

STATUS PAGE
PROTOCOL 13-051

Closed To New Accrual

Closure Effective Date: 07/26/2017

Reason: Study Accrual Goal Met

No new subjects may be enrolled in the study as described above.
Any questions regarding this closure should be directed to the study's
Principal Investigator

Front Sheet

Report Generated: 08/13/2018 09:29 AM

Title: Phase II Feasibility Study of FOLFIRINOX-Losartan followed by Accelerated Short Course Radiation Therapy with Proton Beam for Locally Advanced Pancreatic Cancer

Overall Institution: Massachusetts General Hospital

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Sponsor Name	Sponsor Protocol No	Roles	Grant Number(s)
DF/HCC Investigator		Regulatory	
Dana-Farber/Harvard Cancer Center		Funding	

Total Study-Wide Enrollment Goal: 50 **Total DF/HCC Estimated Enrollment Goal:** 50

Phase: II

Age: Adults

Age Ranges: 18+

Will all subjects be recruited from pediatric clinics?

CTEP Study: No

Management Group(s):	DF/HCC Gastrointestinal Malignancies (GI) DFCI/BWH Gastrointestinal Oncology MGH Proton Therapy MGH Regulatory Coordinators	Primary Management Group:	DF/HCC Gastrointestinal Malignancies (GI)
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Investigational Drug? Yes

Drug(s), Biologic(s): 5-FU, CAPECITABINE, IRINOTECAN, LEUCOVORIN CALCIUM, LOSARTAN, OXALIPLATIN

IND #: 117719

IND Holder Type: DF/HCC Investigator

IND Holder Name: Theodore Hong

Investigational Device? This study does not use an Investigational Device.

IRB of Record:

Risk Category: Greater Than Minimal Risk

Protocol Involves: Human Material Collection; Other; Questionnaires/Surveys/Interviews; Radiation Therapy; Radiological Exams
Other Reason: Proton Beam Radiation Therapy

Date Range: (Medical Record Review and Specimen Collection studies)

Participating Sites under the DFCI IRB

Institution: Dana-Farber Cancer Institute
Massachusetts General Hospital

Participating Institutions Under Other IRB

None

Protocol Number: 13-051

Approval Date: 03/19/13 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 07/10/13 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date	OHRs Version Date
07/29/13	Reopen to accrual; Protocol, Local Appendices, Consent Form and Front Sheet replaced due to Amendment #1	07/09/13	07/17/13
03/12/14	Study renewal/ Consent Form footer and Local Appendices due to Continuing Review #1	02/27/14	N/A
06/09/14	Protocol, Consent Form and Front Sheet replaced due to Amendment #3 (note: re-consent is required)	05/21/14	06/05/14
02/24/15	Study renewal/ Consent Form footer replaced due to Continuing Review #2	02/19/15	N/A
03/16/15	Consent Form, Protocol and Front Sheet replaced; Survey added in local appendices (EORTC QLQ-C30, ESAS-R, HADS) – due to Amendment #4	01/28/15	03/16/15
04/13/15	Protocol and Front Sheet replaced due to Amendment #5	03/20/15	N/A
05/26/15	Consent Form replaced due to Amendment #6	05/11/15	05/12/15
Date Posted	Revised Sections	IRB Approval Date	OnCore Version Date
01/29/16	Study renewal/ Consent Form footer replaced due to Continuing Review #3	01/12/16	01/28/16
03/18/16	Protocol, Front Sheet and Eligibility Checklist replaced due to Amendment #7	03/10/16	N/A
06/21/16	Study Closed – Study Accrual Goal Met	06/20/16	N/A
09/20/16	Main Consent form, Protocol and Front Sheet replaced due to Amendment #8	09/15/16	09/20/16
09/22/16	Correction: removed status page per AM 8	N/A	N/A
09/29/16	Study Closed – Study Accrual Goal Met	09/28/16	N/A
09/29/16	Study Re-Opened – Study Local Accrual Goal Increased	09/29/16	N/A
Date Posted	Revised Sections	Approved Date	Version Date (OnCore)
01/11/17	Study renewal/Consent Form footer replaced due to Continuing Review #4	12/09/16	12/09/16
03/01/17	Protocol, Consent Form and Front Sheet replaced due to Amendment #9	01/24/17	01/24/17
07/27/17	Study Closed – Study Accrual Goal Met	07/26/17	n/a
07/27/17	Consent Form replaced due to Amendment #10	07/20/2017	07/24/2017
08/16/17	Front Sheet replaced due to Amendment # 11	08/16/17	N/a
08/21/17	No changes to online documents due to Amendment #11	08/16/17	N/a
11/15/17	Study renewal/Consent Form footer replaced due to Continuing Review #5	10/05/2017	11/05/2017
08/13/2018	Front Sheet, Protocol replaced per Amendment #12	08/10/2018	n/a

Protocol Version Date: August 7, 2018

Local Protocol #: 13-051

Title: Phase II Study of FOLFIRINOX-Losartan followed by Accelerated Short Course Radiation Therapy with Capecitabine for Locally Advanced Pancreatic Cancer

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Phase II Study of FOLFIRINOX-Losartan with Short Course Radiation and Capecitabine in Locally Advanced Pancreatic Cancer August 7, 2018

Responsible Data Manager: Christine Bolton, Tarin Grillo

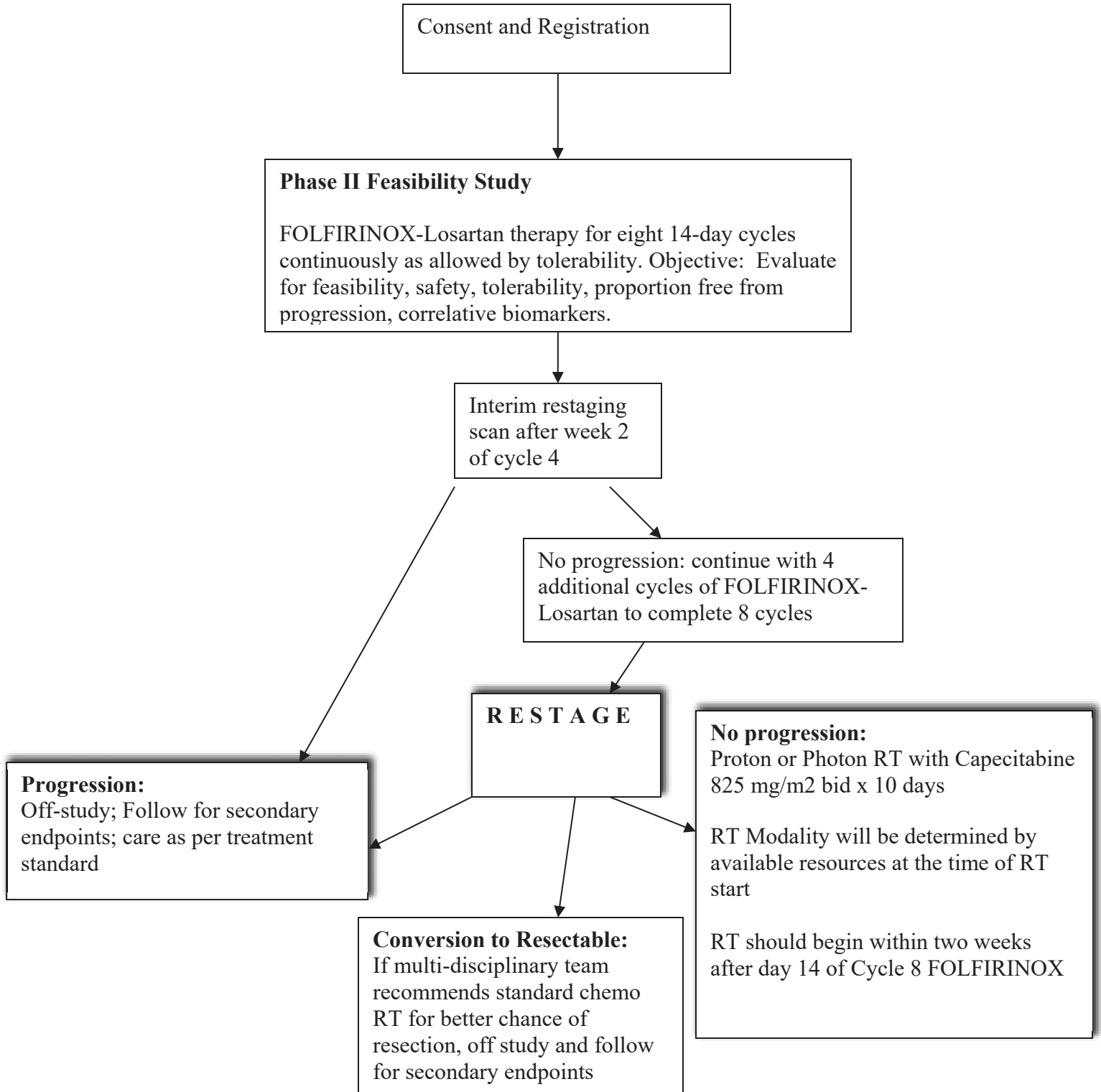
Agent(s): *5-Fluorouracil, Leucovorin calcium, Oxaliplatin, Irinotecan, Losartan, Capecitabine, Radiation Therapy, (no IND)*

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

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1. OBJECTIVES

1.1 Study Design

This is a single-arm, Phase II study of the FOLFIRINOX regimen in combination with the angiotensin II type I receptor blocker Losartan, followed by restaging and radiation therapy with capecitabine, in the treatment of patients with locally advanced unresectable pancreatic adenocarcinoma.

1.2 Primary Objective

- 1.2.1 To determine the rate of R01 resection in patients with locally advanced unresectable pancreas cancer treated with the combination of FOLFIRINOX-Losartan followed by restaging and radiation therapy with capecitabine.

1.3 Secondary Objectives

- 1.3.1 To determine the progression-free survival of patients with locally advanced disease who receive FOLFIRINOX-Losartan and radiation therapy.
- 1.3.2 To determine overall survival in patients treated with FOLFIRINOX-Losartan and radiation therapy.
- 1.3.3 To determine the overall survival of patients with locally advanced disease who receive FOLFIRINOX-Losartan without radiation (i.e. patients who demonstrate progression at restaging.)
- 1.3.4 To determine the toxicity of FOLFIRINOX – Losartan in patients with locally advanced pancreatic cancer.
- 1.3.5 To determine the toxicity of FOLFIRINOX – Losartan and radiation in patients with locally advanced pancreatic cancer.

