A Randomized Phase II/Genomic Trial of two chemotherapy regimens in patients with resected pancreatic adenocarcinoma

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Schema

Patients with operable resected adenocarcinoma of the pancreas:

Randomized:

Arm A: FOLFIRINOX
Irinotecan 180 mg/m2 Day 1
Oxaliplatin 85 mg/m2 Day 1
5-FU 400 mg/m2 bolus with
Leucovorin 200 mg/m2 over 2h, Day 1, then
5-FU 2400 mg/m2 over 46h.

Four cycles over 8 weeks

Chemoradiation:
Radiation to begin no sooner than 28 days from last day of chemotherapy.
On Day 1(± 2days to accommodate scheduling difficulties):
Infusional 5-FU (225 mg/m2 continuous infusion during radiation) and radiation therapy as defined.

FOLFIRINOX
Irinotecan 180 mg/m2 Day 1
Oxaliplatin 85 mg/m2 Day 1
5-FU 400 mg/m2 bolus with
Leucovorin 200 mg/m2 over 2h, Day 1, then
5-FU 2400 mg/m2 over 46h.

Four cycles, if tolerated

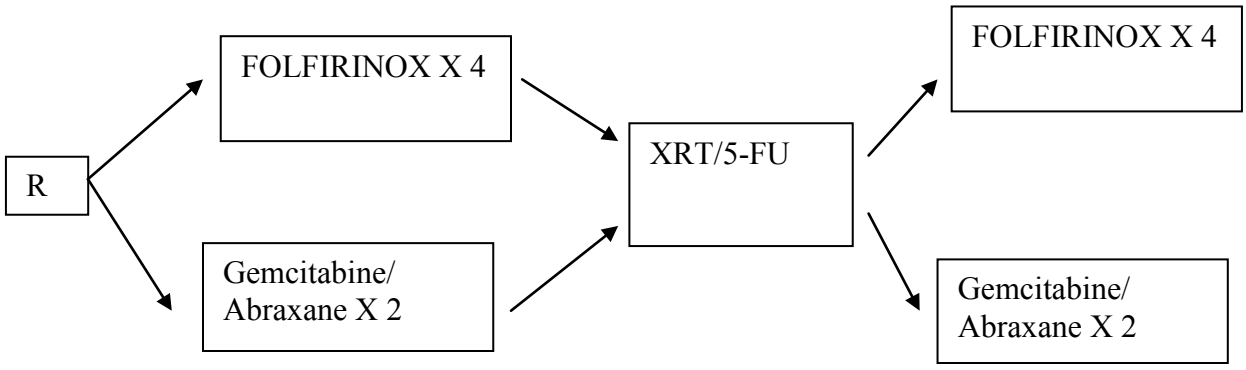
Arm B: Gemcitabine / Abraxane
Gemcitabine 1000 mg/m2 Days 1, 8, 15
Abraxane 125 mg/m2 Days 1, 8, 15

Two cycles over 8 weeks

Chemoradiation:
Radiation to begin no sooner than 28 days from last day of chemotherapy.
On Day 1 (± 2days to accommodate scheduling difficulties)
Infusional 5-FU (225 mg/m2 continuous infusion during radiation) and radiation therapy as defined.

Gemcitabine / Abraxane
Gemcitabine 1000 mg/m2 Days 1, 8, 15
Abraxane 125 mg/m2 Days 1, 8, 15

Two cycles, if tolerated



Note the cycle duration for FOLFIRINOX is 2 weeks, and for Gemcitabine/ abraxane 4 weeks

Study Summary

Title	**A Randomized Phase II/Genomic Trial of two chemotherapy regimens in patients with resected pancreatic adenocarcinoma**
Short Title	same
Protocol Number	UPCC
Phase	Phase II
Methodology	Randomized
Study Duration	2 years
Study Center(s)	Single Institution to start
Objectives	Primary Objective: 1. Determine the relapse-free survival of resected pancreatic cancer patients following two novel regimens Secondary Objectives 1) To assess the toxicity of each of these regimens in this setting 2) To perform exploratory genomic analyses as a means of assessing molecular characteristics potentially associated with risk of relapse with one or both of the regimens 3) To determine the relationship between known mutations and metabolic activity as measured by FDG-PET, and risk of relapse
Number of Subjects	50

Diagnosis and Main Inclusion/Exclusion Criteria	***1.1 Inclusion Criteria*** 3.1.1 Patients must have histologically or cytologically confirmed evidence of pancreatic adenocarcinoma or poorly-differentiated carcinoma. Neuroendocrine tumors are not eligible. 3.1.2 Patients must have had all gross disease resected (R0 or R1 resection). 3.1.3 Patients who underwent an R2 resection are not eligible. 3.1.4 Patients must have had no prior chemotherapy or radiation therapy for pancreatic cancer. 3.1.5 Age > 18 years. 3.1.6 Patient must have ECOG performance status of 0-2 unless surgical morbidity is responsible – in such an event he must be a suitable candidate for adjuvant therapy in the opinion of the PI. 3.1.7 Patients must have normal organ and marrow function measured within 2 weeks prior to registration as follows: ANC > 1,500/μL Platelets > 100,000/μL Total bilirubin less than 3-fold ULN AST (SGOT)/ALT(SGPT) < 5 X institutional upper limit of normal Creatinine clearance > 60 mL/min for patients with creatinine levels above institutional normal 3.1.8 Patients must be > 4 weeks and < 16 weeks post-surgery at time of study registration 3.1.9 Women of childbearing potential and sexually active males are strongly advised to use effective contraceptive measures. 3.1.10 Women must not be pregnant or breast-feeding. All agents used in this study as well as radiation therapy to the abdomen have the potential for teratogenic or abortifacient effects. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. 3.1.11 Patients must not be receiving any other investigational agents.3.1.12 Patients with known metastases are not eligible. 3.1.14 Patients with wounds that have not fully healed are not eligible. 3.1.15 Patients must have no known HIV infection.

Study Product, Dose, Route, Regimen	As detailed above.
Statistical Methodology	Randomized Phase II

Objectives

1.1 Primary Objectives

Determine the relapse-free survival of resected pancreatic cancer patients following two novel regimens with activity in advanced disease.

1.2 Secondary Objectives

1.21 To assess the toxicity of each of these regimens in this setting

1.22 To perform exploratory genomic analyses as a means of assessing molecular characteristics potentially associated with risk of relapse with one or both of the regimens

1.23 To determine the relationship between known mutations and metabolic activity as measured by FDG-PET, and risk of relapse

2 Background

2.1 Resectable Pancreatic Cancer

Pancreas cancer is the fourth leading cause of cancer death in the United States, with the poorest prognosis of the more common cancers (1). Fewer than 5% of patients survive 5 years, and of these, almost all have had complete resection of their primary tumor. However, despite continuing improvements in surgical technique that have yielded low perioperative mortality, survival among resected patients remains low (2). The first adjuvant trial was conducted by the Gastrointestinal Tumor Study Group (GITSG), and randomized 43 patients over 8 years. Though flawed by the long duration of accrual and small number of patients, there was a survival advantage for the chemoradiation plus surgery arm compared to surgery alone (3). A subsequent EORTC study randomized patients to chemoradiation plus surgery versus surgery alone: survival for both treatment groups was similar (4). However, this trial included both periampullary cancers and pancreatic cancers, and when subsets were analyzed, there was a trend to improved overall survival in patients with pancreatic cancer. A trial conducted in the UK, ESPAC-1, randomized patients to chemotherapy versus no chemotherapy, and to chemoradiation versus no chemoradiation (5). Unfortunately, in this study problems included incomplete participation in the 2 x 2 design, and a significant number of patients received different therapy than assigned. This trial did not demonstrate a benefit to chemoradiation, but suggested that adjuvant chemotherapy may be of benefit. A subsequent trial from this group, ESPAC-3, showed no difference between 5-FU and gemcitabine as chemotherapy regimens (6). In the United States, adjuvant chemotherapy with chemoradiation has become standard of care. The intergroup trial, RTOG 9741, studied gemcitabine before and after continuous infusion (CI) 5-FU plus radiation versus 5-FU before and after CI 5-FU plus radiation. The initial report favored the contribution of gemcitabine over 5-FU for head of pancreas lesions (7), but that relationship was not maintained in a 5-year follow-up report, and the differences were not significant (8). The controversy surrounding the conflicting results of previous trials led Oettle and colleagues (9) to perform a trial of gemcitabine as a single agent versus surgery only control, and demonstrated a significant benefit from therapy. While chemoradiation remains the standard of care in the US, these results point to the value of systemic chemotherapy as part

of adjuvant therapy for patients with pancreatic cancer. They also point to the need to enhance the efficacy of systemic chemotherapy to improve outcomes in this disease.

