Cover Letter

TITLE: Phase 2 Study of Preoperative chemotherapy with ABRAXANE and Gemcitabine followed by chemoradiation for Borderline Resectable or Node-positive Pancreatic Cancer

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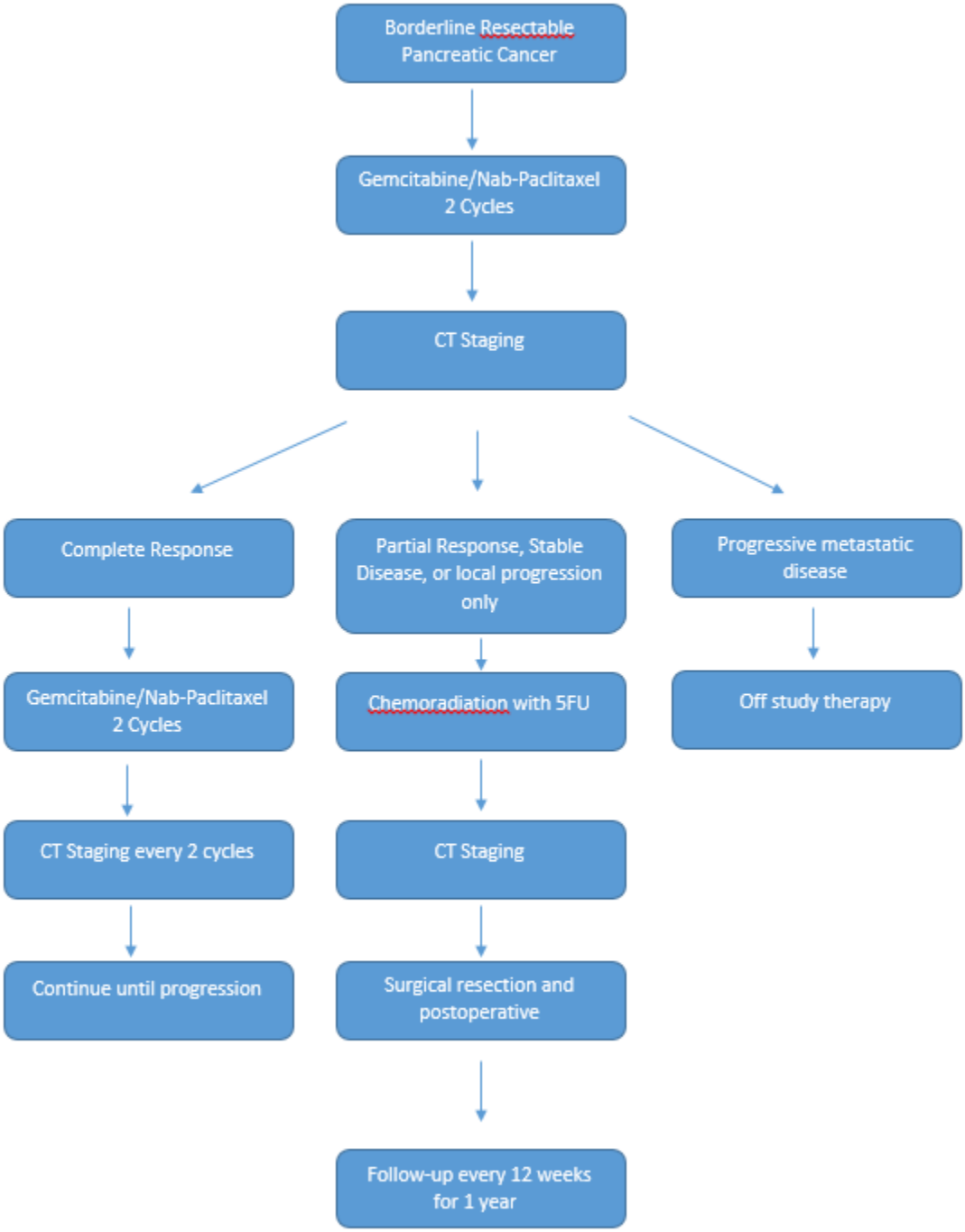
SCHEMA


Borderline Resectable Pancreatic Cancer
Gemcitabine/Nab-Paclitaxel 2 Cycles
CT Staging
Complete Response
Partial Response, Stable Disease, or local progression only
Progressive metastatic disease
Gemcitabine/Nab-Paclitaxel 2 Cycles
Chemoradiation with 5FU
Off study therapy
CT Staging every 2 cycles
CT Staging
Continue until progression
Surgical resection and postoperative
Follow-up every 12 weeks for 1 year

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1.0 OBJECTIVES

1.1 Primary Objective

To determine the R0 resection rate for subjects with borderline resectable or lymph node positive pancreatic adenocarcinoma treated with a multimodality neoadjuvant therapy of preoperative gemcitabine and ABRAXANE followed by 5-fluorouracil based image-guided IG-IMRT chemoradiotherapy

1.2 Secondary Objectives

1.2.1 To determine 1-year relapse-free survival rate with the investigational protocol
1.2.2 To determine 1-year and 2-year overall survival rates
1.2.3 To assess response rate by imaging (RECIST 1.1) and pathologic analysis
1.2.4 To assess the toxicity and safety according to CTCAE v4.0 criteria

2.0 BACKGROUND

2.1 Study Disease

Pancreatic adenocarcinoma (PDAC) is the second most common gastrointestinal malignancy in the United States, with an estimated 45,220 new cases in 2013 and an estimated 38,460 deaths (1). This disease continues to have a poor prognosis with a median survival in all cases of only 6 months. Less than 10% of patients present with clearly localized disease which is limited to the primary site, while the remainder are divided between locally advanced (27%) and distant metastatic disease (53%) at diagnosis (2). The only known curative therapy for PDAC is surgical resection, however even those patients who undergo a complete (R0) primary tumor resection have a relapse rate approaching 90% and a median survival of less than 2 years, while patients who have margin positive (R1) resections have a median survival of ~1 year, similar to locally advanced, unresectable tumors. Long-term follow-up suggests that the 5-year survival rate for all cases of pancreatic adenocarcinoma is poor at approximately 6%, and has not changed in the last several decades. An analysis of SEER data between 1991 and 1996 indicated a 3 year survival rate of 34% for patients who have undergone curative intent surgery (3). Additionally, the most important predictor of survival in this population was postoperative adjuvant chemoradiation therapy. As resection is the only potential pathway to cure, and there is interest in increasing the percentage of patients who are eligible for resection by delivering neoadjuvant therapy.