- 1.3.6 To determine the rate of downstaging to surgical resection of FOLFIRINOX-Losartan followed by radiation in patients with locally advanced pancreatic cancer.
- 1.3.7 To determine the correlation between a panel of somatic genetic mutations (SNaPSHOT) and outcome in locally advanced pancreatic cancer treated with FOLFIRINOX-Losartan +/- radiation/capecitabine.
- 1.3.8 To determine the correlation between circulating biomarkers of TGF- β 1 downregulation, including circulating Collagen I levels, and outcome in locally advanced pancreatic cancer treated with FOLFIRINOX-Losartan +/- radiation/capecitabine.
- 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, palliative care) 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 46-48 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.

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 paresthesias, 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 laryngo-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 arrhythmia, 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.

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.

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 Losartan

Losartan is an angiotensin II type I receptor blocker (ARB) used in the treatment of essential hypertension and diabetic nephropathy. It is a selective competitive angiotensin II receptor antagonist that acts as an antihypertensive by blocking angiotensin II and its two major downstream pathways: direct vasoconstriction, and stimulation of aldosterone secretion. Its mechanisms of action in the cancer milieu will be discussed separately. It is administered orally and the usual starting dose in adults with hypertension is 50 mg, with doses up to 100 mg based on blood pressure response. Patients with baseline volume depletion are started on a dose of 25 mg PO daily with the dose titrated up as tolerated. There are no specific dosing adjustments for hepatic or renal impairment, but use in patients with chronic kidney disease whose calculated GFR is less than 30mL/minute/1.73m² is not recommended. Losartan is associated with the significant adverse reactions (>10% incidence) of chest pain, fatigue, hypoglycemia, diarrhea, urinary tract infection, anemia, weakness, back pain, and cough. Less common, but important, adverse reactions include hypotension, orthostatic hypotension, dizziness, hyperkalemia,

gastritis, muscle weakness, bronchitis. Rarely, losartan is associated with life-threatening angioedema, acute psychosis, and cardiac arrhythmia.

2.1.6 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/m² twice a day concurrently with radiation. They were able to escalate the capecitabine dose to 825 mg/m² twice a day. Dose-limiting grade 3 hand-and-foot syndrome was observed in two of six patients treated at 1,000 mg/m² 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/m² BID) and leucovorin (10 mg/m² 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)

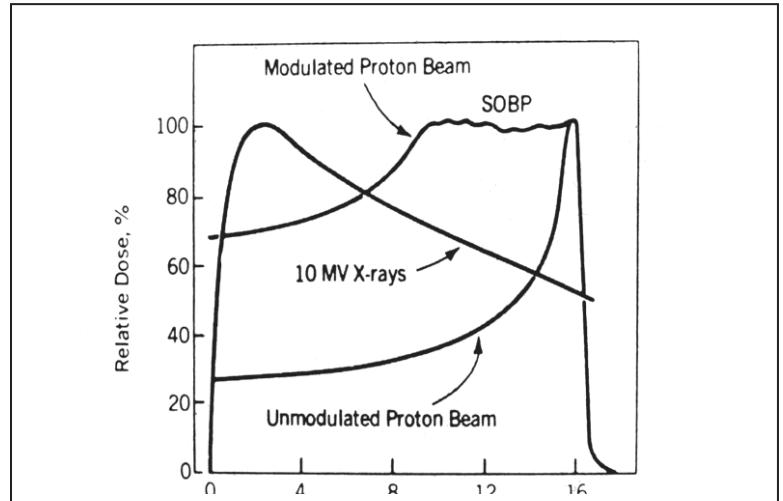
2.1.7 Proton Beam Radiation Therapy

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.

2.1.7.1 The Advantages of Protons for Delivery of Conformal Therapy

Characteristics of Proton Beams

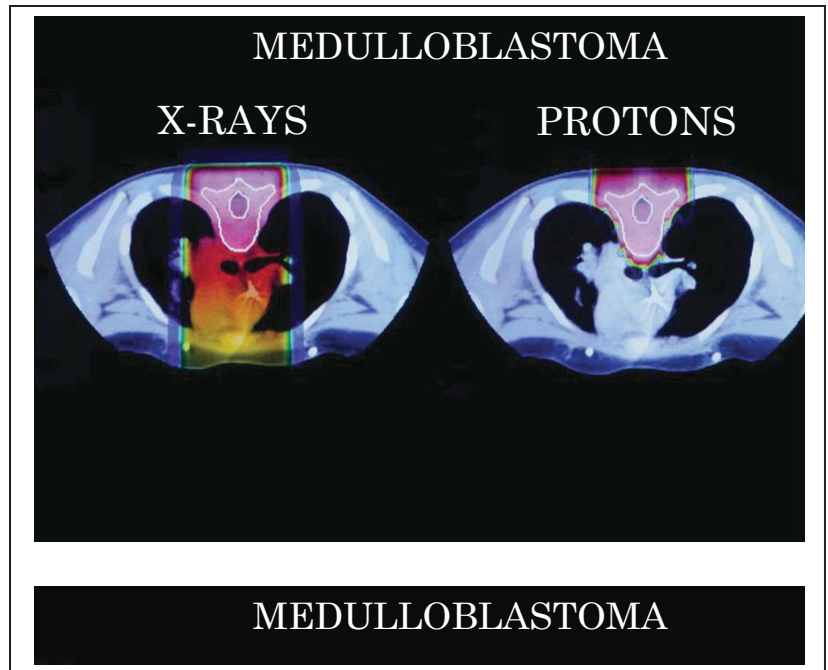
The basis for the advantages of proton beams lies in the physical laws that determine the absorption of energy in tissues exposed to photon or proton beams. In a specific tissue, photons are absorbed exponentially whereas protons have a finite range dependent upon the initial proton energy. Therefore, 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.

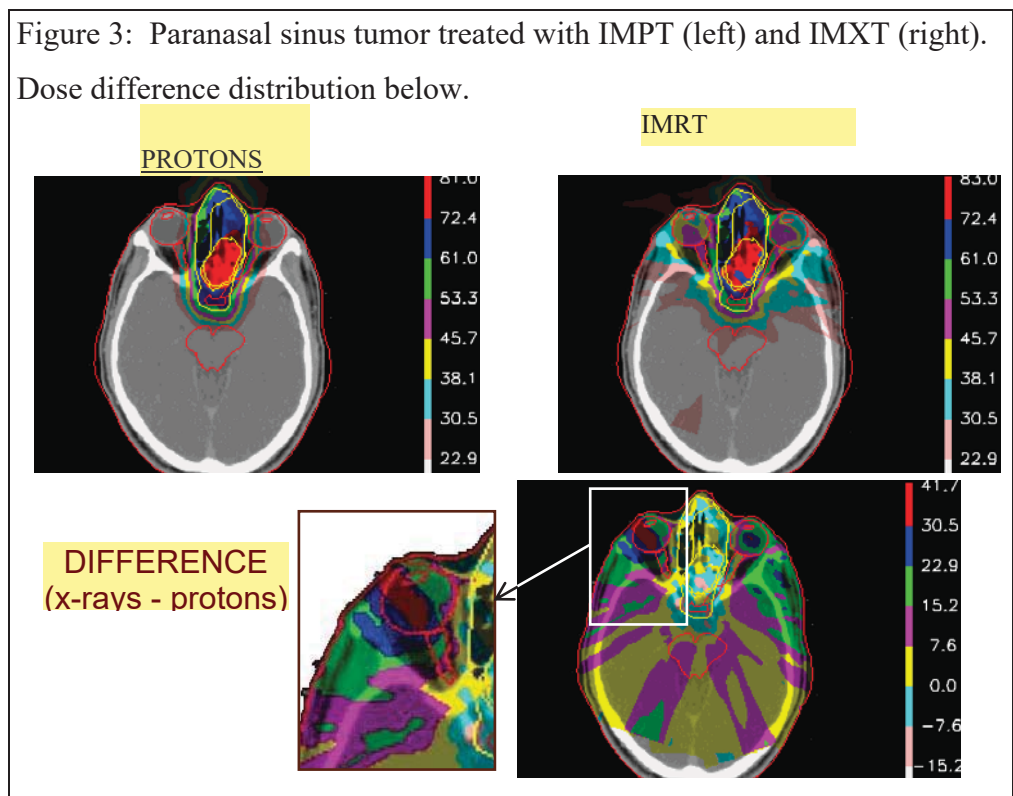
In the usual clinical situation, more than one radiation beam is used in both x-ray and proton treatments. However, the advantage shown for protons using single beams is present for each and every beam used. Therefore, one cannot overcome the physical disadvantage of x-rays by the use of multiple beams 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.

2.1.7.2 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 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 Intensity Modulated Radiation Therapy (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 Chemotherapy and chemoradiation in locally advanced pancreatic adenocarcinoma

Locally advanced unresectable pancreatic tumors represent 30 to 40% of all newly diagnosed pancreatic cancers. These patients lie on a continuum with patients diagnosed with metastatic disease at the outset, as surgical resection offers the only path to cure. Unresectable tumors are classified by the NCCN based on location (6). Tumors of the head that have greater than 180 degrees of SMA encasement or any celiac abutment, unreconstructable SMV or portal occlusion, or aortic invasion or encasement are unresectable. Body tumors with SMA or celiac encasement of greater than 180 degrees, unreconstructable SMV or portal occlusion, or aortic invasion are unresectable. Tumors of the tail with SMA or celiac encasement of greater than 180 degrees are unresectable. Irrespective of location, all tumors with evidence of nodal metastasis outside of the resection field are deemed unresectable.

Patients who present with locally advanced unresectable disease appear to benefit from both local control and timely systemic therapy. In rare cases, combination therapy provides tumor downstaging and conversion to potential surgical resectability. The rate of downstaging to surgery varies by institution – the Massachusetts General Hospital experience is less than 8%,

owing likely to the low threshold to perform early resection in cases of borderline resectability with venous reconstructive surgery.

In the absence of surgery, radiation therapy alone is associated with very high early failure rates, approximately 72 % (7). Since patients diagnosed with locally advanced, unresectable tumors are at very high risk for occult metastatic disease at presentation, subjecting all-comers to upfront chemoradiation delivers toxic therapy to a subset of patients who will not derive benefit. Chemotherapy alone, followed by restaging and selection of the subset of patients who have persistent local disease without metastatic progression, selects out patients who will potentially benefit. This was the basis for the GERCOR series, a retrospective evaluation of 181 patients with locally advanced pancreatic cancer enrolled in prospective phase II and III GERCOR studies (evaluating GEMOX, FOLFUGEM, gemcitabine alone)(8). In this series, 29.3% of patients demonstrated metastatic disease after three months of chemotherapy. Among the 70.3% of remaining patients (128 patients), 56% received chemoradiation while 44% received additional chemotherapy alone. Median progression-free survival in the chemoradiation group was 10.8 months, versus 7.4 months in the chemotherapy alone group ($p=0.005$), corresponding to median OS of 15.0 and 11.7 months, respectively ($p=0.0009$). Similar results were observed in a cohort of patients at MD Anderson, where a retrospective analysis demonstrated 76 patients (out of a cohort of 323) treated with upfront chemotherapy (a median of 2.5 months of gemcitabine) followed by chemoradiation(9). The median survival in patients receiving chemotherapy followed by chemoradiation was 11.9 months (6.4 month PFS), greater than for those receiving chemoradiotherapy from the outset (8.5 months OS and 4.2 months PFS, respectively (both $p<0.01$). These data have made the practice of chemotherapy, followed by restaging and chemoradiation in persistent locally advanced disease, the standard practice at our institution.