2.2 Metastatic Pancreatic Cancer

The development of novel therapies in the adjuvant setting usually follows upon the demonstration of enhanced results in patients with advanced disease. While this model has had its limitations, there have also been notable successes, especially with chemotherapy. Two new chemotherapy regimens have now emerged as superior to gemcitabine alone in metastatic pancreatic cancer. One has a published Phase III trial – FOLFIRINOX was shown to have higher response rates and longer survival than gemcitabine alone (10). Response to FOLFIRINOX was 32% (versus 9.4% for gemcitabine). The median overall survival was 11.1 months in the FOLFIRINOX group as compared with 6.8 months in the gemcitabine group (hazard ratio for death, 0.57; 95% confidence interval [CI], 0.45 to 0.73; P<0.001).

Recent strategies have focused on improving the efficacy of gemcitabine either by improving the method of delivery, or by combining gemcitabine with other non-cross resistant agents. A sequence of Phase III combination studies of gemcitabine in combination (with oxaliplatin, and with the targeted therapies bevacizumab and cetuximab) have been negative, though based on strikingly positive Phase II data generated in cancer centers. Several studies suggest that taxanes are active in pancreatic cancer, but a randomized trial of gemcitabine with taxanes has not been performed, probably on the basis that the differences in Phase II were insufficiently persuasive. The development of a novel taxane conjugate with albumin, abraxane, with established activity in breast cancer, prompted a Phase II trial of gemcitabine/abraxane by Von Hoff (11). Phase I/II data were highly promising, with response rates of 48%, with tolerable toxicity, in an expansion cohort treated at 125 mg/m2. Overall survival in this group was 12.2 months. A phase III trial of gemcitabine versus gemcitabine/abraxane has now been concluded and results are expected this year, and based on these promising data the regimen has served as the control chemotherapy for our SU2C trials.

Abraxane (nab-paclitaxel) is a cremophor-free formulation of nanoparticle paclitaxel stabilized with human serum albumin (130 nm particles). The drug achieves enhanced tumor penetration through gp60 albumin receptor-mediated endothelial transcytosis, which enables transit across the vessel endothelium, and makes the active paclitaxel available to the tumor. An additional pharmacodynamic consideration is that the albumin scaffold also binds a tumor-related protein SPARC, which may further enhance localization of this molecule in the tumor tissue. Preliminary data suggest that SPARC-expressing tumors may have better responses to abraxane.

Both FOLFIRINOX and gemcitabine/ abraxane have neutropenia as their major adverse effect. With FOLFIRINOX 46% of patients experienced grade 3 or 4 neutropenia, with fatigue, nausea/vomiting and diarrhea much less frequently observed. In the gemcitabine abraxane trial, neutropenia was of a similar order (49% at 125mg dose), and additional toxicity included fatigue and neurotoxicity (11).

2.3 Markers of Therapy Effect

Prognostic Markers. Substantial research has been performed in the characterization of molecular abnormalities associated with pancreatic cancer, and samples continue to be analyzed from our ongoing advanced disease studies. The best-characterized aberrations have been mutations and/or chromosomal losses affecting KRAS (>95%), p16/CDKN2A (95%), TP53 (50–75%), and DPC4/SMAD4 (55%), the 4 high-frequency pancreatic cancer driver genes (12-14). The last is of particular interest in that tumors in which the locus is intact may have a higher risk of local relapse (15). A radiation dose intensification

trial is in development in RTOG with smad4 genetic variability as a key correlative endpoint. None of the aberrant pathways identified in this disease has been clearly associated with outcome.

Predictive Markers. Data suggest that genomic variation in drug-metabolizing genes, or in genes in related pathways (eg DNA damage response, DNA repair) might influence the outcome of therapy. In general, little positive association has been found for particular profiles of genetic aberration and response in pancreatic cancer, but candidate genes have emerged recently. There are not many trials with follow-up and detailed genomics in pancreatic cancer, and so we propose in this study to obtain sufficient materials to conduct such research. Recognizing that numbers of patients are small, such studies may provide the basis for targeted analyses in larger trials going forward, and generate hypotheses concerning potential predictive markers.

1. Mutational Analysis. All tumors will be typed using the 48-gene platform of the Center for Personalized Diagnostics. DNA, miRNA, and total RNA will be prepared from microdissected tumor. An aliquot (1 microgram approx) will be submitted for analysis. This analysis will provide mutation and copy number characteristics for genes important to pancreatic cancer including Kras, p53, and smad4.

2. Drug Resistance genes. An aliquot of DNA will be obtained and stored for analysis of polymorphisms in drug transport genes (eg hENT1, MDR), microtubule associated proteins, DNA repair genes, and DNA damage response genes.

3. Isolation of nuclei (in collaboration with Dr M. Barrett, TGEN) for CNV and possible exome sequencing studies.

4. Metabolomics studies where feasible, and the tumor has been operated on at Penn.

5. Circulating Tumor cells as soon as the methodology has been validated.

Complementing the tissue-based studies, we propose to obtain imaging studies pre-operatively in these patients. We will begin with FDG-PET, the use of which is approved for pancreatic cancer, and we will study as many as possible with F-misonidazole-PET for which we now have an IND. This is justified by a metabolomic profile of hypoxia in our early studies (Thompson CB, manuscript submitted, 2012). We will plan at later stages to introduce glutamine-PET and as these tracers become more available, and as funding permits.

2.4 Design

This trial will be a randomized Phase II study of FOLFIRINOX versus gemcitabine/abraxane in patients with completely resected pancreatic cancer (Stages I-III). Patients will receive eight weeks of chemotherapy, then 5-FU/radiation, then another 8 weeks. Most patients will have insurance coverage that should cover these agents at this stage of the disease; however, inevitably there will be some who are not covered. For those patients, a standard gemcitabine plus 5-FU/radiation regimen will be used, and samples obtained and analyzed for comparative purposes.

3 Patient Eligibility

3.1 Inclusion Criteria

3.1.1 Patients must have histologically or cytologically confirmed evidence of pancreatic carcinoma.

3.1.2 Patients must have had all gross disease resected (R0 or R1 resection).

3.1.3 Patients who underwent an R2 resection are not eligible.

3.1.4 Patients must have had no prior chemotherapy or radiation therapy for pancreatic cancer.

3.1.5 Age > 18 years.

3.1.6 Patient must have ECOG performance status of 0-2.

3.1.7 Patients must have normal organ and marrow function measured within 2 weeks prior to registration as follows:

ANC > 1,500/μL

Platelets > 100,000/μL

Total bilirubin less than 2-fold ULN

AST (SGOT)/ALT(SGPT) < 2.5 X institutional upper limit of normal

Creatinine clearance > 60 mL/min for patients with creatinine levels above institutional normal

3.1.8 Patients must be > 4 weeks and < 12 weeks post-surgery at time of study registration

3.1.9 Women of childbearing potential and sexually active males are strongly advised to use appropriate contraceptive measures.

3.1.10 Women must not be pregnant or breast-feeding. All agents used in this study as well as radiation therapy to the abdomen have the potential for teratogenic or abortifacient effects. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.

