PAN009-18
A Phase II Trial of Escalated Dose Proton Radiotherapy with Elective Nodal Irradiation and Concomitant Chemotherapy for Patients with Unresectable, Borderline Resectable or Medically Inoperable Pancreatic Adenocarcinoma

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PROTOCOL SIGNATURE PAGE

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Protocol Version: March 18, 2018

I certify that I have read the protocol. I agree to conduct the protocol according to ethical principles stated in the Declaration of Helsinki, the applicable guidelines for Good Clinical Practice, or the applicable laws and regulations, whichever provides the greatest protection of the individual. I will accept the monitor's oversight of the study.

_____ _____

Signature of the Site Principal Investigator **Date**

_____

Principal Investigator's Printed Name

_____

Name of Facility

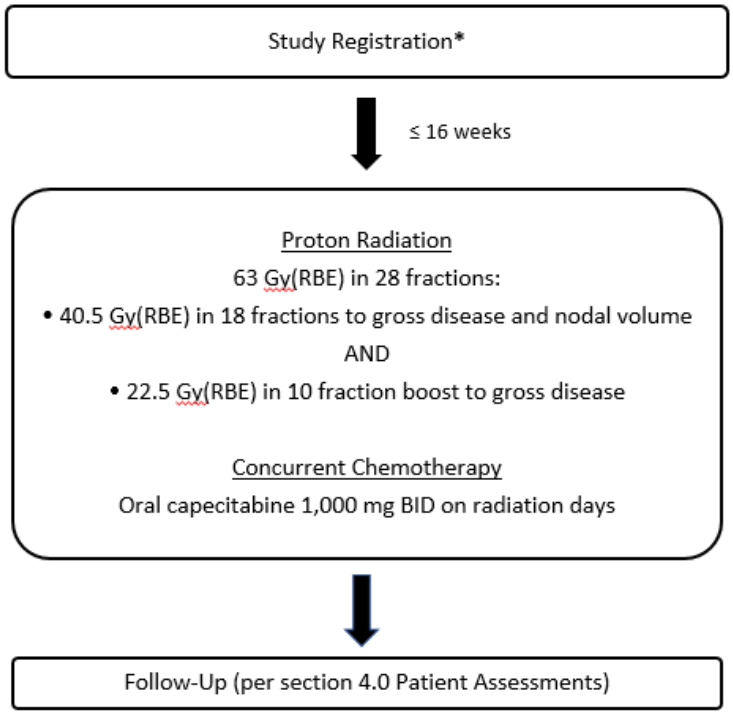
_____

Location of Facility (City, State)

PLEASE COMPLETE AND SEND TO THE PROTON COLLABORATIVE GROUP OFFICE VIA EMAIL: HQ@PCGRESEARCH.ORG

INDEX

SCHEMA



* Prior chemotherapy is allowed.

Patient Population: Unresectable, borderline resectable, medically inoperable or refusing surgery for pancreatic adenocarcinoma

Eligibility Criteria (see section 3.0 for complete eligibility):

- Biopsy proven adenocarcinoma of the pancreas that is unresectable, borderline resectable, medically inoperable, or patient refusing surgery.
- ECOG Performance Status 0-2 within 8 weeks prior to study registration.
- No evidence of metastatic disease, including ascites and/or peritoneal seeding.
- No previous irradiation to the abdomen.
- No prior surgical resection of pancreatic cancer.

Required Sample Size: 60 patients

1.0 INTRODUCTION/BACKGROUND

1.1 Rationale for Intensification of Local / Regional Therapy

The prognosis for patients with localized pancreatic adenocarcinoma who are not surgical candidates is poor. The median survival for patients with unresectable disease enrolled on the LAP-07 trial was between 15.2 and 16.4 months.[1] Patients characterized as having "borderline resectable" disease treated with preoperative chemo-radiotherapy fair somewhat better - although many of these patients are not converted to resectability. A retrospective study from M.D. Anderson Cancer Center (MDACC) looking at 125 patients with borderline resectable disease receiving neoadjuvant therapies found that resections were only performed in 66 patients. Median survival was 40 months in the resected patients but only 13 months for the unresected patients.[2] Comparable data from Mayo clinic for patients with locally advanced disease treated with preoperative chemo-radiotherapy demonstrated a median survival of 23 months after an R(0) resection but only 10 months if extirpative surgery could not be performed.[3]

It may be argued that intensification of local/regional therapy might 1.) Increase the share of patients able to undergo curative surgery and 2.) Improve the local disease control interval and extend survival for patients who remain unresectable.

A phase II study for patients with unresectable disease treated with proton therapy to a dose of 59.4 Gy (RBE) with concomitant low-dose oral capecitabine demonstrated an encouraging 18.4 month median survival and a 69% two year freedom from local progression.[4] Four of eleven patients achieved a radiographic response deemed adequate to justify surgical exploration. Three of these patients were resected and achieved local control of disease. In spite of the aggressive radiotherapy dose delivered, no patient on this study demonstrated any grade 2 or greater gastrointestinal toxicity – suggesting that further intensification of treatment with protons would be feasible. Surgical complications for patients converted to resectability were comparable to those historically experienced by patients who underwent surgery without prior radiotherapy.[5]

The current protocol, based on the excellent tolerance demonstrated in the aforementioned phase II study, offers a 6% increase in total radiotherapy dose with a 25% increase in dose per fraction with the goal of improving local control and extending survival for this group of patients.