The optimal treatment sequence in the management of resectable pancreatic cancer is intensely 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, and upfront higher-risk body and tail lesions. Based on potential unresectability and/or micrometastatic spread at presentation, these two groups represent the

opportune population to offer the combination of highly active systemic chemotherapy (the FOLFIRINOX regimen) with preoperative radiation therapy.

2.2.2 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 Prodigie 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 (10).

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 (11). 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 infused over two hours, 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 (12).

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 – 63.7% in the FOLFIRINOX arm and 64.9% 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 FOLFIRINOX regimen was significantly greater compared to gemcitabine. Rates of Grade 3/4 neutropenia (45.4% versus 18.7%), febrile neutropenia (5.4 versus 0.6%), and thrombocytopenia (9.1 versus 2.4%) 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. 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 Prodigy-4/ACCORD results that mandate moving the regimen into the locally advanced setting are twofold: first, its demonstrated superiority in systemic disease control, and second, its superior objective response rates. In the setting of locally advanced disease, the goal of providing chemotherapy to potentially downstage to surgical resectability while controlling local spread is paramount. The FOLFIRINOX regimen (without Losartan) is currently under investigation in the locally advanced setting in the CALGB/ECOG trial.

2.2.3 The role of ARBs in the treatment of pancreatic cancer

While the epidemiologic data are mixed regarding the contribution of angiotensin converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARBs) to cancer risk, data on clinical outcomes of patients who continue to receive ACEI and ARB therapy during treatment for

a diagnosed cancer more consistently suggest a benefit. In a cohort of 287 patients with advanced non-small cell lung cancer, Wilop *et al.* observed a 3.1 month median survival advantage among ACEI or ARB recipients which could not be attributed to other established risk factors or dose intensity of chemotherapy (11.7 vs 8.6 months, HR 0.56, $p=0.03$) (13). In a cohort of patients with locally advanced or metastatic pancreatic cancer, Nakai *et al.* observed an 8.7 month median PFS among patients receiving ACEI or ARB therapy ($n=27$) versus 4.5 months in a cohort receiving other antihypertensive therapy ($n=25$) versus 3.6 months in a cohort not receiving any antihypertensive therapy ($n=103$) ($p=0.032$) (14). The mechanisms by which ARB and ACEI therapy appear to convey a protective benefit are under intense exploration, and explanations for this potential benefit have implicated the role of the renin-angiotensin system (RAS) in angiogenesis, cell proliferation, apoptosis, inflammation and intratumoral drug delivery. The RAS appears active in pancreatic tissue, more so in malignancy. Ohta *et al.* explored the presence of the local RAS in pancreatic tissue while investigating the observation that pancreatic tumors have vascular-rich and hypovascular regions on angiography of surgically resected specimens (15). Angiotensin II (ATII) can be generated in the pancreas from its proenzyme angiotensinogen by active trypsin, ubiquitous in pancreatic tissue. ATII and ACE levels were measured in a panel of surgical specimens: normal pancreas, pancreatic adenocarcinoma, colon cancer, and hepatocellular cancer. Tissue ATII levels, but not ACE levels, were significantly higher in pancreatic adenocarcinoma samples relative to all other tissue types – suggesting that local vasoconstriction may result in focal hypovascularity and necrosis in an ACE-independent manner. Following this observation, Amaya *et al.* measured angiotensin II type 1 receptor (AT1) expression in three pancreatic cell lines and found strong expression, while one non-pancreatic cell line (the colorectal line HT-29) showed very weak expression (16). The group found that ATII stimulated the growth of pancreatic cancer cells through MAP kinase activation, and also prevented cisplatin-induced apoptosis through NF-kappa B activation and subsequent upregulation of the anti-apoptotic molecules survivin and Bcl-XL. Subsequently, Gong *et al.* demonstrated that administration of losartan to a panel of pancreatic adenocarcinoma cell lines induced dose-dependent decrease in cell survival, increasing p53, p21, p27, and Bax, and reducing Bcl-2 and Bcl-xl expression (17).

The renin-angiotensin pathway in pancreatic carcinoma is also thought to signal through an angiogenesis-mediated pathway. ATII can upregulate VEGF production. Arafat *et al.* analyzed expression and localization of ACE, AT1R, and VEGF levels in 25 human pancreatic tumors

relative to matched surrounding non-malignant tissue, and found that ACE and AT1R levels were upregulated in 75% of tumor samples, and that VEGF expression was much higher in the subset of tumors in which ACE and AT1R were upregulated (18). When cells were incubated with the ACEI captopril or the ARB losartan, cell proliferation was significantly suppressed. Noguchi et al subsequently investigated the synergistic effect of gemcitabine and losartan in a murine pancreatic cancer model (19). While the administration of gemcitabine or losartan alone provided moderate inhibitory effect, the combination of therapies provided a significant inhibition of tumor volume in treated mice. In tumors treated with losartan and gemcitabine they found significantly less CD31-positive vessels, corresponding with a significantly lower intratumoral expression of VEGF.

A final path of inquiry, and the preclinical data forming the basis for the current trial, comes from recent findings showing that the elevated fibrillar collagen content – associated with tumor desmoplasia – is a significant barrier to drug delivery in pancreatic tumor models and other tumor types (20-23). Independent of its potential role in angiogenesis inhibition, losartan has been shown to minimize collagen accumulation and fibrosis in cardiac and renal disease (22, 23). The inhibition of ATII signaling by losartan and other RAS inhibitors reduces the expression and activity of profibrogenic molecules like TGF- β , thrombospondin-1 – an activator of the latent-form of TGF- β –, connective tissue growth factor and osteopontin (10, 26-29). In a recent study, the Jain group investigated the effect of losartan on collagen I levels in several tumor models in mice including an orthotopic pancreatic cancer model (30). Losartan decreased the intratumoral expression of the TGF- β activator TSP-1, and losartan doses of 20 and 60 mg/kg/d for 2 weeks significantly reduced the intratumoral collagen content, while the 10mg/kg/d dose did not affect collagen accumulation. To test if the reduction in collagen content would improve the intratumoral distribution of large therapeutics, nanospheres were injected intratumorally or intravenously following the losartan pre-treatment. The reduction in collagen levels led to enhanced nanospheres diffusion and distribution in tumors. In mice with orthotopic pancreatic cancers losartan did not change the fraction of perfused vessels, but the penetration of nanospheres – injected intravenously – *at distance* from blood vessels was greater in losartan-treated than control tumors. Furthermore, losartan enhanced the efficacy of the nanotherapeutic Doxil. Interestingly, the administration of Doxil or losartan alone did not affect the growth of pancreatic tumors, but tumors were 50% smaller in mice treated with losartan and Doxil. Thus losartan shows potential as an adjunct to

safely enhance the intratumoral penetration and efficacy of therapeutics in patients with pancreatic cancer.

The impact of angiotensin II blockade on collagen remodeling has been clinically validated in the connective tissue disorder Marfan's Syndrome (26). The genetic defect, a mutation in the gene encoding fibrillin-1, leads to excessive TGF- β signaling and a disorganized collagen matrix. Patients with this disorder are susceptible to the life-threatening clinical sequel of aortic root dilatation. In a retrospective cohort analysis of pediatric patients with Marfan's syndrome who had been initiated on an ARB (losartan in 17 patients and ibesartan in 1 patient), the mean change in aortic-root diameter during the period patients were on ARB therapy was far less rapid (0.46 +/- 0.62 mm per year), relative to a baseline rate of increase of 3.54 mm per year. Notably, the Marfan's trial represents a dose escalation schema in which the pediatric patients enrolled were not hypertensive at baseline *per se*, and were often transitioned from beta blocker monotherapy to ARB therapy. Drug dose was escalated from 0.7 mg/kg to 1.4 mg/kg (a dose corresponding to 50-100 mg for the average adult patient) and median change in systolic BP on maximum dose therapy was non-significant when compared to prior monotherapy – i.e. losartan monotherapy does not represent particularly potent anti-hypertensive effects. In normotensive patients with chronic hepatitis C the daily administration of losartan (50 mg/d) reduced liver fibrosis, significantly decreased the systolic pressure by 10 mm Hg but did not affect the mean arterial blood pressure (31).

A recent Phase I trial in advanced and locally advanced PDAC employed candesartan along with gemcitabine chemotherapy in normotensive patients¹. Candesartan was given orally at an escalating dose (4, 8, 16, and 32 mg) q.d. daily, and gemcitabine was given at standard dosing (1000 mg/m²) 30 min i.v. on days 1, 8, and 15, repeated every 4 weeks.) The study enrolled a total of 14 patients and found that hypotension was the limiting DLT at the 32 mg dose (which would be the biologic equivalent of Losartan at 100mg PO qd). Response rate and disease control rate were 0% and 79%, respectively. Progression-free survival and overall survival were 7.6 and 22.9 months, respectively – less so in patients with advanced disease. The 16 mg dose in combination with gemcitabine was the recommended Phase II dose in this cohort (equivalent to Losartan at 50 mg, the planned dose in the current study).

2.2.4 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 hematopoietic function; and ECOG PS 0/1. Dose level 1 consisted of PBT delivered 3 Gy x 10 Monday to Friday. Pts in subsequent dose levels received 5 Gy x 5 in progressively shortened schedules: level 2 (wk 1 M W F, wk 2 T Th), level 3 (wk 1 M T Th F, wk 2 M), level 4 (wk 1 M-F). Proton beam therapy was targeted at pancreatic mass with elective nodal coverage. Pts received Capecitabine 825 mg/m² BID wk 1 and 2 M-F. Surgery was performed 1-6 wks after completion of chemotherapy. Patients were recommended to receive 6 months of gemcitabine after surgery. 31 pts 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. 4/21 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 mo and 17 mo). Metastatic failure has occurred in 15 out of 27 patients (56%). In summary, we found pre-operative CRT with 1 week of PBT and capecitabine followed by early surgery feasible and associated with satisfactory local control.