3.1.11 Patients must not be receiving any other investigational agents.

3.1.12 Patients with known metastases are not eligible.

3.1.14 Patients with wounds that have not fully healed are not eligible.

3.1.15 Patients must have no known HIV infection.

3.1.16 Patients must not have any of the following: acinar cell carcinoma, neuroendocrine carcinoma, cystadenocarcinoma, carcinosarcoma.

3.1.17 Patients with psychiatric or addictive disorders or other conditions that, in the opinion of the investigators, would preclude them from meeting the study requirements are not eligible.

3.1.18 Patients must have the ability to understand and the willingness to sign a written informed consent document.

3.1.19 Patients must have provided consent for tissue collection for the molcecular testing through participation on study UPCC 22210 entitled; "PROTOCOL TO PERMIT THE ACQUISITION OF SAMPLES OF TUMOR AND NORMAL TISSUE FOR BIOLOGICAL ENDPOINTS IN PANCREATIC CANCER"

3.2 Exclusion Criteria

3.2.1 Patients may not be receiving any other investigational agents

3.2.2 Patients with T1, N0M0 disease are not eligible.

4 Treatment Plan

4.1 Study Design

Randomized Phase II, FOLFIRINOX versus gemcitabine/abraxane, both with 5-FU/radiation.. All therapy and testing times in this protocol are approximate and depend on hospital schedules, patient availability, and practicality.

4.2 Treatment Plan

Arm I - FOLFIRINOX

Chemotherapy:
Irinotecan 180 mg/m2 Day 1
Oxaliplatin 85 mg/m2 Day 1
5-FU 400 mg/m2 bolus with
Leucovorin 200 mg/m2 over 2h, Day 1, then
5-FU 2400 mg/m2 over 46h.

This constitutes one treatment, which will be repeated four times (at 14 day intervals) before starting chemoradiation, and four times (as tolerated) after its completion.

Arm II – Gemcitabine/Abraxane

Gemcitabine 1000mg/m2 IV over 30 to 100 minutes, day 1, 8, 15
Abraxane 125 mg/m2 IV over 30 minutes, day 1, 8, 15
Repeat every 4 weeks as tolerated twice before and twice (as tolerated) after chemoradiation.

Chemoradiation:
Radiation to begin no sooner than 21 days after last day of chemotherapy.
On Day 1 (± 2days to accommodate scheduling difficulties):

Infusional 5-FU (225 mg/m2 continuous infusion during radiation) and radiation therapy as defined.

Patients will receive an appropriate anti-emetic regimen usually including dexamethasone 10-20mg IV and a 5-HT3 agent of choice, (i.e. ondansetron or granisetron) prior to administration of chemotherapy to decrease the incidence and severity of chemotherapy-associated nausea and vomiting, at the discretion of the investigator. Drugs such as lorazepam may also be used if clinically indicated.

4.2.2 Duration of Treatment

Patients will receive protocol therapy as outlined, followed by observation. Toxicities related to treatment will be reason for chemotherapy modification, interruption or discontinuation as deemed appropriate by the physician as in the best interest of the patient. All patients in whom protocol therapy has been discontinued will be followed for progression of disease and survival. A schedule of clinic visits quarterly, and imaging at six month intervals for 2 years and annually thereafter for 5 years is suggested, but not mandated, given the rapid course of recurrent pancreatic cancer.

4.2.3 PET

Patients will have a FDG-PET scan pre-operatively where feasible. Lack of such a scan will not preclude entry on the study or constitute a protocol deviation.

4.2.4 Tumor Analysis

Tumor obtained at surgery will be frozen and stored for genomic analysis. Where cellularity and/or necrosis preclude the reliable use of fresh tissue, we will plan to sequence out of FFPE after microdissection.

4.2.5 Circulating Tumor Cells

In addition to standard laboratory assessments prior to administration of chemotherapy, patients will have blood drawn to assess circulating tumor cells. The methods for these analyses are in development, and will be applied as feasible to this protocol by amendment.

5 Dosing Delays/Dose Modifications

Toxicity will be graded using the NCI Common Toxicity Criteria which is available on the NCI website www.ctep.cancer.gov. Laboratory abnormalities on the day of treatment for second and subsequent courses will be considered in treatment decisions. Values that deviate from eligibility criteria for the study may cause a delay of up to four weeks for recovery to occur. If the abnormalities have not resolved by then, the patient should ordinarily be taken off study. Exceptions may be made after discussion with the Principal Investigator.

5.1 Dose Modifications

According to the following recommended tables, the final dose modification should be based upon the worst grade of toxicity experienced. If patients require dose reductions lower than level -2, a 30% reduction will ordinarily be used. Any dose reduction is continued for all subsequent cycles; however, dose re-escalation is allowed following a dose reduction to an intermediate dose. **NOTE:** there are no dose reductions for leucovorin; the dose remains fixed at 400 mg/m2 and without modification.

NOTE: The tables below are provided as quidelines and may be adjusted, as appropriate, by the treating physician, to ensure patient safety and comfort, as is routinely done as part of standard care. The rationale for straying from the guidelines will be documented in the patient's chart and will NOT constitute a protocol deviation.

5.1.1 Dose Modifications for Oxaliplatin, Irinotecan, and 5-FU Toxicity

NOTE: There are no dose reductions for leucovorin. The dose remains fixed at 400 mg/m2. Leucovorin is discontinued only when bolus 5-FU is discontinued.

NOTE: Patients who require discontinuation of one drug may continue to receive the others**.**

Dose Levels of Oxaliplatin and 5-FU

	Starting Dose*	**Dose Level – 1**	**Dose Level – 2**
Oxaliplatin advanced	85mg/m2	65mg/m2	50mg/m2
Oxaliplatin neoadjuvant	50 mg/m2	40 mg/m2	30 mg/m2
5-FU Bolus	400mg/m2	320mg/m2	200mg/m2
5-FU Infusion	2.4g/m2	2gm/m2	1.6g/m2

* All patients will start cycle 1 with doses listed in 'Starting Dose' column

5.1.1.1 Non-Neurologic Toxicity (Oxaliplatin, irinotecan, and 5-FU Toxicity)

The following table describes the recommended, not required, dose modifications at the start of each subsequent course of therapy. All dose modifications should be based on the worst preceding toxicity.

Toxicity NCI Grade (Value)	**Day of Treatment**	**Interval Toxicity**
Neutropenia (ANC)	If ANC <1000 on day of treatment, hold and check weekly until >1000 mm3. Then treat based on interval toxicity.	
Grade 1 (ANC < LLN - 1500/mm³) Grade 2 (ANC <1499 - 1000/mm³) Grade 3 (ANC <999 - 500/mm³) Grade 4 (ANC < 500/mm³)	Maintain dose level Maintain dose level Maintain dose level Reduce all 3 1 dose level (may subsequently increase 5-FU and oxaliplatin to tolerable toxicity) Febrile neutropenia: decrease irinotecan and oxaliplatin one dose level	
Thrombocytopenia[1]	If PLT <75,000 on day of treatment, hold and check weekly until ≥ 75,000 mm3.	
Grade 1 (PLT < LLN - 75,000/mm3)	Maintain dose level	

Grade 2 (PLT 74,999 – 50,000/mm3) Grade 3 (PLT 49,999 – 25,000/mm3) Grade 4 (PLT< 25,000/mm3)	Maintain dose level Reduce oxaliplatin 1 dose level Reduce oxaliplatin 2 dose levels If reducing oxaliplatin dose does not ameliorate toxicity may need to decrease irinotecan, thern 5-FU on subsequent cycles	
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4	Hold if any grade of diarrhea above baseline is present. Reduce 5-FU and irinotecan 1 dose level upon resolution of diarrhea. If diarrhea has not resolved within 2 weeks of scheduled treatment day, wait resolution and decrease two levels	Maintain dose level Maintain dose level Reduce irinotecan and 5-FU 1 dose level Reduce irinotecan and5-FU 2 dose levels and oxaliplatin 1 dose level (may subsequently increase 5-FU and oxaliplatin to tolerable toxicity)
Other nonhematologic toxicities (except neurologic)[*2] Grade 1 Grade 2 Grade 3 Grade 4	 Maintain dose level Hold until resolved to grade ≤1 Maintain dose level Hold until resolved to grade <1 Reduce most likely culprit(s) 1 dose level Hold until resolved to grade <1 Reduce most likely culprits(s) 1 dose level	 Maintain dose level Maintain dose level Reduce most likely culprit 1 dose level educe all three 1 dose level, and may subsequently re-escalate likely unrelated drugs

