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Title:

Perioperative Therapy for Resectable and Borderline Resectable Pancreatic Adenocarcinoma with Molecular Correlates

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

This is an investigator-initiated study. The lead principal investigator (PI), Colin D. Weekes, MD, PhD is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) procedures, instructions from Sponsor representatives, the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines, and the applicable parts of the United States Code of Federal Regulations (CFR) or local regulations governing the conduct of clinical studies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

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Study Reference Number:	AX-CL-PANC-AGICC-004253
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Sponsor-Lead Principal Investigator:

Signature: _____

Colin D. Weekes, MD,PhD **Date:** _____

Site Principal Investigator:

Signature: _____

Printed Name: _____ **Date:** _____

Protocol Synopsis

Study Rationale

Pancreas Cancer. Despite accounting for only 3% of cancer incidence in the U.S. population, pancreas ductal adenocarcinoma (PDAC) was the 4th leading cause of cancer death in U.S. in 2012.[1] A successful, microscopically margin-negative R0 operation is the only potentially curative option for patients with PDAC. However, only 20% of patients with this condition present with early stage disease amenable to curative resection. Even then, the 5-year overall survival rate after curative resection is approximately 20%.[2] Thus, the overall 5-year survival rate for PDAC is 5-8%.

Surgery. Patients who are candidates for potentially R0 resections are now divided into two categories: "resectable" (R) or "borderline resectable" (BR). Maurer et al first used the adjective "borderline" to describe PDACs that were between classically resectable and unresectable because of clear vascular invasion into critical arteries and veins.[3] The clinical definition of borderline resectable pancreas ductal adenocarcinoma (BR-PDAC) has been largely based on multidetector computed tomography (CT).[4] There is general agreement that the prognosis of BR-PDAC will be inferior to patients with resectable pancreas ductal adenocarcinoma (R-PDAC).[5] Unfortunately, BR-PDAC patients present more often than patients with classically R-PDAC. While the definition of BR-PDAC has been debated, for the purposes of this protocol, the 2014 NCCN guidelines will be utilized (see Eligibility Criteria).

Adjuvant Therapy. Postoperative gemcitabine or 5-Fluorouracil (5FU) improves the survival by a meager 10% after an R0 resection for patients with PDAC.[6] Unfortunately, approximately 25% of patients do not receive any form of adjuvant treatment due to post-operative complications and/or poor performance status. Moreover, 25% of patients who undergo curative surgery for resectable disease will experience rapid progression, which is a reflection of its aggressive tumor biology. In this situation, these patients will not benefit from the extensive surgery for resection of their tumor.

Neoadjuvant Therapy. Neoadjuvant therapy offers advantages in the treatment paradigm of PDAC. The probability of delivering therapy prior to surgery is higher compared to initiation of adjuvant treatment. In a well-selected population, 90-100% of patients were able to complete the entire course of planned neoadjuvant treatment.[7] Furthermore, neoadjuvant therapies may enhance the R0 resection rates for the patient with BR-PDAC.[8] This strategy also provides the opportunity to identify patients who would not benefit from curative R0 resection due to early disease progression during the short period of neoadjuvant therapy.[9] Lastly, neoadjuvant therapy provides a window into effective postoperative therapy.

Systemic Therapy. Two combination chemotherapy programs have recently supplanted single-agent gemcitabine in the treatment of patients with stage IV PDAC. FOLFIRINOX, a three drug combination with 5FU, irinotecan and oxaliplatin improved survival for stage IV PDAC with performance status (PS) 0-1 by approximately 5 months over gemcitabine alone.[10] The hematologic and clinical toxicities of FOLFIRINOX are formidable and most clinicians reserve this combination for patients younger than 70. The combination of gemcitabine and nab-paclitaxel demonstrated a remarkably high response rate in association in prolonged median survival of 12.2 months in the phase II study.[11] Interestingly, stromal SPARC was associated with longer OS when treated with this combination in the phase II trial (n=36). Analysis of the subsequent phase III MPACT for stage IV PDAC patients with PS 0-2 demonstrated a response rate for gemcitabine and nab-paclitaxel of 23% with significant improvement in median overall survival (OS) compared to gemcitabine alone (8.5 versus 6.7 months).[12] A more accurate reflection of the value of stromal SPARC in survival outcomes and response rates will be informed by further analysis in the MPACT study. Stromal SPARC was

neither prognostic nor correlated with response in the MPACT biomarker sample set (n=256), which was comprised primarily of metastatic tissue with only 11% of the samples from pancreatic lesions.[13]