2.2 Neoadjuvant treatment of localized pancreatic adenocarcinoma

Pre-operative (neoadjuvant) treatment with chemotherapy and/or radiation therapy for patients with localized PDAC presents a number of potential advantages. These include the early treatment of micrometastatic disease, the ability to deliver more intensive therapy to more patients, as well as a means to identify patients with occult metastatic disease who are spared unnecessary aggressive surgery. Additionally, as the morbidity of surgical resection is high, many patients are not able to receive postoperative adjuvant therapy. Therefore, there is increasing interest in delivering this therapy prior to resection. Several institutions have reported on neoadjuvant chemoradiation using 5-FU based chemotherapy (4) or Gemcitabine based (5) regimens. These studies and others have demonstrated that neoadjuvant therapy is feasible, safe and that resection can be performed with acceptable morbidity. However, there is no standard regimen for neoadjuvant therapy for pancreatic cancer. Meta-analyses have been performed to assess outcomes of neoadjuvant therapy in resectable pancreatic cancer. One recently published analysis included 14 Phase II clinical trials including 536 patients. This analysis showed that in initially resectable patients rates of resection following neoadjuvant therapy were

65.8% compared to 31.6% in the group with initially borderline/unresectable tumors (6). Median survival in all resected patients was 22-23 months. It is not clear from the available data if neoadjuvant therapy followed by resection is superior, equal to, or inferior to upfront resection followed by adjuvant therapy, as randomized trials have not been done to answer this question. National guidelines such as NCCN support the use of neoadjuvant therapy in patients where the risk of margin positivity with upfront resection is high (7).

2.3 Borderline resectable pancreatic cancer

Borderline resectable pancreatic cancer is a unique clinical and radiographic presentation described as vascular involvement of the primary tumor which would result in an unacceptably high rate of non-R0 resection in the absence of vascular reconstruction or pre-operative therapy. Vascular reconstruction is feasible in this clinical setting and produces survival outcomes comparable to patients who undergo resection without needing vascular reconstruction (8). Seventy-five percent of the patients who underwent vascular reconstruction in this report received pre-operative therapy.
It is widely thought that in the case of borderline resectable PDAC, the potential benefit of neoadjuvant therapy is an increased likelihood of margin-negative (R0) resection, resulting in a lower rate of local and possibly distant recurrence, and ultimately increased survival.

The definition of borderline resectable pancreatic cancer has evolved over the last several years. The original definition was suggested in a report from MD Anderson which described acceptable outcomes for these patients treated with neoadjuvant therapy followed by surgery with a median survival of 40 months (9). A consensus conference of AHBPA/SSO/SSAT was held in 2008 and the definition of borderline resectable pancreas cancer was further refined (10):

- Tumor-associated deformity of the SMV (superior mesenteric vein) or PV (portal vein)
- Abutment of the SMV or PV $\geq 180^0$
- Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
- Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction
- Abutment of the SMA $< 180^0$

There is no consensus on the best neoadjuvant regimen to use in this clinical setting. The only multi-institutional trial of neoadjuvant therapy to be performed in this population is ECOG 1200 (Eastern Cooperative Group), which closed early due to poor accrual. Results of this small, randomized Phase II trial demonstrated a median overall survival of 26.3 months in resected patients (11). A recent meta-analysis (including over 4000 patients) evaluated the outcomes of the available studies of neoadjuvant therapy in pancreatic cancer. Patients with initially resectable tumors demonstrated a resection rate of 73% compared to 33% for patients with initially non-resectable (borderline/unresectable) tumors. Median survival for these groups was 23.3 and 20.5, respectably (12).

Because of the real and potential advantages of neoadjuvant therapy for PDAC, there is a pressing need to identify the most active and beneficial neoadjuvant regimen, especially for borderline resectable cases.

2.4 Study Agent(s)

Nab-Paclitaxel (ABRAXANE) is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intralumminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium (13). A protein specifically secreted by the tumor (SPARC) binds albumin, allowing release of the hydrophobic drug to the tumor cell membrane (14). ABRAXANE is the first biologically interactive nanoparticle product leveraging this gp-60/caveolin-1/caveolae/SPARC pathway to increase intra-tumoral concentration of the drug and reducing toxic effects in normal tissue.

2.4.1 Preclinical Studies with ABRAXANE

Preclinical studies comparing ABRAXANE to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for ABRAXANE compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, ABRAXANE treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for ABRAXANE versus solvent based paclitaxel, indicating more effective intratumoral accumulation of ABRAXANE (15).

2.4.2 Indications and Usage of ABRAXANE

ABRAXANE is FDA approved for metastatic breast cancer at a recommended dosage of 260 mg/m^2 intravenously over 30 minutes every 3 weeks. The indication for Non-small cell lung cancer is 100 mg/m^2 intravenously over 30 minutes on Days 1,8, and 15 of each 21-day cycle; carboplatin AUC 6 is given intravenously on Day 1 of each 21 day cycle immediately after ABRAXANE administration. In 2013, ABRAXANE was FDA approved for metastatic adenocarcinoma of the pancreas in combination with gemcitabine (see package insert, Appendix B).

2.4.3 Clinical Studies with ABRAXANE in pancreatic cancer

Members of the taxane family of microtubule stabilizing compounds (paclitaxel and docetaxel) have shown encouraging activity in the first and second-line treatment of metastatic pancreatic adenocarcinoma. More recent retrospective data have shown that the use of neoadjuvant combination chemotherapy including docetaxel improves both resectability and survival in borderline resectable PDAC (16).

Nanoparticle albumin-bound (nab)-paclitaxel (Abraxane) is a novel formulation of paclitaxel initially developed to avoid the infusion-related toxicities of Cremophor-stabilized paclitaxel. Its activity in pancreatic cancer was first suggested when Infante and colleagues (17) identified stromal over-expression of SPARC (secreted protein acidic and rich in cysteine) as a poor prognostic factor in resectable PDAC. SPARC avidly binds albumin, resulting in accumulation of

albumin – and albumin-conjugated drugs – in cells with high SPARC expression. SPARC over-expression is associated with increased response to ABRAXANE in head and neck and breast tumors.