2.2.5 Photon based short course chemoradiation in locally advanced pancreatic cancer

Dholakia and colleagues have studied fractionated stereotactic body radiation therapy (SBRT) of 33 Gy photons in five fractions for locally advanced pancreatic cancer. They demonstrated local control of 83% at one year with minimal acute or late gastrointestinal toxicity and favorable survival compared to historical data. (33) This correlates well with our five fraction proton studies.

2.2.6 Summary

This research study combines several key tenets. First, we hypothesize that pre-radiation FOLFIRINOX therapy will optimize the treatment of patients with locally advanced pancreatic adenocarcinoma based on its superior response rate demonstrated in patients with advanced pancreatic cancer in the Prodiges-4/ACCORD trial. Based on compelling preclinical data regarding Losartan's many potential synergistic benefits in angiogenesis inhibition and collagen matrix stabilization, we posit that the addition of this agent will further potentiate the benefit of FOLFIRINOX therapy via enhanced drug delivery. The subsequent use of radiation therapy aims to consolidate upfront chemotherapy treatment in an effective manner, with tolerable toxicity.

2.3 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.[30, 31] The few studies that have included patients with operable pancreatic cancer included small sample sizes in heterogeneous patients.[32, 33] 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.[34] 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.[35]

Additionally, evaluating patient-reported measures may help highlight patients' difficulties with treatment adherence by demonstrating additional side effects and toxicities of therapy.[36] 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.[37, 38] 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 locally advanced 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).[31] 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 locally advanced 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.[39] We will use the Edmonton Symptom Assessment System-revised (ESAS-r) to measure symptoms, which has been previously validated in patients with advanced cancer.[40] 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.[41] 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.

2.4 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.[42, 43] Patients with pancreatic cancer often experience symptoms related to the cancer itself or the therapies used to treat it.[32] 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.[44] 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.

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 a DFHCC institution pathology department prior to registration.
- 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). All patients must be staged with a physical exam, chest CT, abdominal CT with intravenous contrast (or Abdominal MRI with gadolinium and/or manganese).
- 3.1.3 Patients with locally advanced, unresectable disease will be included. Locally advanced unresectable disease is defined by the NCCN as:

- 1) Tumors of the head that have greater than 180 degrees of SMA encasement or any celiac abutment, unreconstructable SMV or portal occlusion, or aortic invasion or encasement.
- 2) Tumors of the body with SMA or celiac encasement of greater than 180 degrees, unreconstructable SMV or portal occlusion, or aortic invasion.
- 3) Tumors of the tail with SMA or celiac encasement of greater than 180 degrees.
- 4) Irrespective of location, all tumors with evidence of nodal metastasis outside of the resection field are deemed unresectable (6).

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

3.1.5 ECOG-Performance Status of 0 or 1 are eligible.

3.1.6 Life expectancy of greater than 3 months.

3.1.7 Baseline SBP > 100mm Hg. This is based on the average of two values - separate seated, resting measurements taken five minutes apart. BP does not need to be checked in both arms unless a reading is below 110 mm Hg, in which case the other arm can be checked as well, If BP is checked in both arms, the higher value is deemed accurate for calculating the average.

3.1.8 Lab Values:

ANC \geq 1500 cells/mm³

Platelet count \geq 100,000 cells/mm³.

AST and ALT \leq 2.5 x upper limit of normal OR two downtrending values

Total Bilirubin \leq 1.5 x upper limit of normal if no biliary stenting has been done;

OR 2.0 x upper limit of normal if patient is s/p biliary stenting;

OR two downtrending values

Serum Creatinine \leq 1.5 mg/dl Creatinine Clearance \geq 30ml/min (as estimated by Cockcroft Gault Equation):

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

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 treatment plus 30 days from the last date of study drug administration. 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 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 Patients cannot be already treated on ACE or ARB therapy for hypertension or renal protection (with diabetes) at the time of enrollment.
- 3.2.3 Patients cannot have baseline hypotension, defined as systolic BP lower than 100 mm Hg on two readings obtained on two separate days prior to study enrollment.
- 3.2.4 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).
- 3.2.5 Any prior chemotherapy, radiation therapy, or biologic therapy (“targeted therapy”) for treatment of the patient’s pancreatic tumor.

- 3.2.6 Treatment for other invasive carcinomas within the last five years who are at 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.
- 3.2.7 Other serious uncontrolled medical conditions that the investigator feels might compromise study participation.
- 3.2.8 Lack of physical integrity of the upper gastrointestinal tract or malabsorption syndrome.
- 3.2.9 Known, existing uncontrolled coagulopathy.
- 3.2.10 Unwillingness to participate or inability to comply with the protocol for the duration of the study.
- 3.2.11 Prior systemic fluoropyrimidine therapy. Prior topical fluoropyrimidine use is allowed. Prior unanticipated severe reaction to fluoropyrimidine therapy, or known hypersensitivity to 5-fluorouracil or known DPD deficiency.
- 3.2.12 Participation in any investigational drug study within 4 weeks preceding the start of study treatment.
- 3.2.13 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.
- 3.2.14 Major surgery, excluding laparoscopy, within 4 weeks of the start of study treatment, without complete recovery.
- 3.2.15 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.
- 3.2.16 Participants may not be receiving any other study agents.
- 3.2.17 History of allergic reactions attributed to compounds of similar chemical or biologic composition to 5-fluorouracil, irinotecan, oxaliplatin, or losartan.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

We do not expect the inclusion and exclusion criteria to either over or underrepresent women, minorities, or underrepresented 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

5.1 Phase II FOLFIRINOX-Losartan Treatment

Treatment will be administered on an outpatient basis and will include intravenous administration of the FOLFIRINOX regimen every 14 days +3/-1 days at physician discretion (unless a further delay is mandated by toxicity criteria) along with daily oral patient self-

administered Losartan. All chemotherapy will be administered according to institutional standard of care.

Table 1: FOLFIRINOX-Losartan Standard Dosing Schedule

	Losartan	FOLFIRINOX
Dose	25 mg PO qd starting on C1 Day 1. If this dose is tolerated during week 1, escalation to 50 mg PO qd at C1D8, to continue daily until the completion of C8 Day 14. Losartan treatment will continue during any holds for FOLFIRINOX unless losartan is the agent responsible for the treatment hold. (See BP criteria as outlined below)	<p>Q14 day cycle: Day 1-3:OXALIPLATIN (85 mg/m²) IV BOLUS QD Days: 1 Infuse over 2 hours. Any adjustments will follow institutional standard of care. Mix in D5W. Infuse prior to irinotecan. Infusion time should be lengthened to 6 hours for ACUTE larngopharyngeal dysesthasias occurring during or after previous treatment</p> <p>IRINOTECAN (180 mg/m²) IV BOLUS QD Days: 1 Infuse over 90 minutes. Any adjustments will follow institutional standard of care. Instructions: Mix in 500cc. Administer prior to leucovorin and 5-FU on day 1. May infuse irinotecan and leucovorin at the same time, in separate bags, using Y-line. Leucovorin is compatible with both Oxaliplatin and Irinotecan IF MIXED IN D5W. It may be started 1 hour and 30 minutes after start of oxaliplatin IF MIXED IN D5W and continued throughout the irinotecan infusion so that Leucovorin and Irinotecan infusions are completed at the same time.</p> <p>FOR PATIENTS REQUIRING LEUCOVORIN/IRINOTECAN MIXED IN NORMAL SALINE, infuse after oxaliplatin after line flush with D5W.</p> <p>LEUCOVORIN CALCIUM (400 mg/m²) IV BOLUS QD Days: 1 Infuse over 2 hours. Any adjustments will follow institutional standard of care. Instructions: Administer</p>

		<p>following irinotecan and before 5-FU on day 1. May infuse irinotecan and leucovorin at the same time, in separate bags, using Y-line. Leucovorin is compatible with both Oxaliplatin and Irinotecan IF MIXED IN D5W. It may be started 1 hour and 30 minutes after start of oxaliplatin IF MIXED IN D5W and continued throughout the irinotecan infusion so that Leucovorin and Irinotecan infusions are completed at the same time.</p> <p>FOR PATIENTS REQUIRING LEUCOVORIN/IRINOTECAN MIXED IN NORMAL SALINE, infuse after oxaliplatin after line flush with D5W.</p> <p>FLUOROURACIL (400 mg/m²) IV BOLUS QD Days: 1 Infuse over 2-4 minutes. Any adjustments will follow institutional standard of care.</p> <p>FLUOROURACIL (1200 mg/m²) IV CONTINUOUS INFUSION QD Days: 1,2 Instructions: Begin after fluorouracil bolus dose. Any adjustments will follow institutional standard of care. For OUTPATIENTS: The IVCI dose is for each of days 1 and 2 and should be delivered as one continuous infusion over 46-48 hours. Pump can be disconnected in a return visit to infusion, by a visiting nurse at home, or by patient self-disconnect at home.</p> <p>For INPATIENTS: Prepare day 1 and day 2 doses as separate doses, for a total of 2 doses. Each dose will be infused over 23 hours, without interruption between doses.</p> <p>ATROPINE SULFATE 0.4-1 MG IV QD PRN: For early cholinergic syndrome related to irinotecan infusion Hold if: Giving sc</p>
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		<p>ATROPINE SULFATE 0.4-1 MG SC QD PRN: For early cholinergic syndrome related to irinotecan infusion Hold if: Giving IV</p> <p><u>Day 3 or 4:</u> Neulasta (Pegfilgrastim)administration 6 mg SC x1 At DFCI, standard has become to administer Pegfilgrastim at the time of 5FU pump disconnect. At MGH, standard is to administer Pegfilgrastim 24 hours after pump disconnect. Both methods are allowed in the protocol. Patients may self-administer at home or have the injection administered in clinic. Any adjustments will follow institutional standard of care.</p> <p>Per Standard of Care, central line will be placed for chemo infusions</p>
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Patients will be restaged after four cycles of therapy (interim scans) as well as following completion of induction chemotherapy (eight cycles of therapy.) Restaging scans may be done in the second week of the preceding cycle. Up to one week’s delay between cycles for restaging is allowed. Patients who do not demonstrate progression on either restaging scan will undergo Radiation Therapy with standard dose capecitabine (825 mg/m² bid x 5 days per week x 2 weeks) in the week of, and the week following, proton beam radiation therapy. Patients who receive photon radiation therapy will take capecitabine (825 mg/m² bid x 5 days per week x 2 weeks) for the two weeks of radiation treatment. Radiation therapy with concurrent capecitabine must begin 15-43 days from Day 1 of the last cycle of FOLFIRINOX chemotherapy. Expected toxicities and potential risks as well as dose modifications for FOLFIRINOX, Losartan, Capecitabine, 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.