1.2 Rationale for Selective Inclusion of Elective Lymph Node Targets

Regional lymph node metastasis is a common finding in patients undergoing curative surgery for resectable pancreatic cancer. The data from Johns Hopkins reviewing the pathology on 905 patients undergoing pancreaticoduodenectomy between 1995 and 2005 showed a 79.3% lymph node positivity rate and a 41.1% margin positivity rate.[6] The data from Memorial Sloan-Kettering Cancer Center in New York reviewing 625 patients undergoing pancreaticoduodenectomy between

2000 and 2009 showed a 70% lymph node positivity rate and a 16% margin positivity rate .[7]

In spite of this high risk of lymph node positivity for patients deemed resectable–a rate which we might expect to be higher for patients with initially unresectable disease – historically, there was limited interest in electively irradiating nodal sites for the initially unresectable patients. Given the encouraging local control and conversion to operability data seen in our pilot study, it can be argued that treating these regional lymph nodes would be oncologically relevant. While, historically, elective nodal irradiation might be inadvisable with x-rays due to the increased volume of normal tissues exposed, the publication by Lee et al.[8] suggests that, using protons, it is possible to expand the treatment volume to cover these elective targets without significantly increasing the volume of critical normal tissue exposed.

In summary, our dosimetric data suggests that elective lymph node irradiation can be done with acceptable toxicity. Given the high rate of conversion of unresectable patients to resectable, we believe that expansion of the radiotherapy to treat these elective lymph nodes may improve regional disease control and perhaps, improve survival expectation.

1.3 Rationale for Elective Nodal Volume Treated

The rationale for the elective nodal volume treated is based on a publication from Johns Hopkins University[9] evaluating pattern of regional treatment failure for 202 patients undergoing pancreaticoduodenectomy. In this study, 90% of recurrences occurred within the volume utilized in this protocol.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 Improve 12 month survival from 50% to 75%.

2.2 Secondary Objectives

2.2.1 Collect and analyze tumor control outcomes:

a. Improve local control
b. Improve regional disease control

2.2.2 Increase share of marginally resectable and unresectable patients being converted to resectable.

2.2.3 Compare GI toxicity of protocol therapy with historical benchmarks.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 One of the following:

- Biopsy-proven unresectable adenocarcinoma of the pancreas as defined by:
  - Greater than 180 degree encasement of the superior mesenteric artery (SMA)
  - Encasement of the celiac axis, hepatic artery, and/or left gastric artery
  - > 180 degree involvement or obstruction of the superior mesenteric vein (SMV); SMV resection and reconstruction is not feasible
  - No evidence of metastatic disease in major viscera (organs), distant metastatic disease, and/or peritoneal seeding.

OR

- Biopsy-proven borderline resectable adenocarcinoma of the pancreas defined by:
  - Abutment up to 180 degrees on the SMA
  - > 180 degree involvement or obstruction of the SMV; SMV resection and reconstruction is feasible
  - Regional lymph node metastases
  - No evidence of metastatic disease in major viscera (organs), distant metastatic disease, and/or peritoneal seeding.

OR

- Patients with resectable, biopsy-proven adenocarcinoma of the pancreas who are deemed medically inoperable or who refuse surgery.

3.1.2 ECOG Performance Status 0-2 within 8 weeks prior to registration.

3.1.3 Required laboratory parameters within 12 weeks prior to study registration:

- Absolute granulocyte count (AGC/ANC) $\geq$ 1.8 thou/mm^3
- Platelet count $\geq$ 100,000/mm^3
- Bilirubin < 2 mg/dl
- ALT/SGPT < 3x upper limit of institutional normal
- Creatinine < 3 mg/dl

3.1.4 Patient must give study specific informed consent on an IRB-approved consent prior to any research-related procedures or study treatment.

3.1.5 Patient must be at least 18 years of age at the time of consent.

3.2 Ineligibility Criteria

3.2.1 Evidence of distant metastasis; metastatic disease in the major viscera (organs); peritoneal seeding.

3.2.2 Previous irradiation to the abdomen.

3.2.3 Prior surgical resection of pancreatic cancer.

3.2.4 Previous history of invasive malignancy (except non-melanoma skin cancer and low to intermediate risk prostate cancer) unless the subject has been disease free for 5 years prior to registration.

3.2.5 Active, untreated infection.

3.2.6 Pregnant and/or breast-feeding women, or patients of child-producing potential not willing to use medically acceptable contraception while on treatment and for at least 12 months thereafter.

3.3 Inclusion of International Subjects

Patients from outside of the United States may participate in the study. Enrollment and treatment must be completed at an approved PCG member institution in the United States.

4.0 PATIENT ASSESSMENTS

Assessments	Pre-Registration	Pre-Treatment	Weekly During Chemo-RT	Follow-Up (From RT End Date)	
				1 Month (+/- 2 weeks)	Every 3 Months (+/- 1 months)
History & Physical[d]	X within 8 wks		X	X[c]	X[c]
ECOG Performance Status	X within 8 wks		X	X	X
Weight	X within 8 wks		X	X[c]	X[c]
Biopsy of Tumor	X				
Physician Clinical Stage Documentation	X within 8 wks				
Examination per Medical Oncology	X within 8 wks		X[e]	X[e]	
Adverse Event Evaluation (CTCAE)		X	X	X	X
Pill Diary Review		X	X		
PET CT (preferred) **OR** CT of chest, abdomen, and pelvis with contrast	X within 8wks			X[c]	X[c] every 6 months +/- 2 months
Nuclear medicine Renal Scan[c]	X within 8 wks				
Planning 4DCT w/ contrast unless contraindicated (≤ 2.5mm cuts preferred)		X			
Non-contrast CT (4DCT or ABC)			X		
CBC w/ Diff	X[a] within 12 weeks		X[e]		
CMP w/ LFTs	X[a] within 12 weeks		X[e]		
CA 19-9 Tumor Marker	X within 12 weeks				X[c] every 6 months +/- 2 months
Prealbumin[c]	X Within 12 weeks		X		
Pregnancy Test, serum or urine	X[b] within 14 days				
Drainage of Biliary Obstruction (required if present)		X			