ABRAXANE has shown encouraging activity as a single-agent, and in combination with gemcitabine in Phase I and II clinical trials in the settings of first- and second-line metastatic pancreatic adenocarcinoma treatment. A recent Phase I/II study of ABRAXANE and gemcitabine in metastatic PDAC showed a median overall survival of more than 12 months, a significant improvement over currently available therapies (18). To date however, ABRAXANE has not been evaluated in the perioperative setting or in combination with radiation therapy.

2.5 Other Agent(s)

2.5.1 *Gemcitabine*

Gemcitabine is a nucleoside metabolic inhibitor approved by the FDA for the treatment of pancreatic adenocarcinoma. It is the standard of care for metastatic or locally advanced unresectable disease (19), as well as resected disease as adjuvant therapy (20). It is approved as a single agent for the treatment of pancreatic cancer, but has undergone extensive study in combination with other antineoplastics. Two Gemcitabine combinations have shown a survival benefit in the advanced disease setting; in combination with erlotinib (21), and in combination with ABRAXANE (22). This phase III trial demonstrated a median overall survival advantage from 6.7 to 8.5 months and an improvement in response rate from 7 to 23%. Given the significant activity of Gemcitabine/ABRAXANE combination chemotherapy in the advanced setting, this trial will evaluate this combination in the borderline resectable patient population.

2.5.2 *5-Fluorouracil*

Fluorouracil is an antineoplastic antimetabolite that is approved by the FDA for the treatment of several malignancies, including pancreatic cancer. It is commonly combined with external beam radiation as a radiation sensitizer for the neoadjuvant treatment of pancreatic cancer (11).

2.6 Study and Dose Rationale

The combination of ABRAXANE and Gemcitabine has been studied in advanced pancreatic cancer. The Phase III study of ABRAXANE and Gemcitabine compared to the reference standard single agent Gemcitabine was reported at ASCO GI in January 2013. Van Hoff and colleagues reported an improvement in median overall survival from 6.7 to 8.5 months and an improvement in response rate from 7 to 23% (22). Based on this data, this regimen is becoming a new reference standard in the advanced disease setting. Therefore, given the significant activity of Gemcitabine/ABRAXANE combination chemotherapy in the advanced setting, this trial will evaluate this combination in the borderline resectable patient population.

2.7 Correlative Studies Background

While significant data exist regarding the molecular effects of chemotherapeutic agents on pancreatic cancer cells *in vitro* and in xenograft experiments, the molecular mechanisms of resistance to chemotherapy in experimental PDAC and primary human tumors is virtually unknown. Molecular fingerprints of pathways altered in the

development and progression of human PDAC have been identified (23,24), however they have not yet been correlated with response to therapy. An initial study by Von Hoff and colleagues showed that SPARC expression in peri-tumoral stroma predicts improved survival in patients with metastatic PDAC treated with Abraxane (18). Recent data from the pivotal MPACT trial has failed to demonstrate a correlation with SPARC and benefit from therapy in metastatic disease (27). It is still possible that SPARC expression may be relevant in localized disease, thus this will still be explored. Elucidation of molecular signatures for response and resistance to therapy in localized disease are clearly still needed. These approaches have been described and are used clinically to direct therapy and provide prognostic information in other tumor types such as breast (25), but it remains investigational in adenocarcinoma of the pancreas.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

3.1.1 Subjects must have histologically or cytologically confirmed adenocarcinoma of the pancreas

3.1.2 Tumors must be localized (non-metastatic) and classified as borderline resectable according to AHPBA/SSO/SSAT consensus criteria (10) or be clinically node-positive via CT or endoscopic ultrasound.

AHPBA/SSO/SSAT criteria *(any one of the following)*:

- Tumor-associated deformity of the SMV (superior mesenteric vein) or PV (portal vein)
- Abutment of the SMV or PV $\geq 180^0$
- Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
- Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction
- Abutment of the SMA $< 180^0$

3.1.3 Subjects must have measurable disease (by RECIST 1.1), defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. (Section 11.1)

3.1.4 No prior therapy for pancreatic cancer, including chemotherapy, radiation therapy, definitive surgery or investigational therapy

3.1.5 Age ≥ 18 years. Both men and women and members of all races and ethnic groups will be included.

3.1.6 ECOG performance status ≤ 1 (See Appendix A).

3.1.7 Subjects must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.5 K/cu mm
- Platelets ≥ 100 K/cu mm
- Hemoglobin ≥ 9.0 g/dL
- Total bilirubin ≤ 1. 5 X ULN

- AST (SGOT) ≤ 5 X institutional upper limit of normal
- Creatinine within normal institutional limits or Creatinine clearance ≥ 60 mL/min

3.1.8 No active prior malignancy within 3 years of registration (with the exception of non-melanoma skin cancer, in-situ cancers, or Rai Stage 0 CLL). If patient is disease free from a prior malignancy between 3-5 years, special consideration can be requested. In these cases, if the risk of recurrence at 5 years is less than 20%, and in the opinion of the investigator the prior malignancy will not affect the patient's outcome in light of newly diagnosed pancreatic cancer, the patient may be eligible. This will require PI review and approval on a case by case basis, and approval will be documented in the medical record. All patients who have been disease free from a prior malignancy for at least 5 years will be eligible.

3.1.9 No baseline peripheral sensory neuropathy ≥ grade 2

3.1.10 Women of child-bearing potential and men must be willing to use adequate contraception during the entire study and for 8 weeks following completion of all chemotherapy on study. This includes hormonal or barrier method, or abstinence.

