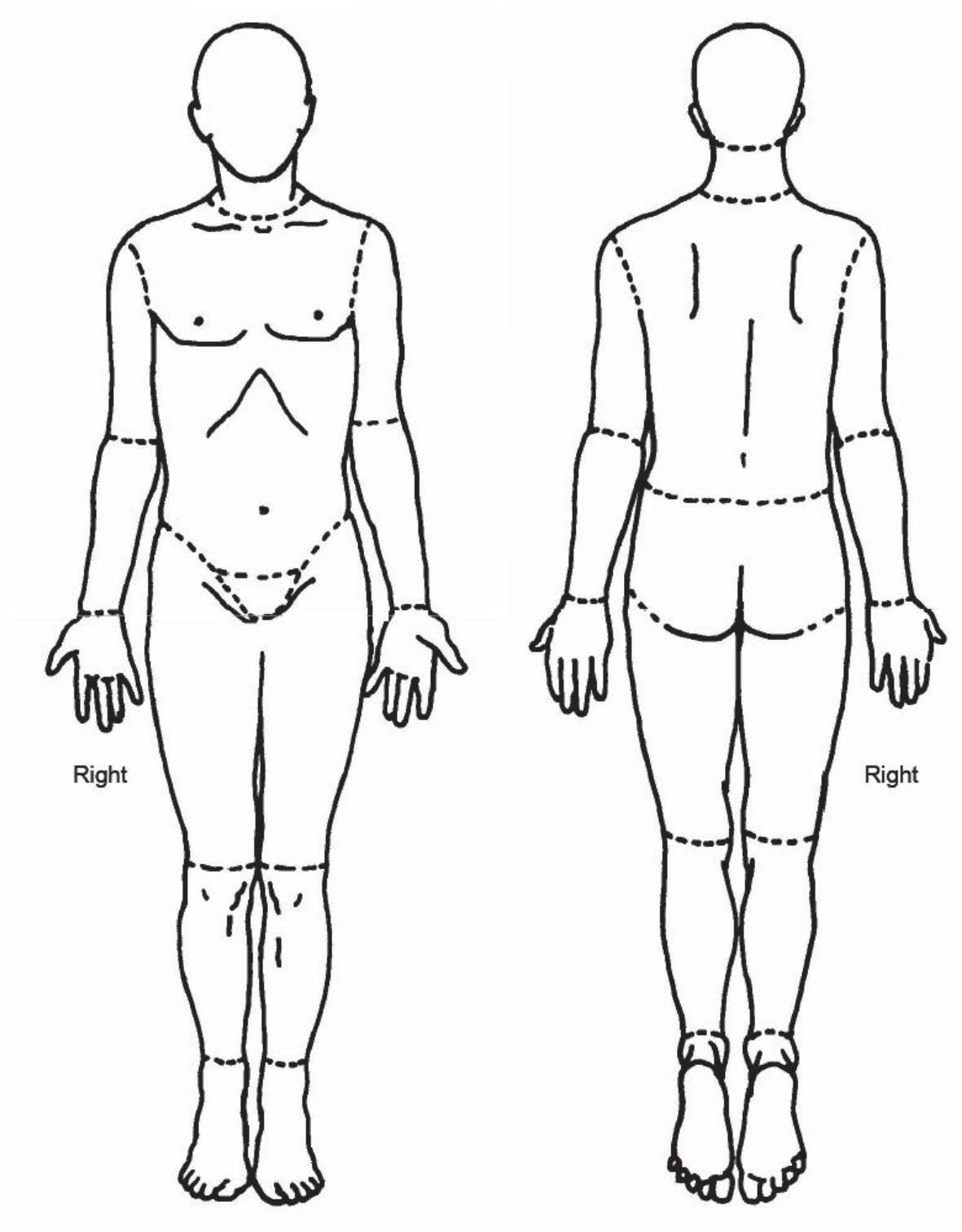
Patient's Name _____

Date _____ Time _____

Completed by (check one):
- ☐ Patient
- ☐ Family caregiver
- ☐ Health care professional caregiver
- ☐ Caregiver-assisted

BODY DIAGRAM ON REVERSE SIDE

Please mark on these pictures where it is that you hurt:



Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Not at all		
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		