a. Repeat within 48 hrs prior to treatment if clinical evidence of patient deterioration per physician discretion.
b. Pregnancy testing is not necessary for women who have had a hysterectomy or have not had a menstrual period for at least 24 consecutive months (documentation required).
c. Highly recommended, not required.
d. RadOnc pre-registration and during treatment. During follow-up, can be any medical professional.
e. At Medical Oncologist discretion.

4.1 Follow-Up Visits

Follow-up visits are based on the time from the end date of radiation treatment. It is highly recommended that patients will be seen in person by the treating investigator for all follow-up visits. If subjects refuse to return to the clinic for other follow-up visits, they must be contacted by phone to obtain information needed for data collection, or information from their visits with other physicians can be used to collect the necessary follow-up information. Collaborating medical records must be obtained if information from visits with other treating physicians is being used to fulfill the follow-up visit requirement. Follow-up assessments performed with the patient over the phone will be sufficient to fulfill the follow-up visits requirements related to obtaining adverse event information and performance status. Any failure to contact subjects for follow-up must be clearly documented in the source record.

4.2 Criteria for Removal from Protocol Treatment (reason must be clearly documented)

4.2.1 Progression of disease during study treatment.

4.2.2 Any serious adverse events or life threatening events where the DSMB (data safety monitoring board) or the Investigator do not deem it is in the patient's best interest to continue on protocol treatment.

4.2.3 Intercurrent, non-cancer-related illness that prevents continuation of therapy.

4.2.4 Changes in a patient's condition that renders the patient unacceptable for further treatment in the judgment of the investigator.

4.2.5 The patient may withdraw from the treatment at any time for any reason.

4.3 Criteria for Removal from the Protocol (reason must be clearly documented)

4.3.1 Major protocol deviation or discovery of information that, if previously known, would have rendered the patient ineligible for study.

4.3.2 The patient may withdraw from the study at any time for any reason.

4.3.3 Intercurrent, non-cancer-related illness that prevents regular follow-up.

5.0 REGISTRATION PROCEDURES

5.1 PCG headquarters must have documentation of each institution's IRB approval of the protocol on file prior to registering patients.

5.2 Verification that the patient meets the eligibility criteria must occur prior to registering the patient. The protocol-specific eligibility checklist provided in the Study Procedures Manual (SPM) must be used to document eligibility and placed in the participant's medical/research record. To be eligible for

registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.

5.3 Patients must be registered through the PCG Electronic Data Capture (EDC) system.

5.4 Treatment plans for the initial 3 cases from the institution will be centrally reviewed by a PCG Medical Physicist and the Study Chair or designee prior to start of treatment. Further cases from the institution may also be reviewed periodically for quality assurance. See the Study Procedures Manual (SPM) for details.

6.0 RADIATION THERAPY

6.1 Dose Specification

6.1.1 The dose will be 40.50 Gy relative biological effectiveness (RBE) in 18 fractions to PTV1 (expansion should be added on the CTV1 as defined below, to compensate for setup tolerances and intra and inter-fraction motion changes due to variable bowel filling and changes in breathing pattern not accounted for in iGTV).

CTV1 to include a Boolean union of:

- Gross tumor (iGTV, as defined below), and
- Elective lymph node regions defined by a 2 cm expansion on the combined celiac artery (CA) (most proximal 1 cm from its origin at the aorta) and superior mesenteric artery (SMA) (most proximal 2.5 cm from its origin at the aorta).

Ninety-five (95) % of PTV1 should receive 100% of the prescribed dose and 100% PTV1 should receive 95% of the prescribed dose.

6.1.2 The dose will be 22.5 Gy (RBE) in 10 fractions to PTV2 (expansion should be added on the iGTV as defined below, to compensate for setup tolerances and intra and inter-fraction motion changes due to variable bowel filling and changes in breathing pattern not accounted for in iGTV).

Plan exclusion of duodenum and combined bowel/gastric space from the boost volume if necessary to meet normal tissue constraints.

Ninety-five (95) % of PTV2 should receive 100% of the prescribed dose and/or 100% PTV2 should receive 95% of the prescribed dose, with exception that PTV2 coverage may be reduced after 40.5 Gy (RBE) as described above to respect organs at risk (OAR) doses.

6.2 Simulation and Immobilization

6.2.1 Patients will be immobilized for treatment according to institutional standards for treating pancreatic cancer, but recommendations are for arms

folded over head (as tolerated). Vacuum bags may be used to improve patient setup reproducibility.

6.2.2 Assisted breathing coordinator (ABC) or comparable device may also be used to minimize organ motion due to respiration.

6.2.3 Patients may undergo placement of internal fiducial markers in the pancreas gland for optimal target localization. Biliary stents and/or surgical clips which are localizable on CT scan may be used for image guidance although fiducial markers are preferred.

6.2.4 Planning CT scans should be done at ≤ 2.5 mm intervals.

- If available or used, an ABC scan should be performed with moderate breath hold (70% of maximum breath hold) 3 times in treatment position to verify reproducibility.
- 4D scan (required) should then be performed with normal free breathing.
- Contrast free breathing scan should be performed with 8 oz oral contrast with an appropriate interval to allow for imaging of the duodenum.