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

3.2 Exclusion Criteria

3.2.1 Subjects with locally advanced, unresectable primary tumors will not be eligible.

This includes any of the following:

- Abutment of the SMA ≥ 180^0
- Occlusion of the SMV or PV with insufficient normal vein above and below with which to perform venous reconstruction
- Involvement of the hepatic artery with insufficient artery proximal and distal to perform reconstruction

3.2.2 Any prior therapy (chemotherapy, radiation or surgery) for pancreatic adenocarcinoma other than biliary decompression

3.2.3 Subjects who are receiving any other investigational agents

3.2.4 Subjects with known metastases

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ABRAXANE or other agents used in the study

3.2.6 Active infection requiring intravenous antibiotics at the time of registration

3.2.7 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 History of interstitial lung disease, idiopathic pulmonary fibrosis, silicosis, sarcoidosis or connective tissue disorders (including rheumatoid arthritis and systemic lupus erythematosus)

3.2.9 Pregnant or breastfeeding women are excluded from this study due to possible harm to the fetus or infant

3.2.10 Subjects known to be HIV-positive, including those on combination antiretroviral therapy, are ineligible because of the potential for pharmacokinetic interactions with chemotherapy. In addition, these subjects are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.11 Subjects with plastic biliary stents will be excluded due to risk of occlusion and cholangitis. Metal biliary stents are allowed and will not be excluded.

4.0 REGISTRATION PROCEDURES

4.1 Subject Registration

4.1.1. Subjects will be identified for eligibility through oncology or surgical referrals to outpatient or inpatient service. Eligibility criteria will be confirmed by the enrolling physician and study staff. Anatomic eligibility (see 3.1.2) will be confirmed by consultation with attending abdominal imaging radiologists at the biweekly Pancreatic and Periampullary Oncology Tumor Board. There will be no randomization for this study.

Registrations from all consented subjects will be entered into the electronic Clinical Research Information System (eCRIS).

4.1.2 Multicenter Registration

A determination of study efficacy will be made following stage I of the study. If feasible, additional study sites may be added and the OHSU coordinating center study team will manage subject registration.
Investigators at participating sites will identify eligible subjects and send screening materials with source documents that support eligibility to OHSU in real time and in accordance with study protocol. Designated Knight clinical staff must review and verify eligibility before the participating site may enroll and treat its subject. The OHSU coordinating center team will verify completeness of documents, enter registration information into eCRIS, and assign a study number/identifier. The coordinating center will send an email to the participating site indicating whether or not the subject is eligible, verify registration, and assign a participant number/identifier.

Registration will include a minimum of the following:

- A completed Subject Enrollment Form (see http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm
- A completed Eligibility Checklist signed by the investigator
- Signed copies of the most recently IRB-approved, informed consent form and HIPPA authorization

For more information, refer to the Knight Cancer Institute Investigator Initiated Trials Coordinating Center Operations Manual at: http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm

Each site must maintain a screening log of all subjects who are approached to go on study, all who sign informed consents, including those who withdraw consent. The log must also document an explanation for exclusion due to screen failure. This log will be submitted to the coordinating center on a monthly basis. Participating sites are required to retain, in a confidential manner, sufficient information on each subject so that the subject may be contacted should the need arise.

5.0 TREATMENT PLAN

5.1 Preoperative Chemotherapy

Treatment will be administered on an outpatient basis. ABRAXANE and Gemcitabine chemotherapy will be given for 2 cycles. Reported adverse events and potential risks associated with ABRAXANE, Gemcitabine and 5-fluorouracil are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Agent	*Dose*	*Route*	*Schedule*	*Cycle Length*
ABRAXANE	*125 mg/m^2*	*IV given per institutional standards*	*Weekly (Days 1,8,15)*	*4 weeks (28 days)*
Gemcitabine	*1000 mg/m^2*	*IV given per institutional standards*	*Weekly (Days 1,8,15)*	

*** ABRAXANE is to be infused prior to Gemcitabine**

5.1.1 Pre-medications for ABRAXANE and Gemcitabine Chemotherapy

Standard pre-medications for the prophylaxis of nausea and emesis will be given per institutional guidelines prior to chemotherapy (including corticosteroids and 5-HT3 inhibitors). If no standard institutional guidelines exist at a study site, it is recommended to administer dexamethasone 8 mg IV/PO and ondansetron 8 mg IV/PO prior to Gemcitabine and ABRAXANE chemotherapy. No pre-medications are recommended or required for 5-Fluorouracil.

5.1.2 Other supportive care medications

Due to the risk of infection during chemotherapy, subjects will be prescribed oral antibiotics and will be instructed to start taking immediately in the event of a fever > 38^0C (100.4^0F). Recommendations include ciprofloxacin or amoxicillin/clavulanate.

5.2 Chemoradiotherapy

Agent	*Dose*	*Route*	*Schedule*
5-Fluorouracil	*225 mg/m^2/d*	*IV continuous infusion*	*7 days per week during radiation*
Radiotherapy (IG-IMRT)	*50.4 Gy total*		*Monday-Friday for 28 fractions*

Protocol radiation treatment must begin no sooner than 3 weeks from the last dose of chemotherapy, and within 6 weeks after completion of the second cycle of Gemcitabine and ABRAXANE.

Radio-sensitizing 5-FU chemotherapy will be administered via central catheter (port or PICC) as a continuous IV infusion during the entire course of radiotherapy at a dose of 225 mg/m^2/d 7 days a week. Any dose modifications regarding 5-FU chemotherapy will

be at the investigators discretion.

Radiation therapy will be performed using image-guided, intensity-modulated radiation therapy (IG-IMRT) techniques at a dose of 50.4 Gy in 28 fractions. Treatment planning simulation must be conducted after performing a restaging pancreatic protocol diagnostic CT. In order to optimize target delineation, the diagnostic images must be fused with the planning CT, or intravenous contrast must be used at the time of simulation unless there is renal insufficiency or iodine allergy, in which case MRI will be obtained and fused with simulation images. Subjects will be simulated (and treated) supine with arms up. Immobilization is required. A thorax board is recommended. Planning scan slice thickness must be no greater than 3 mm.

Target Volumes

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

Volume Definitions

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

Dose Prescription

The prescription dose will be 50.4 Gy in 28 fractions (1.8 Gy per day), given 5 days per week.

5.3 Surgical Resection

The surgical resection will be determined by the treating surgeon in consultation with the treating oncologist

Resectability is defined as no involvement of non-reconstructable vascular structures in the absence of metastatic disease.

Surgical resection, pancreaticoduodenectomy or distal pancreatectomy (based on tumor location) should occur within 4-10 weeks after the last dose of preoperative chemoradiation. Staging laparoscopy may be performed at the time of the planned laparotomy but is not required. Either standard or pylorus-preserving pancreaticoduodenectomy may be performed.