*Exceptions: alopecia, anorexia, nausea/vomiting if can be controlled by antiemetics

1 Hemolytic Uremic Syndrome (HUS)/Thrombotic Thrombocytopenic Purpura (TTP): The hemolytic uremic syndrome should be suspected in individuals who experience unexplained severe hemolysis, hemoglobinemia and renal failure as demonstrated by an increase in serum creatinine. Patients suspected of experiencing HUS or demonstrating symptoms of TTP should have the following laboratory analyses conducted: creatinine, BUN, urinalysis with microscopic evaluation, CBC with differential and platelets, PT/PTT, Fibrinogen, Fibrinogen Degradation Products (FDP), Antithrombin III (ATIII), von Willebrand Factor (VWF), anti-nuclear antibodies (ANA), rheumatoid factor (RhF), C3, C4, CH50, anti-platelet antibodies, platelet associated IgG, circulating immune complexes. **Oxaliplatin should be discontinued for any suspected occurrence of HUS or TTP.**

2 With any suspicion of veno-occlusive disease (VOD) of the liver (hyperbilirubinemia, ascites, unexplained weight gain, hepatomegaly, splenomegaly, esophageal varices or other sign of portal hypertension), chemotherapy must be held. If VOD is diagnosed clinically, chemotherapy must be discontinued.

5.1.1.2 Dose Modifications of Oxaliplatin for Neurologic Toxicity

Neurologic Toxicity [a]		
Parasthesias/Dysesthesias	**1-7 day duration**	**> 7 day duration**
Grade 1 – Paresthesias/dysesthesias that resolve and do not interfere with function	Maintain dose	Maintain dose
Grade 2 – Paresthesias/dysesthesias interfering with function, but not activities of daily living	Maintain dose [b]	Decrease oxaliplatin one dose level [b]
Grade 3 – Paresthesias/dysesthesias with pain or with functional impairment that also interfere with activities of daily living	First episode: Decrease only oxaliplatin one dose level [b] Second episode: Stop oxaliplatin only	Stop oxaliplatin only. After resolution to grade 1 oxaliplatin may be reintroduced at discretion of treating physician.
Grade 4 – Persistent paresthesias/dysthesias that are disabling or life-threatening	Stop oxaliplatin only	Stop oxaliplatin only
Laryngeal Dysesthesias (Grading at physician's discretion)		
Grade 1 – Mild **Grade 2** – Moderate	Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours	Maintain dose and consider increasing duration of oxaliplatin infusion to 6 hours
Grade 3 – Severe	At physician's discretion, either stop oxaliplatin or increase duration of infusion to 6 hours	Stop oxaliplatin only
Pulmonary Toxicity		
Dyspnea ≥ grade 2 Hypoxia ≥ grade 2 Pneumonitis/pulmonary infiltrates ≥ grade 2 Cough ≥ grade 3	Hold all therapy until interstitial lung disease is ruled out. • If non-infectious interstitial lung disease is confirmed, oxaliplatin must be discontinued. • If non-infectious interstitial disease is ruled out and infection (if any) has resolved, patients with persistent Grade 2 dyspnea or hypoxia can resume treatment at the physician's discretion.	
a These toxicity descriptions should be used to determine dose modifications and delays. Use the CTCAE v3.0 to assess neurologic toxicity for adverse event reporting. b Treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy or ≥ grade 2 if intolerable to the patient. Gemcitabine administration can continue during this period at the discretion of the investigator. Nab-Paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1 or re-instituted at the same dose for a grade 2 neuropathy		

5.1.2 Dose Modifications for Gemcitabine and Abraxane Toxicity

NOTE: Patients who require discontinuation of both gemcitabine and abraxane for toxicity will discontinue protocol therapy but will continue to be followed for disease progression and survival.

NOTE: Patients who require discontinuation of one may continue to receive the second chemotherapy agent. This is expected to be common since the cumulative neurotoxicity of abraxane often requires its cessation after 4-6 months.

5.2 Gemcitabine and nab-Paclitaxel

5.2.1 Rules for Dose Omissions and Modified Schedules

Day 1 dose missed:
If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e., 1-2-3-Rest, X-1-2-3-Rest, etc.)

Day 8 dose is missed:
Cycle continues per protocol, with one dose not given (i.e., 1-2-3-Rest, 1-X-3-Rest, 1-2-3- Rest, etc.). Day 15 is administered as per cycle calendar if counts and chemistries permit.

Day 15 dose missed:
That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a x2q3 (21-day) cycle (i.e., 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc).

Doses will be reduced for hematologic and other non-hematologic toxicities. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.0.

Table 3. Dose Levels of Gemcitabine and Abraxane

Dose Level	nab- Paclitaxel (mg/m^2)		Gemcitabine (mg/m^2)[a]
Study Dose	125		1000
-1	100		800
- 2 [b]	75		600

[a]Dose reductions may or may not be concomitant. Please refer to Tables 4-6 for specific recommendations regarding dose reductions
[b]Additional 25% dose modifications are permissible to establish the tolerable dose for an individual patient

Patients who experience study drug-related toxicities that require a delay in scheduled nab-paclitaxel and gemcitabine dosing for ≥ 28 days will be discontinued from further participation in this study. When a dose reduction is required for Day 1 of any cycle, no dose re-escalation will be permitted for the duration of study treatment.

DOSE MODIFICATIONS AT DAY 1
In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, the doses and schedule of nab-paclitaxel and/or gemcitabine may be adjusted as detailed in Tables 4 and 5 below:

Table 4. Dose Modifications for Hematologic Toxicities (<u>Day 1 of Each Cycle</u>)

For counts on Day 1:

Absolute Granulocytes		Platelets	Timing
≥ 1.5 x 109/L	AND	≥ 100 x 109/L	Treat on time
	OR		
< 1.5 x 109/L		<100 x 109/L	Delay by one week intervals until recovery

Table 5. Dose Modifications for Non-Hematologic Toxicity (Day 1 of Each Cycle)

Non-hematologic toxicity (except neuropathy, alopecia) ordinarily should have resolved to Grade 0 or 1 before initiating the next cycle. If such toxicity resulted in a dose hold in the previous cycle, the following will determine dosing for the current cycle:

Non Hematologic Toxicity (except neuropathy) and/ or Dose Hold with Previous Cycle	
Toxicity in previous cycle causing dose to be held	Gemcitabine + nab-paclitaxel dose this cycle [a]
Grade 0, 1 or 2	Same as day 1 previous cycle
Grade 3 toxicity	Decrease gemcitabine by one level
Grade 4 toxicity	Decrease gemcitabine two levels[b]
Dose held in 2 previous consecutive cycles	Decrease gemcitabine by one level

[a]If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced
[b]Pulmonary embolism (a Grade 4 toxicity in CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.

DOSE ADJUSTMENTS WITHIN A TREATMENT CYCLE
In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Table 6, whenever possible.