6.3 Normal Tissue Constraints (NTC)

The following are absolute constraints. If unable to be met, coverage to PTV2 should be reduced. If still unable to meet, please contact PCG.

6.3.1 Duodenal dose limited to:
- 45 Gy (RBE) to 30 cc
- 56 Gy (RBE) to 5 cc
- 59 Gy (RBE) to 0.03 cc

6.3.2 Bowel Space / Gastric dose limited to:
- 45 Gy (RBE) to 75 cc
- 50 Gy (RBE) to 5 cc
- 58 Gy (RBE) to 0.03 cc

6.3.3 Kidney: Bilateral symmetry of renal function should be verified with a nuclear medicine scan (highly recommended). Based on the functioning nephrons identified on the scan, the equivalent of 2/3 of one functioning kidney must receive equal to or less than 18 Gy (RBE). If only a single functioning kidney is present, at least 2/3 of the functioning kidney must be excluded from any radiation port.

6.3.4 Spinal cord max point dose must be equal to or less than 45 Gy (RBE).

6.3.5 Liver mean dose must be equal to or less than 28 Gy (RBE).

6.4 Target Contouring/Treatment Technique

6.4.1 Motion assessment is mandatory for this protocol. Review stent/SMA/CA motion markers on 4DCT: If the motion marker considered to be the most representative of GTV has a maximum motion ≤ 5 mm, patient should be planned on average 4DCT and treated using free breathing technique, with image guidance localization based on bony anatomy for rotational and gross alignment, and stents for final translational corrections. DIPS setup tolerances shall be 2 mm in all directions.

a. GTV and OAR contours shall be drawn on the contrast scan.
b. The contours should then be copied to the 4DCT average scan; the physician should review and if necessary revise the contours. The revised GTV contour should always encompass the whole GTV structure as contoured on the contrast scan and copied across.
c. The GTV should then be expanded to iGTV which encompasses the GTV in every breathing phase of the 4DCT.
d. CTV to be defined with expansion from the iGTV according to 6.1.1.

6.4.2 If 6.4.1 fails, it is recommended to review ABC scans as follows:

a. Fuse the 3 ABC scans by spine segment with margins superior and inferior to the target region.
b. Perform organ motion analysis identical to the case of 4DCT over the 3 ABC scans.
c. If maximum marker movement is ≤ 70% of the maximum marker motion of 4DCT, choose ABC scans for treatment planning and delivery. If not, follow the technique in 6.4.1
d. GTV and OAR contours shall be drawn on the contrast scan.
e. The contours should then be copied to the ABC scan with marker location most representative of average marker location on the 3 ABC scans; the treating physician should review and if necessary revise the contours.
f. Review GTV geometric shape and location on contrast scan, and discuss with treating physician to resolve significant differences if observed.
g. Patient will be planned on the ABC scan with target position closest to the average position of the selected marker.
h. Treatment delivery image guidance shall be same as for free breathing, except all imaging shall be acquired with breath hold as usual.

6.4.3 Range Uncertainties

Proton plans generated for patients receiving treatments under this protocol shall implement measures to mitigate the impact of beam range uncertainties:

a. Appropriate, beam-specific distal and proximal range margins shall be used to deal with the impact of uncertainties in CT Hounsfield Unit (HU) to relative stopping power calibration, daily fluctuations of proton machine beam production, or potential patient anatomy changes over the course of treatment.

b. Beams should be planned to minimize their passage through internal organs, such as bowels and diaphragm region, as the content changes of bowels and

diaphragm motion due to breathing may cause significant beam range errors. Beams passing through these organs shall have their robustness analyzed by overriding HU values of the affected organs alternatively by air or water contents for dose distribution comparison and evaluation to meet the planning goals.

6.4.4 Contour the following OARs on the final selected image set:

- Bowel and gastric potential space (non-pancreatic, non-duodenal)
- Liver
- Kidneys

Bowel segments with presence of gas shall be contoured and their contents overridden with water HU for treatment planning dose calculation. Lung volumes within beam paths shall be reviewed for range uncertainties due to diaphragm motion, and overridden with tissue HU if necessary. A verification plan shall be calculated without overrides to verify that OAR dose limits are respected.

Daily orthogonal kV imaging guidance or Cone Beam CT (CBCT) using bony landmarks, implanted fiducials or stents should be used, if available, for alignment at the discretion of the treating physician.

6.5 Quality Assurance/Assessments During Radiation Treatment

6.5.1 Institutional QA

The initial 3 cases from the institution will be centrally reviewed prior to the start of treatment. Please refer to the Study Procedures Manual (SPM) for details.

6.5.2 Assessments during Radiation Treatment

- To assure accuracy a weekly non-contrast CT will be done. Scanning technique (4DCT or ABC) shall be identical to simulation CT selected for patient treatment delivery. Verification treatment plans shall be calculated and compared to the initial treatment plans to ensure that target and critical organ doses are preserved. PTV coverage may be reduced if verification scans suggest unacceptable normal tissue exposure. Online radiographic imaging or portal films will be performed during proton therapy. Post treatment radiographic imaging is allowed to assess intra-fraction variability of the target position.
- Weekly clinical assessment including weight, performance status, and toxicity assessment will be performed to evaluate for evidence of toxicity or progression during the entire radiation treatment course. Acute and late toxicities related to radiation and chemotherapy will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

6.6 Dose Modifications

Reduce cumulative Boost PTV dose to as low as 50 Gy (RBE) if necessary to meet normal tissue constraints.