Stereotactic Body Radiation Therapy. The role of radiation therapy in the treatment of locally advanced and postoperative adjuvant therapy for PDAC is controversial. Indeed, a current postoperative intergroup trial for PDAC patients who have undergone an R1 or R0 patients is testing 6 cycles of gemcitabine alone versus 5 cycles of gemcitabine plus conventional radiation therapy. Conventional radiation therapy employs a relatively large field and treats patients to 5040 cGy over five weeks.[14] The development of advanced imaging techniques has allowed for compensation for organ movement associated with respiration. The administration of stereotactic body radiation therapy (SBRT) to extracranial organs is now feasible due to these advancements.[15]

Modern studies have introduced multiple fractionation of dosing as well as decreasing the total administered dose. Systemic chemotherapy has also been added to SBRT in an attempt to augment the survival benefit associated with SBRT. Chuong et al. introduced the concept of dose-painting to SBRT.[16] This strategy treats the tumor abutting the vessel with a higher dose (35-50 Gy) with the remainder of the tumor receiving 25-30 Gy over 5 fractions. This SBRT strategy administered after neoadjuvant gemcitabine, taxotere and capecitabine in patients with borderline resectable tumors resulted in a 77% treatment response rate. The addition of 6 cycles of gemcitabine post SBRT of 24-36 Gy administered in 3 fractions resulted in a local control rate of 78% with low frequency of GI toxicity (14% grade 3) and a median survival of 14.3 months. Although SBRT has not been prospectively investigated in the setting of neoadjuvant therapy for PDAC SBRT has been shown to safely facilitate margin-negative resection in patients with borderline resectable disease (96.9%) while maintaining high rate of local disease control in unresectable patients (1-year local control 81%).[16]

Treatment Strategy. This protocol will evaluate the utility of perioperative therapy for patients with both R-PDAC and BR-PDAC, as two independent patient cohorts. Patients will receive 3 cycles of neoadjuvant gemcitabine and nab-paclitaxel (Nab-paclitaxel®) chemotherapy and stereotactic body radiotherapy (SBRT) administered sequentially prior to definitive surgery followed by an additional 3 cycles of adjuvant combination chemotherapy of gemcitabine and nab-paclitaxel. The chemotherapy backbone of gemcitabine and nab-paclitaxel was chosen due to its favorable toxicity profile and its ability to modulate the stroma.

Molecular Objectives

Knowledge of appropriate molecular markers to guide therapy is essential for the development of appropriate modern cancer treatments. Such markers are needed, but lacking for patients with PDAC. The neoadjuvant setting is ideal to compare tissue obtained pre-therapy with post-therapy tissue from the primary pancreatic adenocarcinoma. For patients with PDAC, several intratumoral markers have been tested in attempts to identify predictive biomarkers of therapeutic response. Unfortunately, varying degrees of reproducibility have hampered reliability. For example, the evaluation of intratumoral hENT-1 and cytidine deaminase have been linked to gemcitabine response. However, prospective evaluations of these markers have been unsatisfactory because of methodology issues that may have led to conflicting reports. Attempts to link intratumoral SPARC evaluation with response to nab-paclitaxel (Nab-paclitaxel®) have been inconsistent as well. Recently, Commisso et al published data demonstrating a role for the degree of “macropinocytosis” in KRAS-mutated cells, which may explain the efficacy nab-paclitaxel in KRAS mutant PDAC.[17]