5.2 Pre-Treatment Criteria

Prior to study enrollment patients must undergo the following evaluations:

Within 7 days of study entry: Physical exam, Lab studies (CBC with diff, Na, K, BUN, Cr, Glucose, Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase.) Acceptable laboratory parameters for Day 1 of treatment are as stated in inclusion criteria for the study:

ANC \geq 1500 cells/mm³

Platelet count \geq 100,000 cells/mm³.

AST and ALT \leq 2.5 x upper limit of normal OR two downtrending values

Total Bilirubin \leq 1.5 x upper limit of normal if no biliary stenting has been done

OR 2.0 x upper limit of normal if patient is s/p biliary stenting

OR two downtrending values

Serum Creatinine \leq 1.5 mg/dl Creatinine Clearance \geq 30ml/min (as estimated by Cockcroft Gault Equation):

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

Creatinine clearance for females = 0.85 x male value

If a patient has undergone biliary stent placement, the following eligibility guidelines will apply. If ALT and AST are elevated out of range of eligibility at time of enrollment, but demonstrate two down-trending values, patient should begin treatment without Irinotecan if clinically indicated. The agents 5-FU and Oxaliplatin may be given during Cycle 1 with Irinotecan incorporated in Cycle 2 if 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 only, with Irinotecan incorporated in Cycle 2 if laboratory values permit. If total bilirubin is elevated between 1.0 mg/dl 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 second cycle if laboratory values permit

Additionally, baseline blood pressure should be documented twice during the enrollment visit in a resting, seated position at least five minutes apart. SBP will be documented as the average of the two SBP readings. If SBP is borderline (below 110 mm Hg), it can be checked in the other arm, and the higher of the two arms can be used to calculate the average. Average SBP should exceed 100 mmHg for enrollment in the study at the starting dose of 25 mg PO qd.

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

5.3 Agent Administration

Note: all chemotherapy infusion adjustments will follow institutional standard of care at the discretion of the treating physician.

5.3.1 5-Fluorouracil: 5-FU will be administered at a dose of 400 mg/m² in a 2-4 minute IV push on day one, followed by a 1200 mg/M²/d by continuous infusion via an ambulatory infusion pump for the subsequent 46-48h. 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 reductions are to be made at the discretion of the treating medical oncologist.

5.3.2 Oxaliplatin: Oxaliplatin will be administered as a dose of 85 mg/m² by intravenous infusion over 120 minutes on Day 1 of each treatment cycle. 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 reductions are to be made at the discretion of the treating medical oncologist.

- 5.3.3 **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 (+/- 10 minutes). Any adjustments will follow institutional standard of care per the treating physician.
- 5.3.4 **Irinotecan:** In this study irinotecan will be administered as a dose of 180 mg/m² by intravenous infusion over 90 minutes on Day 1 of each treatment cycle. Early flushing, diarrhea, abdominal pain will be recognized and treated with IV atropine by nursing staff as per treatment standard with this drug. 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.
- 5.3.5 **Losartan:** Losartan will be administered orally as a tablet to be taken by the patient at home every day during treatment with FOLFIRINOX (i.e. during the eight cycles of induction chemotherapy) without breaks except when appropriate due to toxicity concerns. Missed or vomited doses will not be made up. Instances of missed or vomited doses will not constitute a violation of the protocol unless expressly deemed so by the overall PI. A dose shall be considered missed if it is 3 hours beyond the time usually taken. In the first week of treatment (C1 D1-7), patients will take 25 mg PO qd of Losartan presuming they met minimum BP criteria at enrollment of 2 readings with an average SBP greater than 100 mm Hg. Patients will return for C1 Day 8 at which time blood pressure will be rechecked (again, two separate resting, seated readings.) If SBP still exceeds 100mm Hg average between two separate, seated checks, patients may be escalated to a dose of 50 mg PO qd for the remainder of the study. BP checks will be mandated for each study visit. Please refer to the dose reduction section for information on dose reductions for hypotension and/or hyperkalemia resulting from Losartan. Study participants will be asked to return unused pill bottles at each follow up visit and drug accountability will be documented by pill counts. All dose modifications are to be made at the discretion of the treating physician.

5.3.6 . **Capecitabine:** The dose of capecitabine will be given orally 825 mg/m² BID (total 1650 mg/m² per day) for a total of 10 days M-F of weeks 1 and 2 (the week of, and the week after, proton beam 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, per institutional standard. The BSA will be rounded to the nearest tenth and the investigator will prescribe capecitabine per the institutional standard. The dose of capecitabine will not exceed 2000mg po bid. A dose shall be considered missed if it is 10 hours beyond the time usually taken.

5.3.7 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. All dose reductions are to be made at the discretion of the treating medical oncologist.

5.3.8 Radiation Therapy

5.3.8.1 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 at the physician’s discretion. For patients treated with photon SBRT, no elective nodal coverage will be used.

Radiation therapy may be delivered with either protons or photons; treatment modality assignment will be based on available resources at the time of radiation planning. Total dose

will be prescribed to the 95 to 100% isodose line based on coverage and will be 25 CGE in 5 fractions (5 Gy/day) with multifield techniques. A dose-painted in-field boost to a potentially at risk margin at the SMA, celiac axis, or SMV/PV to 6 Gy/day (30 Gy total) is permitted as long as all normal tissue constraints are met.

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. For proton treatments, passively scattered protons and pencil beam scanning are both permitted.

5.3.8.2 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. 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.

5.3.8.3 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.

5.4 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 rate of Grade 2-4 neutropenia with FOLFIRINOX exceeded 70% in the PRODIGE/Accord trial, myeloid growth factors will be used prophylactically, and all patients should receive Neulasta (Pegfilgrastim) 6mg SC x1 24-48 hours after disconnection from CI 5FU as clinically indicated per institutional standard of care. Patients may receive all concomitant therapy deemed necessary to provide adequate support. No other cytotoxic therapy or radiotherapy may be used during therapy.

5.5 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.

5.6 Duration of Follow Up

Patients will be followed until 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.

5.7 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 5.5 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. Participants who develop disease progression will not be removed from the study, but will be followed for survival.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Theodore S. Hong, M.D. at 617-724-1159.

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 NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) which is identified and located on the CTEP website at:

<http://ctep.cancer.gov/reporting/ctc.html>).

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.

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 FOLFIRINOX, capecitabine, proton radiation therapy or Losartan after stent placement. Therapy may be withheld for procedures like repeat ERCP, and restarted at the treating physician's discretion per standard of care.

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 Prodiges-4/ACCORD trial in patients with advanced pancreatic adenocarcinoma (based on ASCO 2010 presentation).

AE, % per patient	Folfinorox N=167	
	All	Grade 3/4
Neutropenia	79.9	45.7
Febrile Neutropenia	7.2	
Anemia	90.4	7.8
Thrombocytopenia	75.2	9.1

6.1.1.2 Anticipated Non-Hematologic adverse events

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

AE, % per patient	Folfinorox N=167	
	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 5-Fluorouracil Anticipated Toxicities

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

6.1.3 Irinotecan Anticipated 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.

6.1.4 Oxaliplatin Anticipated Toxicities

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include, paresthesias, dysesthesias, and hypoesthesia of the hands, feet and perioral region. Jaw spasm,

abnormal tongue sensation, 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 hypoesthesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin. Various agents have been used in an attempt to minimize neurotoxicity of oxaliplatin (e.g. carbamazepine, Mg⁺, Ca⁺⁺). Calcium and magnesium infusions appear to be beneficial in preventing neurotoxicity. 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.

6.1.5 Leucovorin: Anticipated Toxicities

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

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, and late second malignancies.

6.1.7 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.

Patients with moderate renal impairment as measured by serum creatinine (> 1.3) at baseline require dose reduction.

6.1.8 Losartan

Common and anticipated toxicity related to Losartan is an adverse effect on blood pressure (hypotension) and potential for electrolyte imbalance such as hyperkalemia.

Toxicity (Greater than 1%)

Hypotension: Symptomatic first dose hypotension was noted following a 100 mg oral dose, leading to drug discontinuation during a dose finding clinical study (Goldberg et al, 1995b). The incidence appears to be dose-related, increasing from less than 0.5% at doses of 50 mg daily or less, to 2.2% at doses of 100 mg daily (Ellis & Patterson, 1996a).

Hyperkalemia Hyperkalemia has been reported during the postmarketing use of losartan (Prod Info Cozaar(R) , 2005). In hypertensive patients with non-diabetic, chronic renal disease, serum potassium was increased significantly to 4.6 mmol/L (mmol/L) from baseline (4.23 mmol/L) during dosing with 100 mg losartan daily, but not with a lower 50 mg daily dose (Gansevoort et al, 1994a). During fixed-dose treatment with losartan 50 mg plus hydrochlorothiazide 12.5 mg in over 200 patients, 11% of patients had changes upward or downward in serum potassium of at least 0.5 mEq/L after 12 weeks (Critchley et al, 1996b). Among 112 hypertensive patients with mild-to-severe renal failure (including 28 on hemodialysis) followed for 12 weeks during losartan treatment, 8% to 18% experienced decreased serum potassium levels greater than 0.5 mEq/L, while 15% to 23% experienced increases greater than 0.5 mEq/L. One patient was withdrawn due to hyperkalemia to greater than 6 mEq/L (Toto et al, 1998).

Hyponatremia

Hyponatremia has been reported during the postmarketing use of losartan (Prod Info Cozaar(R) , 2005).

Gastrointestinal tract findings

Diarrhea (2.4%) and dyspepsia (1.3%) were the most common gastrointestinal side effects, reported more frequently in losartan patients than those treated with placebo (Prod Info Cozaar(R), 2002a).

Musculoskeletal findings

Back pain, leg pain, muscle cramps, and myalgia were reported in between 1% and 1.8% of patients on losartan monotherapy, and had frequency rates greater than comparable placebo-treated patients (Prod Info Cozaar(R), 2002a). Although no direct causal relationship can be established, the events reported in 2 or more patients but less than 1% of patients in clinical

trials included arm pain, hip pain, joint swelling, knee pain, shoulder pain, stiffness, arthralgia, arthritis, fibromyalgia, muscle weakness, and generalized musculoskeletal pain (Prod Info Cozaar(R), 2002a).

Asthenia

Incidence: 1% or greater (Prod Info COZAAR(R) oral tablets, 2008). Asthenia occurred in 1% or greater of patients receiving losartan potassium treatment compared with patients receiving placebo during clinical studies (Prod Info COZAAR(R) oral tablets, 2008).