Table 6. Dose Modifications for Hematologic Toxicity within a Cycle (days 8, 15)

ANC		Platelets	Nab- paclitaxel	Gemcitabine
≥1500	AND	≥100,000	100%	100%
1000-1499	OR	75,000-99,000	100%	100%
500-999	OR	50,000-74,000	Decrease one dose level [a]	Decrease one dose level
<500	OR	<50,000	hold	hold
Febrile Neutropenia (Grade 3 or 4)			Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment
Recurrent Febrile neutropenia (Grade 3 or 4)			Decrease to next lower dose level and do not re- escalate throughout the rest of treatment	Decrease 2 dose levels and continue throughout the rest of treatment

[a]GCSF may be used (at dose and schedule per institutional guidelines) at the discretion of the investigator to maintain 'nab-paclitaxel dose intensity

5.2.2 Provisions for Fever/Infection

Because of significant risk of non-neutropenic sepsis, at the first occurrence of fever > 38.5°C, regardless of the neutrophil count, either ciprofloxacin (500mg orally bid) or amoxicillin/clavulinate (Augmentin, 500mg orally bid or tid) should be instituted. At initiation of the study treatment, patients should be provided prescriptions for one or other antibiotic, and instructed to begin treatment at the first observation of a fever or 35.5C or more, or if they feel they are developing a fever and a thermometer is not available. They should follow a clear plan for blood count evaluation, and clinical assessment for infection, and/or the need for hospitalization.

Febrile patients will have their treatment interrupted until recovery (temperature below 100°F for >3 days), and will be managed according to standard practice for this disorder. Upon resolution of this condition, abraxane and gemcitabine therapy can resume at the next lowest dose. Dose modifications may also be made for non-hematological toxicity within a cycle as specified in Table 7.

Table 7. Dose Modifications for Non-Hematological Toxicity within a Cycle
CTC Grade

CTC Grade	Percent of Day 1
0-2 (and Grade 3 nausea/ vomiting and alopecia)	100%
3 (except nausea/vomiting and alopecia)	50% or Hold[a]
4	Hold[a]

a This decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator. Treatment may be reinstated on Day 1 of the next cycle.

5.2.3 Peripheral Neuropathy

Nab-Paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy or ≥ grade 2 if intolerable to the patient. Gemcitabine administration can continue during this period at the discretion of the investigator. Nab-Paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1 or re-instituted at the same dose for a grade 2 neuropathy. Patients experiencing peripheral neuropathy may require an extended delay in scheduled nab-Paclitaxel dosing, but can remain on gemcitabine, and have ‘nab-paclitaxel reintroduced at a subsequent cycle should the neuropathy improve as above. Patients receiving a reduced dose of nab-Paclitaxel who experience ≥ Grade 3 peripheral neuropathy at that dose level requiring a dose delay ≥ 21 days without resolving to ≤ Grade 1 should have ‘nab-paclitaxel discontinued.

As observed in other clinical trials, ≥ Grade 3 neuropathy related to nab-Paclitaxel is usually seen in later phases of the treatment (cycle 6 and beyond). If ≥ Grade 3 neuropathy occurs in early treatment cycles, other factors predisposing the patient to neuropathy might be present (eg. diabetes, alcohol consumption, concomitant medications). To maintain dose intensity during the first 6 treatment cycles, careful consideration should be exercised when these predisposing factors are present.

5.2.4 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level of both drugs. If the patient continues to experience these reactions, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

5.2.5 Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, study drug should be withheld until resolution to ≤ Grade 1, then reinstituted at the next lower dose level of both drugs. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued

5.2.6 G-CSF

The use of growth factors to support neutrophil counts is permissible after cycle 1 if neutropenia would otherwise require a dose reduction to less than 100 mg/m2 of abraxane. GCSF may also be considered for therapeutic administration in the event of febrile neutropenia as noted above, according to institutional practice.

5.3 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout treatment.

5.4 Duration of Therapy

Patients will receive protocol therapy unless the constraints of this therapy are detrimental to the patient's health. In this event, the protocol should be discontinued. Furthermore, the protocol will be discontinued should the patient withdraw consent.

5.5 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for recurrence and for survival. All patients must also be followed through completion of all protocol therapy.

6 Pharmacologic Data

6.1 Oxaliplatin

For complete instruction regarding preparation, handling, dosing and storage, please refer to the FDA-approved package insert.

6.1.1 Other Names

Eloxatin, trans-*l*-diaminocyclohexane oxalatoplatinum, cis-[oxalato(trans-*l*-1,2-diaminocyclohexane)platinum(II)].

6.1.2 Classification

Platinating agent.

6.1.3 Mode of Action

The mechanism of action of oxaliplatin is similar to cisplatin. The main site of action is intrastrand cross-linking, therefore inhibiting DNA replication and transcription.

6.1.4 Storage and Stability

Oxaliplatin vials are stored at room temperature between 20° and 25°C protected from light. Reconstituted solution in sterile water or 5% dextrose may be stored for 24 to 48 hours at 2° to 8°C. After further dilution in 5% dextrose, the solution is stable for 24 hours at room temperature.

6.2.5 Dose Specifics

85 mg/m² IV in 500 ml D5W.

6.1.5 Preparation

The freeze-dried powder is reconstituted by adding 10mL (for the 50 mg vials) or 20mL (for the 100mg vials) of Water for Injection or Dextrose 5% in Water to yield a 5mg/mL solution. The reconstituted solution must be further diluted in an infusion solution of 250mL Dextrose 5% in Water. The reconstitution or final dilution must never be performed with a sodium chloride solution.

6.1.6 Administration

The diluted solution of oxaliplatin in 500mL D5W is administered intravenously over 2 hours concurrent with leucovorin. Separate infusion bags and lines must be used with Y-line tubing connecting the two lines before the single injection site.

6.1.7 Incompatibilities

When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion should precede that of 5-fluorouracil. Ensure the infusion lines are adequately flushed with 5% Dextrose between administration of the two drugs.
Do not mix or administer with saline or other chloride containing solutions.
Oxaliplatin is unstable in the presence of chloride.
Do not simultaneously administer other drugs by the same infusion line.
Do not mix with alkaline solutions. Oxaliplatin is unstable under alkaline conditions.
Do not use components containing aluminum for the preparation of oxaliplatin administration. There is a risk of drug degradation when in contact with aluminum.

6.1.8 Reported Adverse Events and Potential Risks

Allergy/Immunology: Rhinitis, Allergic/Hypersensitivity reactions (including drug fever). Can be fatal and occur with any cycle of therapy. Manifested by: urticaria, pruritus, flushing of the face, diarrhea (during infusion), shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation, and syncope.