SMAD4: The loss of function of the tumor suppressor gene SMAD4 (also known as deletion in pancreas cancer 4 (DPC4)), occurs as a late event 50% of pancreas adenocarcinomas. SMAD4

forms a protein complex with receptor-specific SMADs to promote signal transduction of the transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) pathways.[18,19] The loss of function of SMAD for occurs by a combination of loss of heterozygosity (LOH) or intragenic mutation.[20,21] The deletion of SMAD4 has been associated with a number of negative clinical implications. Deletion of SMAD4 predicts for a poorer prognosis in patients with surgically resected pancreas adenocarcinoma.[22,23] An evaluation of the relationship between SMAD4 deletion and site of recurrence failed to demonstrate a direct correlation between SMAD4 deletion and post-surgical recurrence site.[24] In contrast, an analysis of site of disease at the time of death utilizing a rapid autopsy program demonstrated the 70% of patients will die of distant metastasis, whilst 30% die of complications of locally aggressive disease. Seventy-five percent of patients with distant metastases harbored SMAD4 deletion analyzed by immunoassay in comparison to 22% of patients with local disease possessed a SMAD4 deletion.[25] A prospective evaluation of the predictive nature of SMAD4 deletion in patients receiving neoadjuvant therapy is yet to be completed.

Circulating DNA Analysis of KRAS: Mutations in KRAS is the most common genetic abnormality found in pancreas adenocarcinoma tumors, occurring in upward of 95%.[26] KRAS is one of three human RAS genes (HRAS, NRAS and KRAS). These are 21 k-Da small GTPases that function to transduce receptor mediated signals to activate the mitogen-activated protein kinase (MAP kinase, MAPK) pathway, amongst others.[27] Mutated KRAS proteins in pancreas cancer are a result of one of three single point mutations at residues G12, G13 and Q61. Oncogenic substitutions at G12 and G13 are activating mutations resulting in constitutive activation of Ras, which effectively results in receptor-independent stimulation downstream signal-regulating cellular functions such as increased proliferation, suppression of apoptosis, altered metabolism, metastasis and alterations of the tumor microenvironment.[28] Q61 point mutations interfere with GTP hydrolysis.[29] Recently it has been demonstrated that circulating DNA found in the peripheral blood possess representative genetic abnormalities originating from tumor DNA.[30] These cell-free fragments of DNA (cfDNA) are shed into the bloodstream by cells undergoing apoptosis or necrosis and the load of circulating cell-free DNA correlates with tumor staging and prognosis.[31] Techniques such as digital polymerase chain reaction, beads, emulsion, amplification and magnetics (BEAMing) or pryrophosphorylsis-activated polymerization (PAP) now allow for the enumeration of rare mutant variants in complex DNA mixtures.[32-34] This approach has been used to follow dynamic changes in colorectal cancers in response to multimodality therapy.[35] This observation supports the use of monitoring circulating tumor DNA a feasible biomarker of therapeutic response. The use of circulating DNA as a dynamic biomarker of therapeutic response in pancreas cancer is appealing due to the difficult nature of biopsying pancreas tumors repetitively over the course of therapy. Analysis of circulating DNA represents a minimally invasive way to evaluate therapeutic response in this patient population. Given the high frequency of KRAS mutations in pancreas adenocarcinoma, quantification of KRAS mutated circulating DNA in patients with a known existing KRAS mutation in the primary tumor may represent a feasible minimally invasive way to assess therapeutic response to therapy. Since all patients will be undergoing surgical resection of their pancreas tumor, a comparison between levels of KRAS mutation in circulating DNA with the primary tumor will be possible to assess the concordance between alterations in circulating DNA KRAS frequency with pathologic response to therapy.

Gene Expression and Mutational Analysis: Next generation sequencing allows for increased base coverage of a DNA sequence, as well as higher sample throughput. This technique also allows for the sequencing of RNA transcripts, which facilitates the evaluation of alternative gene splicing, post-transcriptional modification, gene fusions and mutations. Ingenuity pathway analysis (IPA) can be utilized to analyze the resultant RNA-Seq data to allow for interpretation of the data in terms of genetic pathways. RNA-Seq will be performed from primary tumor samples obtained at baseline, completion

of chemotherapy as well as from the resected tumor.[35] This strategy will provide insight into genetic pathways regulated in response to chemotherapy and radiation, respectively. The RNA-Seq pathway analysis data will be evaluated with respect to clinical outcomes of pathologic response and survival estimates.