Dizziness

Incidence: 3% (Prod Info COZAAR(R) oral tablets, 2008). Dizziness occurred in 3% of patients (n=1075) receiving losartan potassium treatment compared with 2% of patients (n=334) receiving placebo during clinical studies (Prod Info COZAAR(R) oral tablets, 2008)

Insomnia

Incidence: 1% or greater (Prod Info COZAAR(R) oral tablets, 2008). Insomnia occurred in 1% or greater of patients receiving losartan potassium treatment compared with patients receiving placebo during clinical studies (Prod Info COZAAR(R) oral tablets, 2008).

Cough

The incidence of cough in clinical trials with losartan monotherapy was 3.4%, with the placebo-treatment group reporting an incidence of 3.3% (Prod Info Cozaar(R), 2002a). Results from controlled phase III clinical trials suggest that losartan may not produce the cough associated with angiotensin-converting enzyme (ACE) inhibitors (Anon, 1994; Karlberg, 1993a). Preliminary results from a multicenter trial to investigate the incidence of losartan induced cough in patients with a history of ACE-inhibitor (lisinopril) cough support this contention (Anon, 1995; Lacourciere et al, 1994). In comparative trials involving nearly 300 patients using fixed-dose losartan 50 mg plus hydrochlorothiazide, cough was seen exclusively in patients over 65 years old, with a frequency of 2.1%. In this age group, cough was nearly 5-fold more frequent (9.8%) among patients treated with fixed-dose captopril plus hydrochlorothiazide (Critchley et al, 1996b). Additionally, losartan 25 mg induced dry cough in 2 elderly diabetic women (age 73- and 80-years-old), who stopped lisinopril therapy due to cough. Two weeks after discontinuing losartan, symptoms of cough were resolved (Conigliaro, 1999).

Respiratory finding

Upper respiratory infection (7.9%) was the most common adverse effect overall in clinical trials with losartan monotherapy, although the placebo-treatment frequency was 6.9% (Prod Info Cozaar(R), 2002a). Other events with frequencies greater in losartan patients included nasal congestion (2%), sinus disorders (1.5%), and sinusitis (1%) (Prod Info Cozaar(R), 2002a).

6.2 Toxicity Management

6.2.1 FOLFIRINOX therapy

6.2.2 “One cycle” will constitute one administration of FOLFIRINOX therapy, administered on Day 1-3. Each cycle will be 14 days long +3/-1 days at physician discretion, unless further dose delay is warranted by toxicities. Cycles of FOLFIRINOX administration will be repeated every 14 days. 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 All dose reductions are to be made at the discretion of the treating medical oncologist.

Patients who require multiple dose reductions 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 Continuous Infusion
Initial Dose	85 mg/m ²	180 mg/m ²	400 mg/m ²	2400 mg/m ² per 46-48 hours
Level –1	65 mg/m ²	150 mg/m ²	320 mg/m ²	1920 mg/m ² per 46-48 hrs

Level –2	50 mg/m ²	120 mg/m ²	270 mg/m ²	1600 mg/m ² per 46-48 hrs
Level –3	40 mg/m ²	100 mg/m ²	230 mg/m ²	1360 mg/m ² per 46-48 hrs

Leucovorin dose is always 400 mg/m², IV given prior to bolus 5-FU. If any bolus 5-FU is to be skipped, leucovorin can be omitted or alternately can be dose-reduced and given with continuous infusion 5-FU at the discretion of the treating physician.

6.2.2.1 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 Neulasta (Pegfilgrastim) 6mg SC x1 will be administered 24-48 hours after discontinuation of continuous infusion 5-FU as clinically indicated per institutional standard of care.

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 \geq 1500, resume without dose reduction	Hold until ANC \geq 1500, resume without dose reduction	Hold until ANC \geq 1500, resume without dose reduction	Hold until ANC \geq 1500, resume without dose reduction
Neutropenia G3-4, Febrile neutropenia	HOLD ALL THERAPY, Supportive care and	Hold until ANC \geq 1500, resume @	Hold until ANC \geq 1500, resume @	Hold until ANC \geq 1500, resume @	Hold until ANC \geq 1500, resume @

(ANC 1000-500, <500)	antibiotics per institutional guidelines	permanent DL-1 level once resolved	permanent DL-1 level once resolved	permanent DL-1 level once resolved	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

6.2.2.2 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).

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

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: Do not hold oxaliplatin, but reduce oxaliplatin by one dose level for the next cycle and for all cycles thereafter.

For **grade 3 neurotoxicity** resolving to grade 2 between treatments: Do not hold oxaliplatin, but reduce oxaliplatin by one dose level for the next cycle and for all cycles thereafter.

For **recurrent grade 3 neurotoxicity** resolving to grade 2 between treatments: Do not hold oxaliplatin, but 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.

6.2.2.3 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.

6.2.2 Losartan-related side effects

6.2.2.1 Hypotension

6.2.1 Patients must demonstrate a systolic blood pressure (SBP) of greater than 100 mm Hg averaged between two resting, seated readings to qualify for study enrollment and will be started at a dose of 25 mg PO qd. They will return for a Day 8 toxicity check at which time BP will be rechecked. If SBP remains greater than or equal to an average of 100 mm Hg on two separate seated checks taken at rest, then the dose will be titrated to 50 mg PO qd. Blood pressure monitoring for study visits or urgent visits relating to hypotension should be used to determine losartan dosing. Blood pressure measurements taken for other reasons do not require losartan dose adjustments or holds. All dose adjustments and modifications are to be made at the discretion of the treating physician.

1. Week 1 Dose reduction (during 25 mg PO qd dosing). BP is not routinely checked. If patients experience lightheadedness or have any other need for vital sign check during D1-8 and SBP is less than an average of 100 mm Hg on two separate seated rested readings, hold Losartan therapy for one week. Patients should have BP recheck at Day 8. If they remain lightheaded or have persistent average SBP <100 mm Hg, they should be unenrolled from the study.

2. Week 2 onward Dose reduction (during 50 mg PO qd dosing for patients who meet criteria for escalation). BP should be checked at each chemotherapy visit and/or if a patient returns for urgent care evaluation or has symptoms of lightheadedness. If average SBP between two separate readings is less than 100 mm Hg, hold Losartan 50 mg PO qd for one week.

3. If Losartan is held, the patient should return one week later for BP recheck. If the patient had specific impetus for hypotension such as infection or dehydration that has resolved, and SBP is greater than an average of 100 mm Hg between two rested, seated readings on recheck, re-initiate Losartan at 25 mg PO qd. In the case where patients are eligible for re-start, patients should return one week later, and if SBP remains greater than an average of 100 mm Hg, the dose should be re-escalate dose to 50 mg PO qd.

4. If Losartan is held in patients at the 50 mg PO qd dose and when they return for recheck, they have sustained low BP (average SBP <100 mmHg), or sustained symptoms of lightheadedness, Losartan should be permanently discontinued and the patient un-enrolled from the clinical trial.

6.2.2.2 Hyperkalemia

For patients with serum potassium registering greater than or equal to 5.0 mmol/L at any time during treatment cycle (i.e. at any lab check), please first verify that the tube was not hemolyzed. If the potassium result is accurate, Losartan at its current dose should be held. Serum potassium should be checked one week later. Treatment may resume at current dose if serum potassium is less than 4.5 mmol/L. If patients have recurrent hyperkalemia after restarting Losartan (K > or equal to 5.0 mmol/L), the drug should be permanently discontinued and patients will be unenrolled from the study, Treatment of severe hyperkalemia as per routine clinical protocol. All dose adjustments are to be made at the discretion of the treating physician.

6.2.3 Capecitabine and Radiation

Hematologic and Non-Hematologic Toxicity

Capecitabine will be held for any Grade 3 or 4 toxicity. After toxicity resolves to \leq 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 \leq 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.

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

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.

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.

Drug Interactions

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

7.2 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.

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.

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.

7.5 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° C (77° F); excursions permitted to 15° to 30° C (59° to 86° F), keep bottles or storage devices tightly closed.

Compatibility: 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 (see section 4.1.3). 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.

7.6 Losartan

Supply

Losartan will be study supplied for this trial. Study participants will receive Losartan free of charge.

Availability

Losartan will be study supplied in 25mg and 50mg tablets. Study participants will be asked to return unused pills at each follow up visit. Pill counts will be conducted to maintain drug accountability. Once counted, unused pills will be returned to the Research Pharmacy for destruction.

Onset and Duration

Hypertension, oral: 6 hours (Ohtawa et al, 1993a; Weber, 1992). In some studies, the maximal effect occurred in 3 to 6 weeks (Prod Info Cozaar(R), 2000).

Once-daily oral doses of LOSARTAN 50 to 150 mg have produced significant antihypertensive effects for 24 hours (Tsunoda et al, 1993a; Weber, 1992). This was not achieved with lower doses (10 or 25 mg), which were similar in efficacy to placebo (Weber, 1992). Peak and trough responses (adjusted) following 8 weeks treatment with 3 dose levels

are summarized, showing a lack of clearly distinguishable differences (Elliott, 1998):

Losartan dose	Change in Blood Pressure mmHg	
	Peak	Trough
50 mg	13.5/7.2	9.5/4.8
100 mg	11.9/5.7	5.9/4.4
150 mg	11.7/7.5	6.8/4.1

Metabolism

Liver, 14% : LOSARTAN is extensively metabolized by cytochrome P450-2C9 and -3A4. Metabolites include 5-carboxylic acid (E-3174), (active). Animal studies have suggested that E-3174 is up to 40 times as potent as LOSARTAN in angiotensin II blocking activity. Although LOSARTAN is also pharmacologically active, E-3174 appears responsible for the prolonged hypotensive effects observed after oral LOSARTAN administration.

Storage and Stability

Protect tablets from light in a tightly closed container stored at controlled room temperature of 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) (Prod Info Cozaar(R), 2002). Shelf life stability is 3 years from the date of packaging although the commercially available products carry 18 month expiration dating (Tech Info Cozaar(R), 1995).

Administration

Patients will self-administer Losartan tablets at 25mg PO QD or 50 mg PO QD. Blood pressure monitoring will occur in the clinic, and dose modification based on serial low blood pressure will be per toxicity guidelines at the discretion of the treating physician (section 6).

Drug Interactions (major)

Lithium

Interaction Effect: an increased risk of lithium toxicity (weakness, tremor, excessive thirst, confusion) There is evidence that angiotensin II receptor antagonists may substantially increase steady-state plasma lithium levels, sometimes resulting in lithium toxicity. Patients prescribed lithium and losartan should be closely monitored for the development of lithium toxicity. Plasma lithium levels should also be followed.