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

Vascular resection and/or reconstruction of the superior mesenteric vein, portal vein, SMV/portal vein confluence, or hepatic artery will be done at the discretion of the operating surgeon. In general, vascular resection should be performed when necessary to achieve an R0 resection.

Frozen section evaluation of the pancreatic parenchymal and hepatic (or bile duct)

margins should be performed. In the event of a positive frozen section margin at either of these loci, further resection in an effort to achieve microscopically negative margins should be performed if possible. The superior mesenteric arterial (SMA) margin should be evaluated on permanent section.

5.4 Post-operative (Adjuvant) Chemotherapy

Within 8-12 weeks of surgical resection, subjects will undergo adjuvant chemotherapy with Gemcitabine and ABRAXANE for 4 additional cycles. The dosing and schedule will be identical to the preoperative chemotherapy described in Sec. 5.1.

5.5 General Concomitant Medication and Supportive Care Guidelines

Standard pre-medications for the prophylaxis of nausea and emesis will be given per institutional guidelines prior to chemotherapy (including corticosteroids and 5-HT3 inhibitors), as described in Section 5.1.1.

5.6 Duration of Treatment

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Development of metastatic disease progression,
- Delay in chemotherapy greater than 21 days
- Greater than 2 dose decreases
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition which render the subject unacceptable for further treatment in the judgment of the investigator.
- For any reason, at the Investigator's discretion

5.7 Duration of Follow-up

Subjects will be followed for minimum 1 year follow-up after completion of all therapy or until death, whichever occurs first. Subjects removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

If a subject withdraws consent for further treatment, the study team will clarify and document the subject's willingness to continue in the follow-up phase of the study. If the subject does not consent to the follow-up phase of the study every effort should be made to follow them for survival.

5.8 Criteria for Removal from Study

Subjects will be removed from study when any of the criteria listed in Section 5.6 applies. The reason for study removal and the date the subject was removed must be documented in the Case Report Form.

6.0 DOSING DELAYS/DOSE MODIFICATIONS

Day 1 of each cycle ANC must be ≥ 1500 and Platelets ≥ 100,000 to proceed with chemotherapy. Day 1 of each cycle, chemo can be delayed no more than 21 days due to toxicity. If this occurs patient will discontinue study.

Dose Level	ABRAXANE (mg/m^2)	Gemcitabine (mg/m^2)

Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If additional dose reduction required	Discontinue	Discontinue

Dose modifications for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle:

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	ABRAXANE/Gemcitabine
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification:				
	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15: If Day 8 doses were withheld:				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

Dose Modifications for Non-Hematologic Toxicity:

Toxicity	ABRAXANE	Gemcitabine
Febrile Neutropenia (Grade 3 or 4)	Withhold until fever resolves and ANC ≥ 1500: resume at next lower dose level	
Peripheral Neuropathy (Grade 3 or 4)	Withhold until improves to ≤ Grade 1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity (Grade 2 or 3)	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal Toxicity (Grade 3 mucositis or diarrhea)	Withhold until improves to ≤ Grade 1; resume at next lower dose level	

Re-escalation of dosing within a cycle could be performed at the provider's discretion

7.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. All hematologic AEs, in addition to clinically significant non-hematologic AEs will be recorded. Adverse events will be recorded from the first dose of study drug until 28 days after the last chemotherapy dose. Any adverse events that are attributed to the study drug will be followed until resolution. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting.

7.1 Adverse Events and Potential Risks List(s)

ABRAXANE: See attached package insert (APPENDIX B) for complete details. The most common adverse reactions (>= 20%) in metastatic breast cancer are alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, AST elevation, alkaline phosphatase elevation, anemia, nausea, infections, and diarrhea. The most common adverse reactions (>= 20%) in NSCLCA when used in combination with carboplatin are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue. The most common (>= 20%) adverse reactions in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral

edema, diarrhea, pyrexia, vomiting, decreased appetite, rash and dehydration.

Gemcitabine: See attached package insert (APPENDIX C) for complete details. The most common adverse reactions for single agent (>= 20%) are nausea/vomiting, anemia, hepatic transaminitis, neutropenia, increased alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, and peripheral edema.

Fluorouracil: Adverse reactions include stomatitis, diarrhea, anorexia, nausea/emesis, leukopenia, alopecia and dermatitis. (See APPENDIX D)

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Expectedness: Adverse Events can be 'Unexpected' or 'Expected' (see Section 7.1 above for expected AEs) based on available safety data.

Attribution of the AE:

- Definite – the AE *is clearly related* to the study treatment.
- Possible – the AE *may be related* to the study treatment.
- Unrelated – the AE *is clearly NOT related* to the study treatment.

Determination of the CTCAE grading, AE additions, etc is determined by the clinician discretion expertise and the patients specific factors and will be reviewed by the treating physician (PI or Sub-I) for clinical significance and recorded per standard protocol

7.3 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site http://www.ohsu.edu/xd/about/services/integrity/policies/policy-detail.cfm?policyid=265729

Fatal and life-threatening events must be reported to OHSU IRB within 7 calendar days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

All other UP reports will be submitted to OHSU IRB no later than 15 calendar days of notification of the event. If the event requires changes as determined by the PI or the IRB) to the protocol or consent form, the PI will make the changes promptly and submit the revised documents to the IRB. UP and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU IRB.

A serious adverse event (SAE) is defined as an AE that is fatal, is life-threatening, is persistent or significantly disabling or incapacitating, results in inpatient hospitalization or prolongation of hospitalization, results in psychological or emotional harm requiring treatment, creates a persistent or significant disability, causes a congenital anomaly or birth defect, or results in a significant medical incident.

7.4 Central Reporting of Adverse Events for Multicenter Studies

The SAE/UP reporting for multicenter investigator initiated clinical trials will follow the guidelines outlined in the OHSU Knight Cancer Institute Multi-Center Investigator Initiated Trials Coordinating Center Operations Manual.

A participating site must report an SAE to the to the institution's local IRB for action as required, as well as to the OHSU coordinating center study team by phone, fax, or email within 24 hours of learning of the event.