SPARC: Secreted protein acid and rich in cysteine (SPARC) is frequently overexpressed in PDAC. SPARC both positively and negatively effects tumor growth properties. Data shows that SPARC inhibits angiogenesis by inhibiting vascular endothelial growth factor (VEGF) function; whilst, promoting epithelial-to-mesenchymal transition (EMT) and invasion through altering matrix metalloprotease expression.[36,37] These features are particularly intriguing in PDAC where SPARC overexpression in the stroma stands along with inhibition of angiogenesis and promotion of cancer cell invasion and metastasis. SPARC also binds albumin. In this context, intratumoral SPARC may serve as a cellular sink to enhance intratumoral accumulation and pharmacokinetic parameters of nab-paclitaxel. Von Hoff et al have suggested that the effect of nab-paclitaxel's effect with gemcitabine may rest with the former agent's ability to reach the stroma and deplete SPARC.[11] Although SPARC expression in the stroma of metastatic tissues is not prognostic or predictive of response to nab-paclitaxel plus gemcitabine, it has been demonstrated that SPARC expression in primary pancreatic lesions is associated with poor prognosis and worse response to gemcitabine.[13,38,39] Therefore, the correlation of SPARC expression with response to therapy will be evaluated in the resected primary tumor using the IHC assay developed for the MPACT trial.

Macropinocytosis: Oncogenes such as Ras and its down-stream effector, BRAF, stimulate nutrient uptake by up regulation or translocation of nutrient transporters to the plasma membrane.[40] Macropinocytosis is an endocytic process that Ras-transformed cells utilize to internalize extracellular albumin. In turn, albumin serves as a rich source of amino acids that drive cancer cell metabolism upon its degradation in the lysosome.[41] In addition to its metabolic functionality, macropinocytosis has also been characterized as a drug delivery mechanism for various therapeutics, including nanoparticles. More recently, it has been shown that macropinocytosis occurs in an oncogenic KRAS-mutated mouse model of PDAC.[17] Indeed, fluorescent-labeled nab-paclitaxel is selectively internalized into oncogenic K-Ras-expressing pancreatic cancer cells through macropinocytosis.[42] The extent of macropinocytosis in cancer cell lines varies, therefore, we propose to study whether macropinocytic uptake in human tumors is predictive of clinical outcomes associated with nab-paclitaxel and gemcitabine treatment. This analysis will be performed on fresh tumor specimens from patients at NYU in the laboratory of Dr. Dafna Bar-Sagi with NYU.

Stromal Elasticity: Pancreas ductal adenocarcinoma is characterized by the extensive deposition of desmoplastic stroma. The stroma functions to support the growth of the malignant pancreas cells. The dense stromal compartment results in an increase in intratumoral turgor pressure, which in turn collapses the tumor vasculature. This phenomenon impairs the intratumoral pharmacokinetic properties of chemotherapy. It has recently been demonstrated that the combination of gemcitabine and nab-paclitaxel denude the desmoplastic stroma resulting in increased intratumoral vasculature patency to promote increased chemotherapy intratumoral penetration.[11] The dynamic change in the stroma architecture can be measured both by immunohistochemical staining as well as by endoscopic ultrasound (EUS). Alvarez et al have utilized immunohistochemical analysis of type I collagen to demonstrate that nab-paclitaxel induces a reduced stromal content by the formation of low density collagen bundles comprised of disrupted and disorganized fibers.[43] Concordantly they observed a decrease in tumor stiffness (increased tumor elasticity) as measured by EUS elastography in tumors responding to combination therapy with gemcitabine and nab-paclitaxel.