Auditory: Middle ear/hearing (ototoxicity, mild), inner ear/hearing (mild hearing loss).
Blood/Bone Marrow: decreased hemoglobin, hemolysis (e.g. immune hemolytic anemia, drug-related hemolysis), decreased leukocytes, decreased platelets, neutropenia. Single-agent oxaliplatin produces only mild myelosuppression with minimal to severe neutropenia, anemia or thrombocytopenia. In combination, more grade 3/4 neutropenia or thrombocytopenia may be noted.
Cardiovascular (Arrhythmia): Sinus tachycardia, supraventricular arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmias (PVCs/bigeminy/trigeminy/ventricular tachycardia).
Cardiovascular (General): Edema, hypertension, hypotension
Coagulation: DIC (disseminated intravascular coagulation), thrombosis/embolism (including pulmonary embolism), prolonged prothrombin time, increased INR, thrombotic microangiopathy (thrombotic thrombocytopenic purpura, hemolytic uremic syndrome). The hemolytic uremic syndrome (HUS) should be suspected in individuals who experience the following: unexplained severe hemolysis, hemoglobinemia and renal failure as demonstrated by an increase in serumcreatinine. Patients suspected of experiencing HUS should be carefully evaluated.
Oxaliplatin should be discontinued for any suspected occurrence of hemolytic uremic syndrome.
Constitutional Symptoms: Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x l09L), fatigue (lethargy, malaise, asthenia), rigors/chills, insomnia, sweating, weight gain, weight loss.
Dermatology/Skin: Erythema or skin eruptions, alopecia, hand-foot skin reaction, injection site reaction, rash/desquamation, urticaria, pruritus/itching, dry skin, nail changes, pigmentation changes.
Endocrine: Hot flashes/flushes.
Gastrointestinal: Anorexia, ascites (non-malignant), colitis, constipation, dehydration, diarrhea, dysphagia, enteritis, esophagitis, flatulence, gastritis, gastrointestinal reflux (heartburn, dyspepsia), ileus (or neuroconstipation), intestinal obstruction, nausea, odynophagia (painful swallowing), stomatitis /pharyngitis (oral/pharyngeal mucositis), taste disturbance (dysgeusia), typhilitis, ulcer, vomiting, xerostomia (dry mouth).
Hemorrhage: CNS hemorrhage/bleeding, hemoptysis, hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, melena, GI bleeding, rectal bleeding/hematochesia, pulmonary hemorrhage, vaginal hemorrhage, other (hemorrhage NOS).
Hepatobiliary/Pancreas: increased alkaline phosphatase, increased bilirubin, increased GGT (gamma glutamyl transpeptidase), hepatic enlargement, increased SGOT (AST) (serum glutamic oxaloacetic transaminase), increased SGPT (ALT) (serum glutamic pyruvic transaminase), pancreatitis, hepatic veno-occlusive disease (manifested by hepatomegaly, ascites, and jaundice).
Infection/Febrile Neutropenia: Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented fever (ANC <1.0 x $l0^9$/L fever >38.5°C), infection (documented clinically or microbiologically with grade 3 or 4 neutropenia (ANC <1.0 x l09L), infection with unknown ANC, infection without neutropenia.
Metabolic/Laboratory: Acidosis (metabolic or respiratory), hypoalbuminemia, hypocalcemia, hyperuricemia, hyperglycemia, hypoglycemia, hypokalemia, hypophosphatemia, hyponatremia, hypomagnesemia
Musculoskeletal: Involuntary muscle contractions, trismus.
Neurology: Ataxia (incoordination, including abnormal gait), cerebrovascular ischemia, confusion, dizziness, extrapyramidal movements/restlessness, insomnia, mood alteration (depression, anxiety), neuropathy cranial (ptosis), vertigo, acute sensory neuropathy induced or exacerbated by cold (including acute laryngopharyngeal dysesthesias, Lhermitte's sign, upper extremity paresthesia), chronic peripheral neuropathy (paresthesias, dysesthesias, hypoesthesias), seizure, somnolence, speech impairment, syncope.
Ocular/Visual: Conjunctivitis, vision abnormalities including blindness, optic neuritis, papilledema, hemianopsia, visual field defect, transient blindness.

Pain: abdominal pain or cramping, athralgia (joint pain), bone pain, chest pain (noncardiac and non-pleuritic), headache (including migraine), myalgia (muscle pain including cramps and leg cramps).
Pulmonary/Upper Respiratory: Bronchospasm/wheezing, pulmonary fibrosis, cough, dyspnea (shortness of breath), hiccoughs (hiccups, singultus), pneumonitis/pulmonary infiltrates (including eosinophilic pneumonia, interstitial pneumonitis, and interstitial lung disease), laryngospasm, nasal cavity/paranasal sinus reactions, voice changes (hoarseness, loss or alteration in voice, laryngitis).
Renal/Genitourinary: Increased creatinine, renal failure, urinary retention, urinary urgency, dysuria. Hemolytic Uremic Syndrome (HUS) – see coagulation.
Vascular: Phlebitis, thrombosis
Also reported on oxaliplatin trials but with the relationship to oxaliplatin still undetermined: tongue paralysis, anemia, aphasia, abnormal hepatic function, hyporeflexia, anxiety, depression, dysarthria, insomnia, increased sweating, rhinitis, epistaxis, gout, pancreatitis, idiopathic thrombocytopenia (5 cases), thrombocytopenia associated with hemolytic anemia (2 cases).

NOTE: Oxaliplatin in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

6.1.9 Nursing/Patient Implications

- Premedicate with antiemetics (5 HT3 antagonist and steroid) to prevent severe nausea and vomiting.
- Monitor for diarrhea and treat symptomatically.
- Monitor for neuropathies (parasthesias of hands, feet and toes, pharynx; occasionally cramps). If they occur, they tend to be brief (less than one week) during the first course but longer with subsequent courses. Advise patients to avoid cold exposure and against touching cold objects. Sensory neuropathies develop with continued treatment. Ask patient if changes in ambulation, swallowing, breathing or fine motor activity have been noted.
- Prolonging the oxaliplatin infusion time to 6 hours may alleviate acute neurologic toxicities.
- Monitor for respiratory changes, such as shortness of breath.

WARNING: The hemolytic uremic syndrome should be suspected in individuals who experience the following: unexplained severe hemolysis, hemoglobinemia, and renal failure as demonstrated by an increase in serum creatinine.

6.2 Fluorouracil

6.2.1 Other Names

5-Fluorouracil, 5-FU, Adrucil, Efudex.

6.2.2 Classification

Antimetabolite

6.2.3 Mode of Action

Fluorouracil 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.

6.2.4 Storage and Stability

Stable for prolonged periods of time at room temperature if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

6.2.5 Dose Specifics

400mg/m², then 2.4g/m².

6.2.6 Administration

5-FU will be administered at 400mg/m² IV bolus, followed by 2.4g/m² continuous infusion over 46 hours on day 1 and day 2.

6.2.7 Incompatibilities

Incompatible with doxorubicin and other anthracyclines. When giving doxorubicin IV push or through a running IV, flush line before giving fluorouracil. May form precipitate with fluorouracil in some concentrations.

6.2.8 Availability

Commercially available in 500mg/10ml ampules and vials, and 1g/20mL, 2.5g/50mL, and 5gm/100mL vials.

6.2.9 Side Effects

Hematologic: Leukopenia, thrombocytopenia, anemia; can be dose limiting; less common with continuous infusion.
Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia.
Gastrointestinal: Nausea, vomiting, anorexia; diarrhea, can be dose limiting; mucositis, more common with 5-day infusion, occasionally dose limiting; severe, cholera-like diarrhea which can be fatal when given with leucovorin.
Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia).
Cardiac: Angina, noted with continuous infusion.
Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.
Hepatic: Hepatitis with hepatic infusion.

6.2.10 Nursing/Patient Implications

- Monitor CBC, platelet counts.
- Administer antiemetics as indicated.
- Monitor for diarrhea. Encourage fluids and treat symptomatically - may be dose limiting.
- Assess for stomatitis - oral care recommendations as indicated.

- Monitor for neurologic symptoms (headache, ataxia).
- Patients on continuous infusions may need instruction regarding central IV catheters and portable IV or IA infusion devices.
- Inform patient of potential alopecia.

6.3 Leucovorin

For complete prescribing information, please refer to the approved package insert.

6.3.1 Other Names

Leucovorin Calcium, Wellcovorin, citrovorum factor, folinic acid, 5-formyl tetrahydrofolate, LV, LCV.

6.3.2 Classification

Tetrahydrofolic acid derivative.

6.3.3 Mode of Action

Leucovorin acts as a biochemical cofactor for 1-carbon transfer reactions in the synthesis of purines and pyrimidines. Leucovorin does not require the enzyme dihydrofolate reductase (DHFR) for conversion to tetrahydrofolic acid. The effects of methotrexate and other DHFR-antagonists are inhibited by leucovorin.

Leucovorin can potentiate the cytotoxic effects of fluorinated pyrimidines (i.e., fluorouracil and floxuridine). After 5-FU is activated within the cell, it is accompanied by a folate cofactor, and inhibits the enzyme thymidylate synthetase, thus inhibiting pyrimidine synthesis. Leucovorin increases the folate pool, thereby increasing the binding of folate cofactor and active 5-FU with thymidylate synthetase.

6.3.4 Storage and Stability

All dosage forms are stored at room temperature. The reconstituted parenteral solution, 10mg/ml, is stable for at least 7 days at room temperature. At concentrations of 0.5-0.9 mg/ml the drug is chemically stable for at least 24 hours at room temperature under normal laboratory light. The oral solution, 1 mg/ml, is stable for 14 days refrigerated and 7 days at room temperature.