6.7 Proton Unavailability

If proton therapy is unavailable for any reason, patient may receive Intensity Modulated Radiation Therapy (IMRT) at a maximum dose of 22.50 Gy at 2.25 Gy/fx. The decision regarding whether IMRT should be given versus waiting for proton therapy to be available should be made by the treating physician. Dose modifications and/or treatment interruptions (unplanned missed treatments) must be documented in the medical record and will be collected in the EDC system. The number of days and reason why must be documented.

7.0 DRUG THERAPY

Chemotherapy prior to proton radiation is allowed. Concurrent chemotherapy is required and will be administered at the discretion of a medical oncologist per the treatment schedule guidelines suggest below.

7.1 Capecitabine (Xeloda®) Overview

7.1.1 Formulation

Capecitabine is supplied as a biconvex, oblong film-coated tablet for oral administration in 500 mg or 150 mg tablets. Peak plasma levels occur in 90 minutes, and elimination half-life is 45 minutes.

7.1.2 Storage and Stability

Tablets should be stored at controlled room temperature (~25˚ C/77˚ F) in tightly closed containers with excursions to 15-30˚ C/59-86˚ F permitted.

7.1.3 Administration

The capecitabine daily dose (1000 mg twice a day) is given orally in two divided doses (approximately 12 hours apart) at the end of a meal, and the tablets should be taken with water. Patients will be asked to maintain a pill diary documenting self-administration of capecitabine (SPM). They will need to review the diary with study staff weekly while on treatment. The pill diary must be available in the participant's medical/research record. Study staff should make a copy of the pill diary at each weekly review.

7.1.4 Adverse Events Associated with Capecitabine: See package insert.

7.1.5 Drug Interactions

7.1.5.1 Antacids

The administration of 20 mL of an antacid containing aluminum hydroxide and magnesium hydroxide may result in an increase in the area under the concentration-time curve (AUC) and maximum concentration (Cmax) of capecitabine of 16% and 35%, respectively. These changes were not considered clinically significant.

7.1.5.2 Oral Anticoagulants

Altered coagulation parameters and/or bleeding, including death, have been reported in patients receiving capecitabine and coumadin-derivative anticoagulants. Post-marketing reports have revealed clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants when capecitabine was initiated. These events occurred within several days to several months after concurrent therapy was initiated. Patients receiving capecitabine and coumadin should be closely and regularly monitored.

7.1.5.3 Phenytoin
Some patients receiving capecitabine and phenytoin may experience phenytoin toxicity as a result of increased phenytoin plasma levels. Phenytoin levels should be closely monitored in patients taking concomitant phenytoin and capecitabine. The dose of phenytoin may need to be reduced or the drug changed entirely to an alternative effective antiepileptic.

7.1.6 Supply

Capecitabine (Xeloda®) is commercially available.

7.1.7 Schedule

Oral capecitabine (Xeloda®) 1,000 mg BID. Treatment will start on day 1 of radiation and continue for the entire duration of radiotherapy, but will only be taken on radiation days (Monday-Friday). The patient will be provided with a pill diary (see the SPM) to be filled out daily and reviewed with study staff weekly to help aid medication schedule compliance.

Table 1: Capecitabine with Concurrent Radiation

Agent	Dose	Route	Schedule
Capecitabine (Xeloda®)	1,000 mg BID	PO	Doses Q 12 hours Monday through Friday on radiation days only

7.1.8 Dose Modifications:

All dose reductions for Xeloda® will be at the discretion of the treating Medical Oncologist.

8.0 OTHER THERAPY

8.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the treating physician within the parameters of the protocol and documented in the medical record as concomitant medication.

8.2 Required Concomitant Medications

All patients should be on a proton pump inhibitor (lansoprazole, omeprazole, pantoprazole sodium, rabeprazole sodium) while on Xeloda®. If Xeloda® is

discontinued; the proton pump inhibitor may be discontinued. If any new epigastric pain develops, ulceration should be expected and sucralfate should be started. Upper endoscopy should be performed as clinically directed.

All patients should be prescribed loperamide (Imodium) and educated on appropriate use for chemotherapy and radiation-induced diarrhea.

8.3 Prohibited Concomitant Medications

Patients may receive all concomitant therapy deemed necessary to provide adequate support, with the exception of the therapies detailed below:

- Other investigational agents
- Other cytotoxic agents or radiotherapy

9.0 SURGERY

9.1 In patients with a marked response to treatment, surgical resection may be attempted at the discretion of the attending surgeon ideally within 8 to 16 weeks of completing chemoradiotherapy.

10.0 PATHOLOGY

10.1 Pathology report showing histology from the initial diagnosis and post surgery if the patient has a surgical resection must be collected. If report is "suspicious" of pancreatic adenocarcinoma, subject can be included per the clinical judgment of the treating physician (must be documented).

11.0 ADVERSE EVENTS/ SERIOUS ADVERSE EVENTS

11.1 Adverse Events

11.1.1 An adverse event is any unintended or undesirable experience that occurs during the course of the clinical investigation, whether or not it is considered to be therapy related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the initiation of study treatment or intervention.

11.2 Grading of Adverse Events

11.2.1 The Common Terminology Criteria for Adverse Events (CTCAE) will be utilized to grade the severity of adverse events. CTCAE version 4.0 will be utilized until May 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning June 1, 2018.