The OHSU coordinating center study team will review and submit SAEs to the FDA, OHSU IRB, and any other required contacts as required by the Knight Data Safety Monitoring Plan. The principal investigator at the Coordinating Center is responsible for distributing IND and/or IDE Action Letters or Safety Reports, as applicable, to participating institutions for review and submission to their institution's local IRB.

7.5 MedWatch Reporting

For this investigator-initiated study, the investigator is the study sponsor. The investigator/sponsor is required to report adverse experiences to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent. Adverse experiences to be reported include any unexpected (not listed in the package label), serious adverse experiences with a suspected association to the study drug. Adverse events that occur during clinical studies are to be reported to FDA as specified in the investigational new drug/biologic regulations using Form FDA 3500, the MedWatch Voluntary Reporting form, which is available online at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf.
Investigators may also complete Form FDA 3500 online at: https://www.accessdata.fda.gov/scripts/medwatch/ .

When the serious adverse event is reported to the FDA, copies of Form FDA 3500 and supporting materials will be submitted to the OHSU Knight Cancer Institute and the IRB. A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

For sponsor-investigators who hold an IND, Form FDA 3500 will be submitted to the IND/IDE associate who will assist the study team in a formal safety report to the FDA.

7.6 Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-PANC-PI-0053) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient

records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr.
Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

8.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent. This function will be performed by the OHSU research pharmacy. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage).
http://ctep.cancer.gov/investigatorResources/investigators_handbook.htm

8.2 Study Agent(s)

Availability: ABRAXANE will be supplied by Celgene Corporation.

Product description: ABRAXANE for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state.

Solution preparation: ABRAXANE is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. ABRAXANE is free of solvents. The active agent in ABRAXANE is paclitaxel.

Storage requirements: Store the vials in original cartons at 20º C to 25º C (68º F to 77ºF). Retain in the original package to protect from bright light.

Stability*:* Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial: Reconstituted ABRAXANE should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion.

Stability of Reconstituted Suspension in the Infusion Bag: The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25º C) and lighting conditions for up to 8

hours.

Route of administration: ABRAXANE is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line liter is not recommended.

Drug distribution: ABRAXANE® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject. Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

Drug Return: If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

Drug Destruction: If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

Supplier:
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Industry Contact:
Martha Kennedy
Associate Director, Medical Operations
Celgene Corporation
400 Connell Drive, 7th Floor
Connell Corporate Park
Berkeley Heights, NJ 07922
Mobile: 973-271-3579
Fax: 908-673-2779
Email: Jdoyle@celgene.com

8.3 Commercial Agent(s)

8.3.1 Gemcitabine:

Product description: Gemcitabine is commercially available. Gemcitabine (for injection USP) is a white to off-white lyophilized powder available in sterile single-use vials containing 200 mg or 1 g gemcitabine.

Solution preparation: See package insert (Appendix C)

Route of administration: Gemcitabine is for intravenous use only.

8.3.2 Fluorouracil

Product description: Fluouracil is commercially available. Fluorouracil injection is a sterile, nonpyrogenic injectable solution for intravenous administration. Each 10 mL contains 500 mg fluorouracil.

Solution preparation: See package insert (Appendix D)

Route of administration: Fluorouracil is for intravenous use only.

9.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

All biomarker studies described below will be done as ancillary/exploratory studies and will not affect any study procedures or subject specific outcomes. All patients will be offered enrollment in the Oregon Pancreas Tumor Registry (IRB #00003609, P.I. Brett Sheppard), which allows for the collection of blood and tissue samples that are stored for future research and may include genetic research. Not all subjects will have adequate preoperative tissue available for analysis, but all patients that undergo resection will have adequate tissue for analysis. Only those subjects who consent to the Oregon Pancreas Tumor Registry (IRB #00003609) will have these special studies performed.

9.1 Biomarker Studies

Our group, in collaboration with Drs. Joe Gray and Paul Spellman at the OHSU Center for Spatial Systems Biomedicine, may subject fresh frozen tumor samples to the following based on available tissue obtained through the Oregon Pancreas Tumor Registry:

- Global gene expression analysis using RNASeq
- Copy number/genome instability analysis using whole genome arrays
- Methylation/epigenetic modification using MethylSEQ and Illumina methylation arrays
- Analysis of SPARC expression in pre and post-treatment tumor and stroma samples
- RNA and protein expression of lysyl oxidase (LOX) that has been found to be dramatically upregulated following treatment of aggressive pancreatic cancer cell lines with paclitaxel (preliminary data, not shown).
- To assess molecular predictors of response and survival (serum CA 19-9 and SPARC expression)

10.0 STUDY PROCEDURES AND SCHEDULE OF EVENTS

10.1 Screening/Baseline Visit

Baseline screening evaluations are to be conducted within 14 days prior to start of protocol treatment. Scans and labs must be done within 21 days prior to the start of protocol treatment. Labs collected within 72 hours of C1D1 do not need to be repeated.

The following will be performed:

- Informed consent
- Demographics
- Medical history, concurrent medications
- Physical exam including vital signs, height, weight and ECOG performance status
- Laboratory studies: CBC with 3 part differential, CMP (see Sec 10.4 for details)
- CT chest/abdomen/pelvis with contrast (acceptable scans include CT multiphase Pancreas and Pelvis with IV contract and CT Chest with or without contrast)
- Serum β-hCG (for women of childbearing potential only)

10.2 Study Visits (+/- 2 day window)

Cycles 1-2

Day 1

- Concurrent medications (including herbal and nutritional supplements)
- Physical exam including vital signs, oxygen saturation, weight and ECOG performance status
- Laboratory studies: CBC with 3 part differential, CMP (see Sec. 10.4 for details), CA 19-9
- Serum β-hCG (for women of childbearing potential only)
- Adverse event evaluation
- ABRAXANE/Gemcitabine IV chemotherapy

Day 8, 15

- Laboratory studies: CBC with 3 part differential, CMP
- ABRAXANE/Gemcitabine IV chemotherapy

Staging 1

- CT chest/abdomen/pelvis with contrast (acceptable scans include CT multiphase Pancreas and Pelvis with IV contract and CT Chest with or without contrast)

CRT (chemoradiotherapy)

Subjects will be seen at least every other week for 6 weeks with the following:

- Concurrent medications (including herbal and nutritional supplements)
- Physical exam including vital signs, oxygen saturation, weight and ECOG performance status
- Laboratory studies: CBC with 3 part differential, CMP, CA 19-9 (week 1 only)

- Serum β-hCG (for women of childbearing potential, week 1 only)
- Adverse event evaluation
- IG-IMRT to 50.4 Gy in 28 fractions (5 days per week, Monday-Friday)
- Fluorouracil 225 mg/m^2 IV continuous infusion (via ambulatory infusion pump changed weekly)

Staging 2

- CT chest/abdomen/pelvis with contrast (acceptable scans include CT multiphase Pancreas and Pelvis with IV contract and CT Chest with or without contrast)
- CA 19-9 serum level

Resection

Appropriateness for surgical resection will be determined by the treating surgeon in consultation with the treating oncologist as standard of care. The procedure described in Sec. 5.3 will be followed.