Naproxen and other NSAIDS

Interaction Effect: decreased antihypertensive effects and an increased risk of renal impairment. Reports indicate that the concomitant use of an NSAID with an angiotensin II receptor blocker (ARB) may decrease the antihypertensive effect of the ARB (Prod Info CELEBREX(R) oral capsules. Additionally, renal deterioration and acute renal failure may result , especially in volume-depleted patients. Renal function should be monitored periodically in patients receiving ARB and NSAID therapy

8 OPTIONAL CORRELATIVE STUDIES

8.1 Laboratory Correlative Studies

8.1.1 Circulating Biomarkers: Anti-fibrotic effects

In pre-clinical and clinical studies circulating levels of collagen or profibrogenic molecules are used as surrogate biomarkers of the efficacy of RAS inhibition or other anti-fibrotic agents. We will determine how losartan affects plasma levels of ATII, collagen I and IV, and downstream mediators of ATII signaling [transforming growth factor β 1 (TGF β 1), connective tissue growth factor (CTGF), thrombospondin-1 (TSP1), osteopontin] and profibrogenic cytokines [stromal derived factor-1 α (SDF-1 α), interleukin (IL)-1 β , IL-4, IL-10, and IL-13]. Granulocytes are a major source of TGF β in PDAC. Therefore, we will measure how losartan affects the number of granulocytes in peripheral blood using flow cytometry and CBC. Because losartan modulates the levels of vascular endothelial growth factor (VEGF) and angiogenesis, we will also determine the circulating levels of angiogenic molecules. The changes in plasma biomarkers will be correlated with therapeutic response, outcome, tumor uptake of ^{18}F -5FU and microvascular imaging parameters (see section 8.1.2).

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.

Blood samples will be collected on Day 1, 8, 29 and 92. The day 29 and 92 blood draws may be completed +/- 3 days from their scheduled date. Blood can be drawn for this study at any time most convenient for the study participant.

Based on findings from preliminary studies, we propose here to evaluate the changes in blood circulating SDF1 α 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.). We will use ELISA kits to measure plasma levels of collagen I (Cosmo Bio Co.), collagen IV (Echelon BioSciences Inc), human cross-linked carboxy-terminal telopeptide of collagen I (Cusabio), ATII (Assaypro), CTGF, TGF β 1, TSP-1, osteopontin, soluble vascular endothelial growth factor receptor 2, angiopoietin 2 and SDF-1 α (R&D Systems). Multiplex ELISA plates (Meso-Scale Discovery) will be used to analyze plasma levels of VEGF, placenta growth factor (PlGF), soluble VEGF receptor 1 (sVEGFR1), basic fibroblast growth factor (bFGF), VEGF-C, VEGF-D, sTie2, tumor necrosis factor alpha (TNF- α), and IL-1 β , IL-4, IL-10, and IL-13. Granulocytes (CD11b+Ly6G+CD115-) will be enumerated in fresh samples using a standard flow cytometry protocol. In addition, we will analyze the correlation between plasma SDF1 α and circulating myeloid cells with multiple measures of outcome (ORR, TTP, OS) in pancreatic cancer patients after losartan treatment.

8.1.2.1 Experimental Design

Blood for correlative research may be drawn via port-a-cath or peripheral venipuncture. The blood draw site should remain consistent across all correlative lab timepoints for each patient throughout their participation in the trial. The first 7-10 ml blood will be excluded or used for other analyses. 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 cytokines and circulating myeloid cells with multiple measures of outcome (ORR, TTP, OS) in patients with borderline resectable pancreatic cancer before, during, and after treatment.

8.1.2.2 Collection

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

- (i) Pretreatment
- (ii) Throughout FOLFIRINOX therapy, including at restaging for C4 and C8
- (iii) After proton beam radiation therapy
- (iv) One month after completion of capecitabine therapy
- (v) One month post-operatively
- (vi) At the time of disease progression

Samples (2 tubes) will be collected at the following timepoints:

- a. Prior to the start of therapy
- b. Day 8 , 29, and 92 of FOLFIRINOX
- c. At restaging for Cycle 4 (and Cycle 8 if received) of FOLFIRINOX
- d. After chemoradiation OR pre-operatively
- e.. 1 month after completion of capecitabine therapy
- f. 1 month after pancreaticoduodenectomy (Whipple procedure)
- g. Within 2 weeks after radiologic progression

8.1.2.3 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:

Steele Laboratory
Cox-734
100 Blossom Street
Boston, MA 02114
Tel: 617-724-1352/3
Fax: 617-724-5841
Pager: 14082

8.1.2 Correlative Studies: SNaPshot analysis

Diagnostic specimens (if available) will be tested using the “SNaPshot” profile, a multiplex molecular diagnostics platform which is part of routine clinical testing at the MGH Cancer Center. This assay quickly and efficiently identifies 58 separate mutations in 13 genes commonly altered in solid tumors: EGFR, KRAS, NRAS, APC, BRAF, FLT3, JAK2, Kit, Notch, PI3K, PTEN, TP53, and beta-catenin. It utilizes DNA extracted from formalin fixed paraffin embedded tumor tissue. The DNA of interest is amplified using multiplexed PCR. Genotypes are determined using a single-base extension sequencing reaction, in which allele-specific probes interrogate loci of interest and are extended by fluorescently labeled dideoxynucleotides. The allele-specific probes have different sizes and are subsequently resolved by electrophoresis and analyzed by an automated DNA sequencer. The SNaPshot profile has been validated and is being performed in a CLIA-certified lab.

Data obtained from SNaPshot will be used in exploratory analyses correlating mutational status with chemotherapy response, radiation response, and outcome.

8.2 Patient-reported outcomes

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

8.2.1 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. During the follow up period, these measures will be assessed at the 3 month post-operative follow-up visit, then every 6 months for the first 2 years of follow up, then yearly until completion of year 5. We will include a window of +/- 2 weeks for obtaining the PROs during treatment, to cover timing adjustments for treatment delays. In follow up, these outcomes will be assessed within +/- 21 days of a correlating follow up visit. The patient may complete the questionnaires by hand or over the phone with a study team member, as well as an interpreter (if needed).

8.3 Health care utilization

Hospital admissions, emergency department (ED) visits, intensive care use and palliative care consultation will be monitored and recorded for each patient throughout the study.

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 ≤ 42 days (6 weeks) prior to study entry. All 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 treatment	Cycles 1-8 of FOLFIRINOX/Losartan	After cycles 4 and 8 of FOLFIRINOX/Losartan (re-staging) (5)	Radiation	Follow Up Post-Proton RT (2)
Signed informed consent	X				
History	X				
Physical Examination	X	X once per cycle	X	X weekly	X
Vital Signs and performance status	X	X once per cycle	X	X weekly	X
Height/Weight/Surface Area	X	X once per cycle			
Blood Pressure Assessments and Monitoring	X	X once per cycle			
Toxicity Assessment	X	X weekly during cycle 1; every other week during subsequent cycles unless clinically indicated	X	X weekly	X
Laboratory :					
CBC/plts/diff	X (1)	X weekly during cycle 1; every other week during subsequent cycles unless clinically indicated	X	X weekly	X
Serum chemistries (Na, K, BUN, Cr, Glucose, , Calcium, Albumin, AST, ALT, Total bilirubin, Alkaline phosphatase)	X (1)	X weekly during cycle 1; every other week during subsequent cycles unless clinically indicated	X	X weekly	X

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Tests and Observation	Prior to treatment	Cycles 1-8 of FOLFIRINOX/Losartan	After cycles 4 and 8 of FOLFIRINOX/Losartan (re-staging) (5)	Radiation	Follow Up Post-Proton RT (2)
Creatinine clearance calculation (Cockcroft Gault)	X (1)	X weekly during cycle 1; every other week during subsequent cycles unless clinically indicated	X	X D1 and D8 of capecitabine	
CA19-9	X (1)	X Monthly	X		X
CEA	X (1)	X Monthly	X		X
Pregnancy test*	X (1)				
Research Blood for Correlative Analysis: Antifibrotic Effect (6)		X D1 (pre-treatment), D8, D29, and D92			
Tumor submitted for SNaPSHOT mutational analysis	X				
Staging:					
Chest CT Abd-pelvic CT (or MRI)	X (3)	X Mid-treatment and post-treatment	X		X (4)
Radiation Planning				X prior to RT start	
Tumor measurements (8)	X		X		X
PRO (EORTC QLQ-C30, ESAS-r, HADS) (7)	X	X	X	X	X

Notes

- (1) Pre-study Laboratory values need to be obtained within 7 days of study entry.
- (2) Post-study follow up schedule is clinic visit and labs every three months until disease progression. The first visit will be 1 month after surgery. Then follow up visits will be every 3 months. CT scans will be at least every six months for the first two years and yearly for years 3-5. All follow up assessments will be performed +/- 21 days of protocol-specified date.
- (3) Staging CT or MRIs need to be obtained within 42 days of study entry
- (4) CT scans will be performed at least every 6 mo for the first 2 years and yearly for years 3-5. All follow up CT scans will be performed +/- 21 days of protocol-specified date
- (5) Restaging scans can be performed after pump disconnect during FOLFIRINOX cycles 4 and 8.

- (6) Blood for correlative studies will be obtained with clinical labs at pretreatment, day 8 of Cycle 1 FOLFIRINOX, at mid-FOLFIRINOX restaging, at post-FOLFIRINOX restaging, after chemo radiation therapy, 1 month after completion of capecitabine therapy, 1 month post-operatively (if surgery is performed), and within two weeks of radiographic progression (these blood draws are optional).
- (7) See section 8.2 for patient reported outcomes assessment timing.
- (8) Tumor measurements will be completed within +/-6 months of the scans. These measurements will be completed by the overall PI of the study.

10 MEASUREMENT OF EFFECT

10.1 Evaluation Of Response

10.1.1 Imaging Response: Standard Imaging

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 Progression-free survival

Progression-free survival will be defined as the time from the start date of protocol therapy 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.

10.1.3 Time to death

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

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 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 Duration of Response

10.6.1 Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

10.6.2 Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

10.6.3 Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

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 severe 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

For the purposes of this study, the following grade 4 toxicities are expected in the setting of dehydration, diarrhea or reduced oral intake and will not require expedited serious adverse event reporting: low magnesium, low potassium, and low phosphorus. The following grade 4 toxicities are expected and will not require expedited serious adverse event reporting: low white blood cell count, and neutropenia.

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.

Except as described in Section 4.2.1.5, 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 unless expected AND specifically listed in the protocol as not requiring expedited 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.

617-724-1159, email tshong1@partners.org, fax 617- 726-3603

Within the following 24-48 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.