11.3 Reporting of Adverse Events

11.3.1 **For the PAN009-18 protocol, only possibly, probably or definitely related (to either radiation, chemotherapy and/or surgery (if applicable)) adverse events will be collected in the EDC system.** Refer to the

SPM for additional information regarding collection and reporting of adverse events.

11.4 Documentation

11.4.1 All applicable data must be reviewed and confirmed by the PI or their designee for any Grade 3-5 adverse events with the attribution of definite, possible, or probable relation to protocol therapy (radiation, chemotherapy, and surgery).

11.5 Serious Adverse Events

11.5.1 Serious Adverse Events (SAE): An adverse event that results in any of the following outcomes:

- A life-threatening adverse experience
- A persistent or significant disability, incapacity, or is a congenital anomaly or birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Death

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

11.6 Reporting Serious Adverse Events

11.6.1 SAE reporting is safety related, separate from and in addition to data management toxicity reporting requirements on the case report form. For the PAN009-18 study, investigators and other site personnel must report all SAEs within 1 business day of discovery of the event.

SAEs should be reported on an SAE Form via email to safety@pcgresearch.org. The SAE Form is available on the PCG website (http://pcgresearch.org, PCG Member Portal). If email is unavailable, a phone call to PCG Headquarters should be made to alert that an SAE Form will be forthcoming.

It is expected that all information may not be available at the time the initial SAE report is submitted. A follow-up report with complete information is expected within 10 business days of the initial report. As new information related to the SAE is made known to the investigator, the SAE report should be updated and resubmitted to PCG Headquarters. All de-identified supporting source documentation, if requested, must be emailed to PCG Headquarters as soon as available. SAEs will also be recorded in the PCG EDC system. In addition to notifying PCG, the Investigator is responsible for reporting SAEs to the IRB per their requirements. Copies of these reports will also be filed in the regulatory files for the study.

12.0 DATA COLLECTION

Patients must be registered through the PCG Electronic Data Capture (EDC) system. All required study information will be entered and verified in the EDC system. Detailed guidelines for patient registration and electronic Case Report Form (eCRF) completion can be found in the SPM and EDC Instructional Manual. Timelines for data submission must be followed closely in order to assure human subject safety.

The PI must make study data accessible to the PCG Study Monitor, to other authorized representatives of the study chair, and to the appropriate regulatory authority inspectors. The data in the EDC system will be checked against source documents by the PCG Study Monitor.

The below are items expected to be present in the medical record for subjects enrolled in this protocol:

12.1 Pre-Treatment Data

12.1.1 History and physical exam including weight, performance status, baseline toxicity assessment

12.1.2 AJCC 7th Edition (prior to 1/1/18) or 8th Edition (starting 1/1/18) clinical TNM staging

12.1.3 Pathology report

12.1.4 Laboratory results and assessments

12.1.5 Imaging results with measurements when appropriate

12.2 On Treatment Data

12.2.1 Weekly physical exam including weight, performance status, acute toxicity (with scoring per CTCAE)

12.2.2 Laboratory results/ review and any dose modifications

12.2.3 Imaging results with measurements when appropriate

12.2.4 Chemotherapy (Xeloda®) pill diary

12.3 Dosimetric Data

12.3.1 Radiation dose calculations

12.3.2 Radiation treatment record

12.3.3 Radiation isodose distribution

12.3.4 Radiation localization imaging

12.3.5 Planning CT scans

12.3.6 Dose volume histograms

12.4 Surgical Data (if surgical resection is performed)

12.4.1 Surgical procedure notes showing results

12.4.2 Operative report(s)

12.4.3 Pathology report(s)

12.5 Follow-up Data

12.5.1 Exams including weight, performance status, toxicity assessments (with scoring per CTCAE), and disease response

12.5.2 Imaging results

12.5.3 Laboratory results

12.5.4 Death certificate, autopsy, or similar document required, if applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

- Improve proportion of patients alive at 1 year from the completion of treatment. This would be an improvement from the historical rate of 50% to the goal of 75%.

13.1.2 Secondary Endpoints

- Collect and analyze tumor control outcomes
- Improve local and regional disease control
- Increase share of marginally resectable and unresectable patients being converted to resectable
- Compare GI toxicity of protocol therapy and quality of life with historical benchmarks

13.2 Sample Size

13.2.1 Sample Size Derivation

The immediate objective of the study is to improve the proportion of patients alive at 1 year. The historical proportion alive at 1 year is 50%,[4] and we anticipate that proton therapy will improve this rate to 75%. With a minimum of 45 patients, there will be 96% power to detect this difference if it does indeed exist. There will also be 95% confidence in a conclusion that the rate is not $\geq$ 75% if that is in fact true. If $\geq$ 29 patients are alive at 1 year, we will accept the research hypothesis that 1 year survival is $\geq$75%; if $\leq$ 28 patients are

alive, we will instead accept the null hypothesis that survival in this proton cohort is not ≥ 75% at 1 year. We plan to accrue an additional 15 patients to account for as much as 33% loss to follow-up and/or patient withdrawal, so a total sample size of 60 patients is necessary.

13.3 Patient Accrual and Study Duration

RTOG Phase II pancreas studies (98-12, 00-20, and RTOG 1201) accrued an average of 7.9 patients per month nationwide. Based upon this accrual rate, and the average number of patients seen at the participating sites, we anticipate approximately 3 patients per month to be accrued so it will take 20 months to reach 60 patients. Allowing an additional 6 months for all required reviews (IRB, etc.) and approval, accrual should be completed in approximately 26 months. However, we may extend the length of the study depending on the rate of enrollment.