6.3.5 Dose Specifics

400 mg/m²

6.3.6 Dose Preparation

The 50 and 100 mg vials for injection are reconstituted with 5 and 10 mL of sterile water or bacteriostatic water, respectively, resulting in a 10 mg/mL solution. The 350 mg vial is reconstituted with 17 mL of sterile water resulting in a 20 mg/mL solution.

6.3.7 Administration

Intravenous infusion over 2 hours, concurrent with oxaliplatin.

6.3.8 Compatibilities

Leucovorin (0.5-0.9 mg/mL) is chemically stable for at least 24 hours in normal saline, 5% dextrose, 10% dextrose, Ringer's injection or lactated Ringer's injection. Leucovorin (0.03, 0.24 and 0.96 mg/mL) is stable for 48 hours at room and refrigeration temperatures when admixed with floxuridine (FUDR, 1, 2 and 4 mg/mL) in normal saline. Leucovorin is compatible with fluorouracil and oxaliplatin.

6.3.9 Availability

Commercially available in parenteral formulations (50 mg, 100 mg and 350 mg vial).

6.3.10 Side Effects

Hematologic: Thrombocytosis.
Dermatologic: Skin rash.
Gastrointestinal: Nausea, upset stomach, diarrhea.
Allergic: Skin rash, hives, pruritus.
Pulmonary: Wheezing (possibly allergic in origin).
Other: Headache; may potentiate the toxic effects of fluoropyrimidine therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects.

6.3.11 Nursing/Patient Implications

- Observe for sensitization reactions.
- When given with fluoropyrimidines, monitor closely for diarrhea and stomatitis.

6.4 Gemcitabine

6.4.1 Generic Name

2'-Deoxy-2',2'-difluorocytidine monohydrochloride, Gemzar

6.4.2 Classification

Antimetabolite (nucleoside analog)

6.4.3 Mechanism of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate

competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated intoDNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

6.4.4 Storage and Stability

Unreconstituted drug vials are stored at controlled room temperature. Reconstituted solution should be stored at controlled room temperature and used within 24 hours. Solutions of gemcitabine should not be refrigerated; crystallization may occur. The unused portion should be discarded.

6.4.5 Dose Specifics

For pancreatic cancer, a dose of 1000mg/m2 over 30 minutes once weekly for up to 7 weeks followed by a week of rest, then once weekly for three weeks of every four weeks is used. Other dosing schedules currently are being studied.

6.4.6 Preparation

Reconstitute the 200mg vial with 5ml and the 1Gm vial with 25ml preservative free normal saline to make a solution containing 38 mg/ml. Shake to dissolve.

6.4.7 Administration

The drug may be administered as prepared above or further diluted with normal saline to a minimum concentration of 0.1mg/ml. Gemcitabine is commonly diluted in 100 ml or 250ml of saline.

6.4.8 Availability

Gemcitabine is commercially available in 200mg and 1Gm vials.

6.4.9 Side Effects

1. Hematologic: Myelosuppression is usually mild to moderate and is more pronounced for the granulocyte count. Thrombocythemia is also commonly reported.
2. Dermatologic: A rash is seen in about 25% of patients and is associated with pruritus in about 10% of patients. The rash is usually mild, not dose-limiting, and responds to local therapy. Desquamation, vesiculation, and ulceration have been reported rarely. Alopecia is reported in <1% of patients.
3. Gastrointestinal: Nausea and vomiting are reported in about two-thirds of patients and requires therapy in about 20% of patients. It is rarely (<1%) dose-limiting, and is easily manageable with standard antiemetics. Diarrhea is reported in 8% of patients,

constipation in 6%, and oral toxicity in 7%.
4. Hepatic: Abnormalities of hepatic transaminase enzymes occur in two-thirds of patients, but they are usually mild, nonprogressive, and rarely necessitate stopping treatment. However, gemcitabine should be used with caution in patients with impaired hepatic function.
5. Pulmonary: Bronchospasm after injection has been reported in less than 1% of patients and is usually mild and transient, but parenteral therapy may be required. Dyspnea within a few hours of injection is reported in 10% of patients. It is usually mild, short-lived, rarely dose-limiting, and usually abates without any specific therapy. Cough and rhinitis are also commonly reported.
6. Neurologic: Somnolence has been reported in 10% of patients, and insomnia is common.
7. Cardiovascular: A few cases of hypotension were reported. Some cases of myocardial infarction, congestive heart failure, and arrhythmia have been reported, but there is no clear evidence that gemcitabine causes cardiac toxicity. Peripheral edema is reported in about 30% of patients. Some cases of facial edema have also been reported. Edema is usually mild to moderate, rarely dose-limiting, sometimes painful, and reversible after stopping gemcitabine treatment.
8. Other: Flu-like symptoms are reported for about 20% of patients. This includes fever, headache, back pain, chills, myalgia, asthenia, and anorexia. Malaise and sweating are also commonly reported.

6.4.10 Nursing Implications

1. Administer over 30 minutes.
2. If the patient reports burning at the injection site, slow down rate to allow the dose to run in over 1 hour.
3. Rash can be treated with topical therapy or the administration of diphenhydramine and dexamethasone prior to administration.
4. Flu-like symptoms can be treated with acetaminophen.

6.4.11 References

1. Anon. Clinical Brochure: Gemcitabine HCl (LY188011 HCl). Lilly Research Laboratories, Indianapolis, IN.
October 3, 1994.
2. Eli Lilly & Company. Package Insert. August 26, 1998.

6.5 nab-paclitaxel [Abraxane]

6.5.1 Formulation

Nab- paclitaxel is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm. Each 50 mL vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin, as a white to yellow sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection. Protocol Amendment 4, date August 16, 2010 21
Nab- paclitaxel is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. It has been developed to reduce the toxicities associated with Taxol (paclitaxel) Injection (in which paclitaxel - from the native crystalline form - is in solution with Cremophor

EL/ethanol as the solvent) while maintaining or improving its chemotherapeutic effect. Nab- paclitaxel has been approved in the US, Canada, India, the EU, Korea and China (and is under review in a number of other countries) for the treatment of women with metastatic breast cancer (MBC). Nab- paclitaxel alone and in combination is being evaluated in a number of cancers including: metastatic melanoma, pancreatic cancer, cervical cancer and other solid tumors. Conditions which are responsive to paclitaxel such as non-hematological solid tumor malignancies are good clinical candidates for treatment with nab-paclitaxel.

6.5.2 Preclinical studies with nab- paclitaxel

A range of preclinical studies in the appropriate species have been completed with nab- paclitaxel including single and repeat-dose toxicity studies, carcinogenicity evaluations, reproductive toxicity assessments, and mutagenicity and toxicity studies. A thorough discussion of these is included in the Investigator's Brochure (IB).
Preclinical studies comparing nab-paclitaxel to Taxol demonstrated lower toxicities, with a MTD approximately 50% higher for nab-paclitaxel compared to Taxol. At equitotoxic doses of paclitaxel, nab-paclitaxel was found to be markedly more efficacious in animal models than Taxol.

6.5.3 Potential Risks for nab- paclitaxel based on previous clinical studies

Nab- paclitaxel is not formulated in Cremophor and thus the risk of hypersensitivity reactions is much less than that of Taxol. The major risks of nab- paclitaxel have been assessed in clinical trials in patients with a variety of malignances and reflect the known toxicities of paclitaxel. See the IB for a complete description of all toxicities reported in conjunction with nab- paclitaxel administration.
The most common toxicities reported in previous clinical trials included:
• Myelosuppression, predominantly neutropenia. Grade 4 neutropenia was reported and typically resolved in < 7 days and did not require colony stimulating factor support.
• Peripheral neuropathy, predominantly sensory. Grade 3 peripheral neuropathy was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the nab-paclitaxel dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart nab-paclitaxel dosing at a lower dose levels.
• Nausea and vomiting. Nausea and vomiting were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens.
• Myalgias and arthralgias. Myalgias and arthralgias were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication.
• Mucositis. Mucositis was reported typically Grade 1 or 2. It was not dose limiting
• Alopecia. Alopecia was reported by most patients and was similar to that seen with Taxol.