Phone: 617-726-6050, Email : tshong1@mgh.harvard.edu, Fax : 617- 726-3603

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 ODQ

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 FOLFIRINOX-Losartan therapy
Chemoradiation Treatment Form	Within 10 days of completion of combined capecitabine and proton radiation
Toxicity/Adverse Event Report Form	Every two weeks during FOLFIRINOX - Losartan; weekly during chemoradiation; and within 14 days of protocol defined follow up visit
Surgery/Pathology Form	Within 14 days of surgery, if applicable
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

14.2 **The single-arm protocol is a phase II study to investigate combining Losartan with FOLFIRINOX for induction chemotherapy followed by restaging and radiation therapy with capecitabine in the treatment of patients with locally advanced pancreatic cancer. The primary endpoint is the rate of R0 (negative margin) resection determined by final pathology of the surgical specimen. Our historical data show a <10% rate of R0 resection among unresectable patients treated with induction chemotherapy followed by chemoradiation. The protocol will have demonstrated an improvement in efficacy if R0 resection were achieved in at least 9 of 50 patients. The decision rule is associated with 91% power if FOLFIRINOX-Losartan with short-course radiation and capecitabine were to improve the R0 resection rate to 25%. In contrast, the probability of a type 1 error is only 6% if the underlying rate of R0 resection were truly the same as the historical level of 10%. All protocol patients who start induction chemotherapy will be included in the denominator for R0 resection analysis, including those who do not undergo surgery due to early progression or other reasons. Sample Size/Accrual Rate** The accrual goal of 50 patients is projected to be enrolled over a total period of 4.5 years. The estimate is based on the overall rate of accrual based on the first 32 patients since the protocol was first open to patient entry. Therefore, we project the enrollment of the remaining 18 patients will require no more than 1.5 years.

14.3 Analysis of Secondary Endpoints

- 14.3.1 **Progression-free survival:** All patients who start induction chemotherapy will be analyzed based on the definition in Section 10.1.2. The progression-free survival duration of patients who are alive and progression will be censored at their date of last follow-up. The Kaplan-Meier method will be used to estimate progression-free survival with 90% confidence intervals constructed by Greenwood's formula.
- 14.3.2 **Overall survival:** Overall survival will be defined as the duration between the start date of protocol therapy and death. The survival time of patients who are not known to have died will be censored at the date they are last known to be alive. The Kaplan-Meier method will be used to estimate overall survival estimation with 90% confidence intervals constructed by Greenwood's formula.
- 14.3.3 **Toxicities:** All patients who begin induction chemotherapy will be included in the toxicity profile of Losartan combined with induction FOLFIRINOX. Summaries of toxicities will include the frequency and proportion of patients experiencing each toxicity, as well as summaries by toxicity category and toxicity grade. We shall report separately the additional treatment-related toxicity following radiation in patients who do not have progressive disease at the restaging interval after induction chemotherapy.
- 14.3.4 **Downstaging:** A fraction of patients may proceed to surgical resection following the conclusion of protocol therapy if the tumor shrinkage were sufficient to be considered resectable. The rate of downstaging to surgical resection will be determined as the proportion of initially unresectable patients who eventually undergo pancreaticoduodenectomy or distal pancreatectomy. The pathologic downstaging rate will be calculated as the proportion of resected patients with the primary tumor and nodes downstaged based on final pathology of the surgical specimen.
- 14.3.5 **Correlation of biomarkers with outcome:** Correlative studies will be conducted to characterize circulating collagen and angiogenesis biomarkers (8.1.1), as well as somatic genetic mutations characterized by the SNaPshot platform (8.1.2). Due to the modest patient numbers, analysis will be limited generally to two-group comparisons of each

biomarker. Continuous values will be dichotomized at the median or a biologically meaningful threshold. The logrank test will be used to assess differences in progression-free survival and overall survival by biomarker status if at least 5 failure events have been observed within each subgroup. The correlative analysis will be purely exploratory due to the limited numbers expected per biomarker subgroup. In particular, analysis will be descriptive when the frequency of a genetic mutation is low.

14.3.6 ***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.

14.3.7 ***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.

4.3 Reporting and Exclusions

All patients who begin protocol treatment will be included in the primary and the relevant secondary endpoints.

15 PUBLICATION PLAN

The results will be made public within 24 months of the end of data collection for the primary objective. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical

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Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of data collection.

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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 to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		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.

OTHER MEDICATIONS TAKEN

If you take a daily medication (prescribed or otherwise), please use one line per drug and indicate the start and stop dates under the "Date(s) Taken" section (i.e., 6/2/09 - 6/5/09).

Drug Name	Dose	Dates Taken	Reason Taken

FOR STUDY TEAM USE ONLY	
Staff Initials:	
Date diary was given:	Date returned:
# pills/caps/tabs that should have been taken:	
Discrepancy Notes:	

Investigator signature: _____

Date: _____

<p>Study Participant Self-Administration Study Drug Diary Dana-Farber/Harvard Cancer Center</p>
--

Participant Identifier: _____

Protocol #: 13-051

Your MD _____ Phone _____

Your NP _____ Phone _____

STUDY DRUG INSTRUCTIONS:

Study Drug: Capecitabine (Xeloda)

How Much: Your capecitabine dose is ____ mg twice daily.

How Often: Capecitabine is taken twice daily.

When: Take capecitabine Monday through Friday during weeks 1 and 2 of chemoradiation treatment.

SPECIAL INSTRUCTIONS:

1. Capecitabine comes in the form of tablets
2. Take tablets for a total of 10 days Monday-Friday.
3. Medication should be taken with 8 oz of water within 30 mins after the end of a meal or snack.
4. Tablets may be crushed if necessary
5. If you miss a dose, do NOT take an additional or make-up dose. If you vomit around the time you take the medicine, do not take additional doses. A dose is considered missed if it is 10 hours after the time it is usually taken.
6. If you have any comments or notice any side effects, please record them in the comment column and bring these forms with you to your next appointment.



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 <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> 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 <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> 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

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

Patient's Name _____

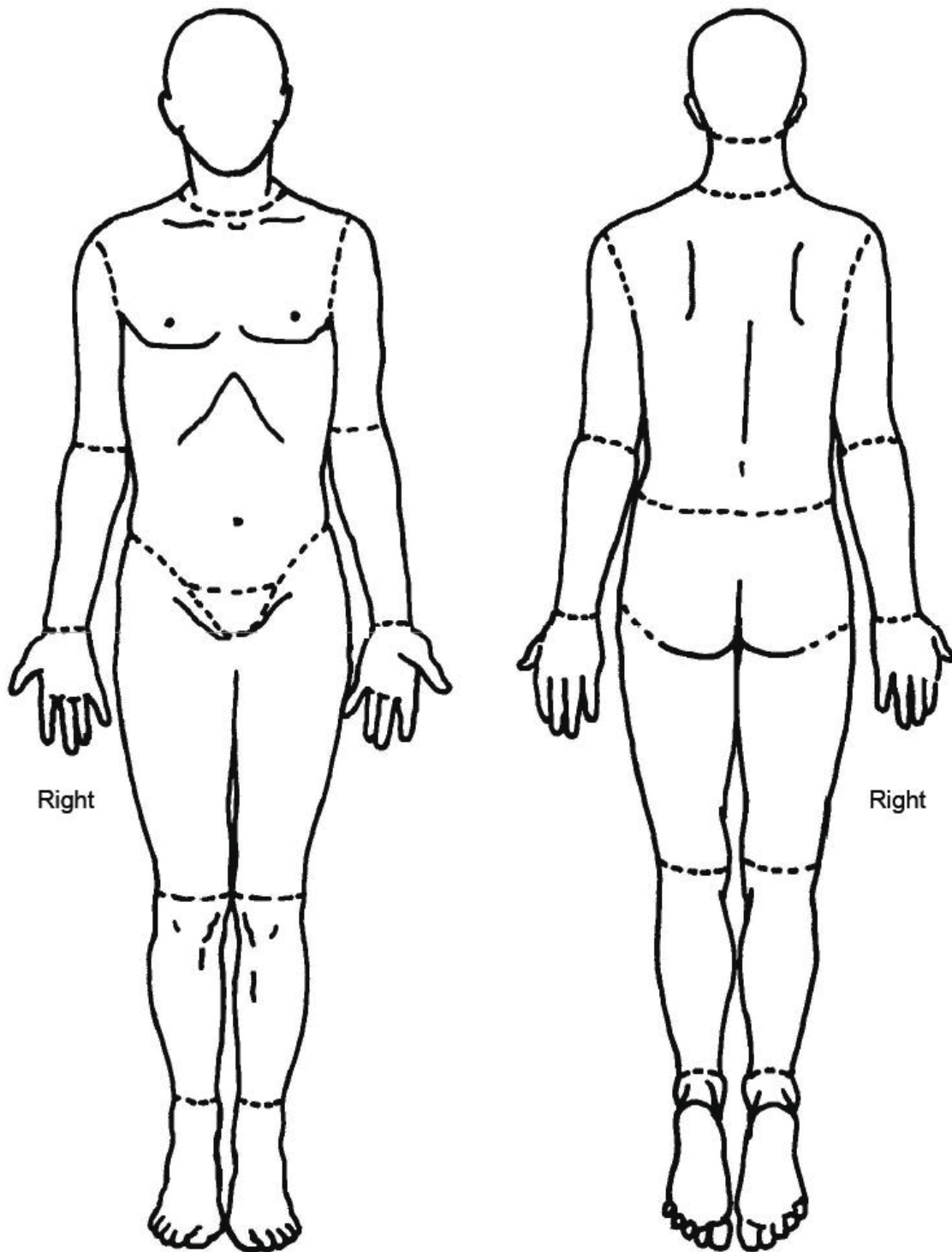
Date _____ Time _____

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)



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		3
2		A lot of the time		2
1		From time to time, occasionally		1
0		Not at all		0
		I still enjoy the things I used to enjoy		
0		Definitely as much		0
1		Not quite so much		1
2		Only a little		2
3		Hardly at all		3
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		3
2		Yes, but not too badly		2
1		A little, but it doesn't worry me		1
0		Not at all		0
		I can laugh and see the funny side of things		
0		As much as I always could		0
1		Not quite so much now		1
2		Definitely not so much now		2
3		Not at all		3
		Worrying thoughts go through my mind		
3		A great deal of the time		3
2		A lot of the time		2
1		Not too often		1
0		Very little		0
		I feel cheerful		
3		Never		3
2		Not often		2
1		Sometimes		1
0		Most of the time		0
		I can sit at ease and feel relaxed		
0		Definitely		0
1		Usually		1
2		Not often		2
3		Not at all		3
		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

TOTAL

A	D
<input type="text"/>	<input type="text"/>

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This edition first published in 1994 by nferNelson Publishing Company Ltd,
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