13.4 Analysis Plan

13.4.1 Interim Reports

Interim reports will be prepared for the PCG Data Safety Monitoring Board (DSMB) at least annually until the study is complete (subjects no longer being followed). In general, they will contain information about:

- Patient accrual rate with projected completion date of the trial
- Status of compliance rate of study treatment per protocol
- Frequencies and severity of Grade 3-5 toxicities that are at least possibly related, including deaths.

13.5 Inclusion of Minorities and Women

13.5.1 In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race and gender with treatments. We project that 20% of patients in the study will be non-white. The sample size for this subset would only be 12 patients, so there is 30% power to draw the same conclusion as the full sample.

13.5.2 We project that 50% of patients in the study are female. Thus, 30 men and 30 women are expected to complete the study. If the same analysis is performed within each gender group, the statistical power in each is 80%.

14.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

This study will be conducted in full compliance with the Institutional Review Board regulations in 21 CFR 56. This study will be conducted in full compliance with the informed consent regulations in 21 CFR 50. Only staff members who have completed human subject protection training will obtain informed consent from the study participants.

Written informed consent and authorization of use and disclosure of PHI (as applicable in the U.S.) must be obtained from each patient before performing any Screening/Baseline evaluations that are specifically study related (outside the scope of routine care). One copy of the signed informed consent document and authorization will be given to the patient, and the investigative site will retain the original or a verified copy of the original. The consent document must contain the 20 elements of informed consent described in ICH E6 4.8. The authorization for use and disclosure of PHI must contain the elements required by 45 CFR 164.508(b) for valid authorizations.

14.1 Study Data Storage and Confidentiality

If paper documents are collected, they should be stored in locked cabinets at all times when not in use. If electronic forms are used, they will be kept in a folder in a password protected form on a secure server. Electronic data will be in compliance with FDA CFR Title 21 Part 11.

No study documents will be destroyed or moved to a new location without prior written approval from the sponsor. If the site investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator or the institution where the study was conducted.

All information regarding the nature of the proposed investigation provided by the Study Chair to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

The anonymity of participating patients must be maintained. Patients will be identified by their initials and assigned patient numbers on all documents submitted to the PCG Study Monitor. Documents that will not be submitted to the PCG Study Monitor and that identify the patient (e.g., the signed informed consent document) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the PCG Study Monitor, or sponsor representatives.

14.2 Risk Benefit Assessment

By definition this study is determined as greater than minimal risk. Patients treated in the protocol will have the potential benefit of treatment with state of the art technologies and thorough treatment quality assurance that is not available in common clinical practice. The risks of treatment (including acute and long term side effects) with this technology (proton therapy), should be lower than with conventional treatment as delivered with photon radiation in common clinical practice. However, a DSMB will review the potential harmful effects of the treatment at least annually and stop the trial if deemed necessary.

APPENDIX I

Performance Status

KARNOFSKY PERFORMANCE SCALE

100 Normal; no complaints; no evidence of disease
90 Able to carry on normal activity; minor signs or symptoms of disease
80 Normal activities with effort; some sign or symptoms of disease
70 Cares for self; unable to carry on normal activity or do active work
60 Requires occasional assistance, but is able to care for most personal needs
50 Requires considerable assistance and frequent medical care
40 Disabled; requires special care and assistance
30 Severely disabled; hospitalization is indicated, although death not imminent
20 Very sick; hospitalization necessary; active support treatment is necessary
10 Moribund; fatal processes progressing rapidly
0 Dead

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all pre-disease activities without restriction *(Karnofsky 90-100).*
1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80).*
2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours *(Karnofsky 50-60).*
3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40).*
4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20).*

APPENDIX II

Staging System
AJCC, 7th Edition

PANCREAS STAGING FORM

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS	PATHOLOGIC *Extent of disease through completion of definitive surgery*
☐ y clinical – staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____	☐ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)	
☐ TX	Primary tumor cannot be assessed	☐ TX
☐ T0	No evidence of primary tumor	☐ T0
☐ Tis	Carcinoma *in situ**	☐ Tis
☐ T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension	☐ T1
☐ T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension	☐ T2
☐ T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	☐ T3
☐ T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	☐ T4
	*Note: This also includes the "PanInIII" classification	
	REGIONAL LYMPH NODES (N)	
☐ NX	Regional lymph nodes cannot be assessed	☐ NX
☐ N0	No regional lymph node metastasis	☐ N0
☐ N1	Regional lymph node metastasis	☐ N1
	DISTANT METASTASIS (M)	
☐ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
☐ M1	Distant metastasis	☐ M1

ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
☐ 0	Tis	N0	M0	☐ 0	Tis	N0	M0
☐ IA	T1	N0	M0	☐ IA	T1	N0	M0
☐ IB	T2	N0	M0	☐ IB	T2	N0	M0
☐ IIA	T3	N0	M0	☐ IIA	T3	N0	M0
☐ IIB	T1	N1	M0	☐ IIB	T1	N1	M0
	T2	N1	M0		T2	N1	M0
	T3	N1	M0		T3	N1	M0
☐ III	T4	Any N	M0	☐ III	T4	Any N	M0
☐ IV	Any T	Any N	M1	☐ IV	Any T	Any N	M1
☐ Stage unknown				☐ Stage unknown			

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

(continued on next page)

PANCREAS STAGING FORM

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS)

REQUIRED FOR STAGING: None

CLINICALLY SIGNIFICANT:

Preoperative CA 19-9 _____

Preoperative Carcinoembryonic Antigen (CEA) _____

Preoperative plasma chromogranin A level (CgA) (endocrine pancreas) _____

Mitotic count (endocrine pancreas) _____

Histologic Grade (G) *(also known as overall grade)*

Grading system	*Grade*
☐ 2 grade system	☐ Grade I or 1
☐ 3 grade system	☐ Grade II or 2
☐ 4 grade system	☐ Grade III or 3
☐ No 2, 3, or 4 grade system is available	☐ Grade IV or 4

ADDITIONAL DESCRIPTORS

Lymphatic Vessel Invasion (L) and Venous Invasion (V) have been combined into Lymph-Vascular Invasion (LVI) for collection by cancer registrars. The College of American Pathologists' (CAP) Checklist should be used as the primary source. Other sources may be used in the absence of a Checklist. Priority is given to positive results.