Staging 3

- CT chest/abdomen/pelvis with contrast (acceptable scans include CT multiphase Pancreas and Pelvis with IV contract and CT Chest with or without contrast)

Cycles 3-6

Day 1

- Concurrent medications (including herbal and nutritional supplements)
- Physical exam including vital signs, oxygen saturation, weight and ECOG performance status
- Laboratory studies: CBC with 3 part differential, CMP, CA 19-9
- Serum β-hCG (for women of childbearing potential only)
- Adverse event evaluation
- ABRAXANE/Gemcitabine IV chemotherapy

Day 8,15

- Laboratory studies: CBC with 3 part differential, CMP
- ABRAXANE/Gemcitabine IV chemotherapy

Follow-up every 12 weeks for minimum of 1 years

- Concurrent medications (including herbal and nutritional supplements)
- Physical exam including vital signs, oxygen saturation, weight and ECOG performance status
- Laboratory studies: CBC with 3 part differential, CMP, CA 19-9
- Adverse event evaluation

- CT chest/abdomen/pelvis with contrast (acceptable scans include CT multiphase Pancreas and Pelvis with IV contract and CT Chest with or without contrast)

Toxicities and adverse events will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events 4.0.

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

10.4 Schedule of Events

	Pre-Study	Cycles 1-2			Staging 1	CRT[c.d]	Staging 2	Resection	Staging 3	Adjuvant Therapy Cycles 3-6		Restaging every 12 wks
		Day 1	Day 8	Day 15						Day 1	Day 8,15	
Study Agent		A	A	A						A	A	
Other Agent(s)		B	B	B		C,D				B	B	
Informed consent	X											
Demographics	X											
Medical history	X											
Concurrent meds	X	X				X				X		X
Physical exam	X	X				X				X		X
Vital signs	X	X				X				X		X
Height	X											
Weight	X	X				X				X		X
Performance status	X	X				X				X		X
CBC w/diff, plts	X	X	X	X		X				X	X	X
Serum chemistry[a]	X	X	X	X		X				X	X	X
CA 19-9		X				X	X			X		X
Adverse event evaluation		X				X		X		X		X
CT chest/abd/pelvis with contrast	X				X		X		X			X
β-hCG	X[b]	X				X[b]				X[b]		

A: ABRAXANE 125 mg/m2 IV
B: Gemcitabine 1000 mg/m2 IV
C: IG-IMT 50.4 Gy over 28 fractions
D: Fluorouracil 225 mg/m2/d continuous IV
a: CMP= Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein ,AST, ALT, sodium
b: Serum pregnancy test (women of childbearing potential)
c: CRT= chemoradiotherapy
d: Subjects will be evaluated weekly during CRT

11.0 MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, subjects with measurable disease will be assessed by standard criteria. In addition to a baseline CT scan, CT scans will also be obtained at the conclusion of neoadjuvant chemotherapy and following neoadjuvant chemoradiotherapy. Follow-up imaging to evaluate for recurrent disease will be performed before adjuvant chemotherapy begins and during standard follow-up.

11.1 Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with neoadjuvant chemotherapy.

Evaluable for objective response: Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease response. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as $\geq$20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable)

since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs but, in addition, should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Conventional CT: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Tumor markers: Tumor markers alone cannot be used to assess response. This data will be collected, but not used for purpose of response evaluation.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or principal investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best overall response assessment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.2 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met

for CR until the first date that progressive disease is objectively documented.

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

11.3 Relapse-Free Survival

Relapse-free survival, is defined as the duration of time from surgical resection to time of progression or death, whichever occurs first.

11.4 Histopathologic Determination of Resection Status

"Macroscopic disease" will be assessed by the surgeon, and "microscopic disease" will be assessed by the pathologist.

Margins to be assessed by the pathologist are standard, and include: SMA margin, common bile duct and pancreatic neck.

R0- defined as macroscopically complete tumor removal with negative microscopic surgical margins

R1- defined as macroscopically complete tumor removal with positive microscopic margins (any margin)

R2- defined as incomplete tumor removal with known or suspected residual gross disease

12.0 DATA REPORTING/REGULATORY REQUIREMENTS

12.1 Data Collection and Storage

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Study outcome data will be captured in electronic case report forms (eCRFs) in the following electronic data capture (EDC) system. The web-based system is password protected and encrypted with role-based security, and administered by Knight Clinical Research Quality and Administration (CRQA) informatics staff. Study team members will have login credentials and have been trained in procedures for entering, accessing and storing data. This will facilitate information being stored in a unified format and location. Data from correlative studies will be entered by research personnel at OHSU.

Additional confidentiality will be preserved by limiting PHI captured in an EDC system to just birth date and visit dates. Data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in the Section 12.7, Quality Assurance And Quality Control.

12.2 Protocol Review

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and the appropriate Institutional Review Board (IRB) prior to any subject being consented on this study.

12.3 Informed Consent

Written informed consent will be obtained from all subjects participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. Documentation of the consent process and a copy of the signed consent shall be

maintained in the subject's medical record.

12.4 Changes to Protocol

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the subject. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol. All protocol revisions will also be sent to Celgene for review.

12.5 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Trials Office. Records must be maintained according to sponsor or FDA requirements.

12.6 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.7 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each subject treated on this protocol. OHSU Knight Cancer Institute, through the auditing function of the Knight Clinical Trials Office, is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies and in accordance with the Data and Safety Monitoring Plan policies and procedures http://ozone.ohsu.edu/cancer/sharedres/kctoresdocs.cfm

Locally initiated studies will be audited by OHSU Knight CI Auditor. Newly approved studies may be audited anytime after enrollment has been initiated. Each OHSU Knight approved treatment protocol will be audited on an annual basis in accordance with the

Knight Data and Safety Monitoring Plan.