6.5.4 Drug Supply

Nab-paclitaxel is commercially available..

7. Statistical Plan

7.1 Sample Size Determination and Methods and Randomization

The primary goal of this study is to estimate the overall and relapse-free survival rates of the two test adjuvant chemotherapy/chemoradiotherapy regimens in resectable pancreatic cancer. We will

randomize n=50 patients between the two arms (n=25/arm). Although we will not have sufficient power to test for differences between arms on the primary endpoints, randomization will permit unbiased estimation of these differences that can later be used in metanalyses if larger studies are conducted.

We will create the randomization sequences at the Abramson Cancer Center Biostatistics Core Facility in the Department of Biostatistics & Epidemiology of the University of Pennsylvania Perelman School of Medicine. Randomization will be stratified by center (Penn or Pittsburgh) and blocked in blocks of random sizes to prevent investigators from deducing the treatment assignments of future patients. Randomization sequences will be generated by pseudo-random number generator and made available to investigators as subjects are enrolled. Because the treatment arms differ considerably in the type and timing of treatment, and moreover outcome variables are hard endpoints that are not subject to placebo effects or evaluation bias, randomizations will not be masked to either patients or clinical staff.

The design calls for treating 25 resectable pancreatic cancer patients with each of the two regimens. We do not plan formal interim analyses for futility, but we will conduct continuous interim monitoring for safety. In each arm we will record serious, dose-limiting adverse events as they occur and calculate the Bayesian posterior probability distribution of the adverse event rate, updating after each patient. We will raise a red flag for safety if the posterior probability that the event rate is greater than 30% exceeds 60%. Assuming a Beta (2,6) prior for the event rate, the red flag will occur as indicated in the Table below. That is, if the first two serious events occur in the first n=2 patients, we will consider terminating the study or modifying the treatment. Similarly, the occurrence of the third serious AE by the 5th patient will generate a safety signal, and so forth.

Table. Number of events/number of patients to trigger a safety signal.

Number of events	Minimum number of patients	Maximum number of patients
2	2	2
3	3	5
4	6	8
5	9	11
6	12	15
7	16	18
8	19	21
9	22	24
10	25	25

We will tabulate rates of all adverse events. With n=25 subjects per arm, 95% confidence intervals around event rates will extend no more than ±20% around observed rates. With 25 subjects per treatment arm, we can identify with 90% power any unanticipated toxicity that has prevalence at least 8.8%.

The primary goals of the study are to obtain preliminary estimates of overall and progression-free survival rates. We will estimate survival distributions by the Kaplan-Meier product-limit survival curve. In R9704, the median survival for patients with head lesions (the majority of the patients) was 20.5 months in the arm that received gemcitabine and 5-FU/XRT. In the German trial of gemcitabine without radiation the progression-free survival was 13.4 months. In this small trial we will regard a median progression-free survival of 20 months, or a median survival of 30 months, as indicative of potential therapeutic benefit meriting additional study. Under these assumed rates, expected 95% confidence intervals for the median will extend from 20 to 46 months for overall survival and from 14 to 29 months for progression-free survival.

The genomic analyses of the patients will be accomplished using biopsy samples obtained at the time of surgery. Tissue containing >70% tumor will be stored at −70°C, and sequenced using the best available technology – tissues will be batched for this purpose and analyzed when approximately half the accrual has been accomplished, and again on completion. Bioinformatic analyses will be descriptive.

Imaging studies will be analyzed using at a minimum SUV values, and correlated with outcome. In addition, these findings will be correlated with mutational profiles as obtained from the genomic studies. These analyses will be considered exploratory.

8 Safety and Adverse Events

8.1 Adverse Event Reporting and Definitions

In the event of an adverse event the first concern will be for the safety of the subject. Serious adverse events include:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

Please note, clearly disease-related hospitalizations will be exempted from this requirement.

8.2 Reporting of Serious Treatment Emergent Adverse Events

All serious adverse events should be recorded on a MedWatch 3500 Form and faxed to:

Principal Investigator
Peter J. O'Dwyer, M.D.
12 Penn Tower,
3400 Spruce Street,
Philadelphia PA 19104
Phone: 215-662-7606
Fax: 215-243-3269

AND:

Cancer Center's DSMC via VELOS. Reporting to the IRB will follow the IRB's rubric for Unexpected Events.

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500 report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event.

8.2.1 IRB and Cancer Center DSMC Notification

Reports of all serious adverse events (including follow-up information) must be submitted to the IRB within 10 working days, according to IRB guidelines.

Reporting Process to IRB

Principal Investigators are encouraged to submit reports of unanticipated problems posing risks to subjects or others using the form: "**Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events**" via HS-ERA or a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation) within 10 working days.

Reporting Process to the DSMC

In addition, all on-site SAEs for Penn subjects regardless of attribution or expectedness must be submitted to the DSMC within 10 days via VELOS. You should continue to send reports to the DSMC for **90 days** following the last date the subject received study treatment/therapy or was exposed to an investigational device. Please do not send reports after the 90 day window. They will not be accepted or processed.

All unexpected deaths or deaths related to the study agent(s)/device(s) must be reported within 24 hours. All other deaths should be reported within 30 days.

8.3 Definitions

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay as a result of administration of the study drug
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled

visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization to allow efficacy measurement for the study.
- Hospitalization for therapy of disease that is clearly related to the target disease and not the treatment as judged by the clinical investigator.

8.4 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (EDC) via VELOS.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10 Study Monitoring, Auditing, and Inspecting

10.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and The Cancer Center monitors of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

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7.0 Schedule of Events

7.1 Arm A

Screening procedures are to be performed within 4 weeks of cycle 1 day 1 with laboratory results within 14 days.

Test	Screening	C1&2 Day 1	C1&2 Day 8	C3&4 Day 1	C3&4 Day 8	
Informed Consent	X					
Phys Assessment	X	X				Per standard practice Not recorded in study database
Height/Weight	X					
Vital Signs/PS	X	X	X	X	X	Per standard practice Not recorded in study database
Clinical Labs CBC/Chemistry/ Tumor Markers[2]	X	X	X	X	X	Per standard practice
AE assessment	X	X	X	X	X	Until completion of treatment
Disease Assessment (routine CT or MR)	X					Unless rising markers, perform at end of treatment, then at 4-6 months, and annually thereafter
FDG-PET	X[1]					
Circulating Tumor cells*	X					Before start of radiation/5-FU and at end of treatment, and at approximately 6 month intervals therafter where possible

1 If covered by insurance. If not, can be omitted.
2 Tumor markers only need to be drawn monthly
*to be initiated when feasible

7.2 Arm B

Screening procedures are to be performed within 4 weeks of cycle 1 day 1 with labs laboratory results within 14 days.

Test	Screening	C1&2 Day 1	C1&2 Day 15	C1&2 Day 28	
Informed Consent	X				
Phys Assessment	X	X			Per standard practice Not recorded in study database
Height/Weight	X				
Vital Signs/PS	X	X	X	X	Per standard practice Not recorded in study database
Clinical Labs CBC/Chemistry/ Tumor Markers	X	X	X	X	Per standard practice
AE assessment	X	X	X	X	Until completion of treatment
Disease Assessment (routine CT or MR)	X				Unless rising markers, perform at end of treatment, then at 4-6 months, and annually thereafter
FDG-PET	X[1]				
Circulating Tumor cells*	X				Before start of radiation/5-FU and at end of treatment, and at approximately 6 month intervals therafter where possible

1 If covered by insurance. If not, can be omitted.
*to be initiated when feasible