- ☐ Lymph-Vascular Invasion Not Present (absent)/Not Identified
- ☐ Lymph-Vascular Invasion Present/Identified
- ☐ Not Applicable
- ☐ Unknown/Indeterminate

Residual Tumor (R)

The absence or presence of residual tumor after treatment. In some cases treated with surgery and/or with neoadjuvant therapy there will be residual tumor at the primary site after treatment because of incomplete resection or local and regional disease that extends beyond the limit of ability of resection.

- ☐ RX Presence of residual tumor cannot be assessed
- ☐ R0 No residual tumor
- ☐ R1 Microscopic residual tumor
- ☐ R2 Macroscopic residual tumor

General Notes:
For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y," "r," and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

m suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

y prefix indicates those cases in which classification is performed during or following initial multimodality therapy. The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy.

r prefix indicates a recurrent tumor when staged after a disease-free interval, and is identified by the "r" prefix: rTNM.

a prefix designates the stage determined at autopsy: aTNM.

surgical margins is data field recorded by registrars describing the surgical margins of the resected primary site specimen as determined only by the pathology report.

neoadjuvant treatment is radiation therapy or systemic therapy (consisting of chemotherapy, hormone therapy, or immunotherapy) administered prior to a definitive surgical procedure. If the surgical procedure is not performed, the administered therapy no longer meets the definition of neoadjuvant therapy.

☐ Clinical stage was used in treatment planning (describe): _____

☐ National guidelines were used in treatment planning ☐ NCCN ☐ Other (describe): _____

_____

Physician signature Date/Time

HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

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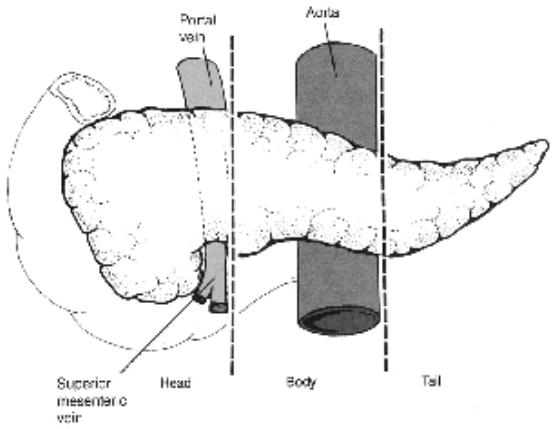
PANCREAS STAGING FORM

Illustration

Indicate on diagram primary tumor and regional nodes involved.



HOSPITAL NAME/ADDRESS	PATIENT NAME/INFORMATION

Staging System
AJCC, 8th Edition

4 Definitions of AJCC TNM

Always refer to the specific chapter for explicit instructions on clinical and pathological classification for this disease.

4.1 Definition of Primary Tumor (T)

✓	*T Category*	*T Criteria*
	TX	Tumor cannot be assessed
	T1	Tumor limited to the pancreas,* <2 cm
	T2	Tumor limited to the pancreas,* 2–4 cm
	T3	Tumor limited to the pancreas,* >4 cm; or tumor invading the duodenum or common bile duct
	T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery)
**Limited to the pancreas* means there is no invasion of adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or the superior mesenteric artery). Extension of tumor into peripancreatic adipose tissue is NOT a basis for staging.		
Note: Multiple tumors should be designated as such (the largest tumor should be used to assign T category): • If the number of tumors is known, use T(#); e.g., pT3(4) N0 M0. • If the number of tumors is unavailable or too numerous, use the *m* suffix, T(m); e.g., pT3(m) N0 M0.		

✓	*T Suffix*	*Definition*
	(m)	Select if synchronous primary tumors are found in single organ.

4.2 Definition of Regional Lymph Node (N)

✓	*N Category*	*N Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node involvement
	N1	Regional lymph node involvement

✓	*N Suffix*	*Definition*
	(sn)	Select if regional lymph node metastasis identified by SLN biopsy only.
	(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only.

4.3 Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

✓	*M Category*	*M Criteria*
	cM0	No distant metastasis
	cM1	Distant metastases
	cM1a	Metastasis confined to liver
	cM1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
	cM1c	Both hepatic and extrahepatic metastases
	pM1	Distant metastases
	pM1a	Metastasis confined to liver
	pM1b	Metastases in at least one extrahepatic site (e.g., lung, ovary, nonregional lymph node, peritoneum, bone)
	pM1c	Both hepatic and extrahepatic metastases

5 AJCC Prognostic Stage Groups

Always refer to the specific chapter for rules on clinical and pathological classification of this disease.

✓	*When T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	T1	N0	M0	I
	T2	N0	M0	II
	T3	N0	M0	II
	T4	N0	M0	III
	Any T	N1	M0	III
	Any T	Any N	M1	IV

Hospital Name/Address	Patient Name/Information

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