12.8 Inclusion of Women, Minorities and Children

12.8.1 Inclusion of Women and Minorities

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 1: Population Demographics - Oregon (%)

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino			11.7
Not Hispanic or Latino			88.3
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.4
Asian			3.7
Black or African American			1.8
Native Hawaiian or other Pacific Islander			0.3
White			83.6
More than one race			3.8
Unknown/Other			5.3
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

Table 2: Projected Accrual for the Present Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	2-3	2-3	0	5-6
Not Hispanic or Latino	20-21	20-21	0	40-41
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	23	23	0	46*
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0	0-1
Asian	0-1	0-1	0	1-2
Black or African American	0-1	0-1	0	0-1
Native Hawaiian or other Pacific Islander	0-1	0-1	0	0-1
White	19-20	19-20	0	38-39
More than one race	0-1	0-1	0	1-2
Unknown	1-2	1-2	0	2-3
Racial Category: Total of all subjects*	22	22	0	44*

Source: Adapted from U.S. Census Bureau, 2010 *Totals may not equal 100 due to rounding.

12.8.2 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects' research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children.

This protocol does not include children because the number of children with this type of cancer is limited.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a single-arm, non-randomized Phase II trial. The primary objective is to assess the R0 resection rate for the neoadjuvant regimen. The secondary objectives are to assess one-year relapse-free survival, overall survival, response rate by RECIST 1.1, toxicity and safety profile (per CTCAE v4.0) and molecular predictors of response and survival. The projected sample size is 44 subjects over 24 months, with a minimum follow-up of 1 year following completion of all therapy.

13.2 Primary and Secondary Endpoints

<u>Primary endpoint:</u>

R0 resection rate is defined as macroscopically complete tumor removal with negative microscopic surgical margins by pathologic assessment.

Secondary Endpoints:

Relapse-free survival at one year, is defined as the percentage of subjects who are without recurrence or death at one year from surgical resection of the primary tumor.

Overall survival is defined as the percentage of subjects alive at the one and two year time points.

Response rate by RECIST 1.1 is defined as the number of subjects with complete (CR) or partial (PR) disease response as confirmed through tumor imaging with CT. This will be assessed following neoadjuvant chemotherapy (Staging 1) and following neoadjuvant chemoradiotherapy (Staging 2).

Toxicity and safety profile will be clinically assessed and graded at the time points described. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. Attribution of the adverse event to the study will be determined as definite, possible or unrelated as described in Sec. 7.2.

Molecular predictors of response and survival will be exploratory only, as described in Sec. 9.0.

13.3 Analysis Populations

Intent to treat (ITT) analysis will be used for the primary analysis. Subjects to be analyzed are defined as enrolled subjects who have received at least one administration of study drug and have at least one efficacy evaluation.

Safety analysis set (i.e., those who receive at least one does of the drug or treatment) will be used for analysis of toxicity, safety and adverse events.

Per protocol analysis set (i.e., those who complete the treatment protocol) will be used for the secondary analyses to further evaluate the treatment efficacy.

13.4 Statistical Analysis Plan

13.4.1 Analysis of Primary Endpoint

The R0 resection rate will be computed with 95% confidence interval. A 2-sided binomial test will be used to determine whether the R0 resection rate is significantly greater than 0.37 at 10% significance level. The null hypothesis is p=0.37, and the alternative hypothesis is p not equal to 0.37.

13.4.2 Analysis of Secondary Endpoints

The expected 1-year relapse-free survival rate, and the 1-year and 2-year overall survival rates will each be reported with an associated 95% confidence interval. In addition, the relapse-free survival function and the overall survival function of will be estimated and displayed using a Kaplan Meier curve. The median relapse-free survival and the overall survival will also be estimated with an associated 95% confidence interval.

The expected pathologic response rate will be computed with the associated 95% confidence interval using Binomial exact method. Frequency and severity of adverse events will be tabulated based on the actual treatment and the number of circles the

patient receives. In particular, Grade 3 and 4 toxicity rates will be computed and summarized for all patients received at least one dose of the assigned treatment. Logistic regression will be conducted to associate the Serum CA 19-9 levels and SPARC expression with response, and Cox proportional hazard regression will be used to associate the Serum CA 19-9 and SPARC expression with overall survival endpoints.

SAS 9.4 (SAS Institute Inc., Cary, NC, USA) will be used for statistical analysis. There is no separate statistical analysis plan and table specification documented elsewhere.

13.4.3 Interim Analyses and Stopping Rules

The Simon's two-stage minimax design will be used based on the null and alternative hypothesis (37% vs. 56%). For the first-stage, we will enroll 19 subjects, and the trial will be stopped if 7 or fewer subjects undergo R0 resection. If the first-stage is met, we will continue to enroll 25 subjects to the second stage. The new treatment will be claimed not promising if 21 or fewer subjects undergo R0 resection in all 44 subjects. A determination of study enrollment feasibility will be made at that time, and the study may add additional study sites as needed.

13.5 Sample Size and Power

The R0 resection rate is approximately 37% for standard therapy. We expect the R0 resection rate for the multimodality therapy is 56%, which, if achieved, is a clinically meaningful improvement in treatment effect.

We expect to enroll 44 evaluable patients to achieve 83% power using a 2-sided binomial test at 10% significance level.

13.6 Randomization Method

This is a single-arm, non-randomized study.

13.7 Handling of Missing Data

Missing information or results will be evaluated by the study investigators to determine if what is available is sufficient to include in the data analysis. If it is determined that there is insufficient data available, the subject will be excluded from the analysis and recorded as such. Missing data will not be imputed.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B
Abraxane Package Insert

http://www.abraxane.com/downloads/Abraxane_PrescribingInformation.pdf

APPENDIX C
Gemcitabine Package Insert

http://pi.lilly.com/us/gemzar.pdf

APPENDIX D
Fluorouracil Package Insert

http://www.accessdata.fda.gov/drugsatfda_docs/anda/2000/40333_Fluorouracil_Prntlbl.pdf