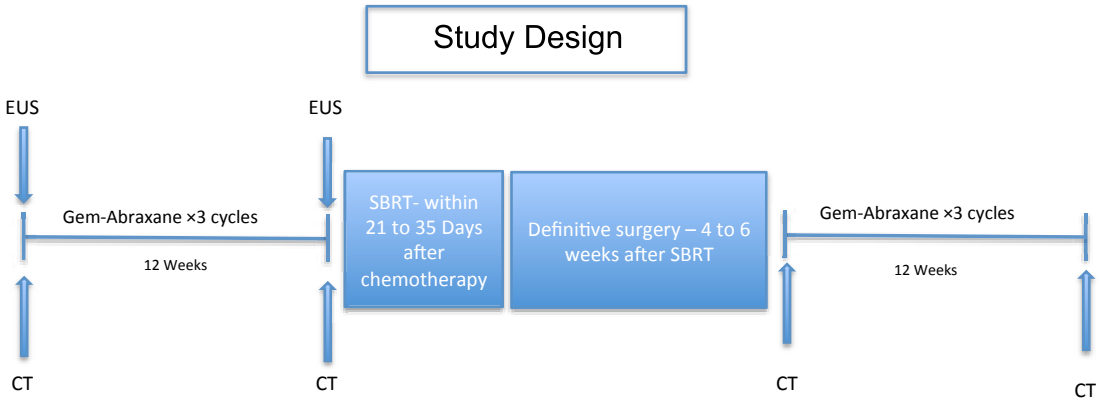
Study Design:

The study is designed as a multi-institutional, open-label phase II trial to obtain safety and preliminary efficacy data for a new peri-operative treatment regimen consisting of neoadjuvant gemcitabine and nab-paclitaxel combined with stereotactic body radiation therapy (SBRT) in a sequential manner followed by surgical resection and adjuvant combination chemotherapy for two independent patient cohorts with previously untreated R-PDAC (20 patients) or BR-PDAC (30 patients). Neoadjuvant therapy will consist of 3 cycles of combination chemotherapy with gemcitabine and nab-paclitaxel. Patients without evidence of metastatic disease on restaging CT after completion of neoadjuvant chemotherapy will subsequently receive SBRT followed by definitive surgical resection. Adjuvant therapy consisting of 3 cycles of gemcitabine and nab-paclitaxel will be administered to patients without evidence of metastatic disease, **Figure 1**. Gemcitabine 1000 mg/m2 and nab-paclitaxel 125 mg/m2 will be administered intravenously on days 1, 8 and 15 of a 28-day cycles in accordance to the dosing schedule in the completed phase III MPACT.[12] SBRT will be administered at least 21 days and no longer than 35 days after completion of the 3 cycles of neoadjuvant combination chemotherapy. Ideal administration of SBRT will between 21 and 28 days after completion of neoadjuvant chemotherapy.

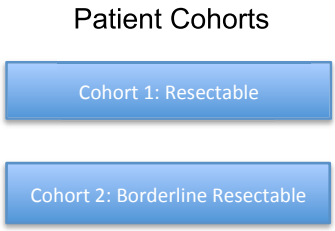
Resectable Pancreas Ductal Adenocarcinoma. R-PDAC is defined as having no evidence of distant metastasis and tumor mass showing no extension to superior mesenteric artery (SMA) and hepatic artery. There must be a clearly defined fat plane between SMA and celiac axis. Patent superior mesenteric vein (SMV/portal vein (PV) with no distortion of venous architecture.

Borderline Resectable Pancreas Ductal Adenocarcinoma. BR-PDAC is defined as localized PDAC with 1 or more of the following features: a) an interface between the primary tumor and superior mesenteric vein (SMV)-portal vein (PV) measuring 180^{o} or greater of the circumference of the vein wall, and/or b) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction and/or c) short-segment interface of any degree between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction , and/or d) an interface between the tumor and SMA or celiac trunk measuring less than 180^{o} of the circumference of the artery wall.[43]

Endpoints. The primary study endpoint is rate of R0 resection. Additionally upon completion of therapy, patient will be followed for survival with physical exam, CT scan, the serum biomarkers CEA and CA19.9 to estimate overall survival and disease-free survival. Study endpoints will be evaluated independently for each study cohort. There is no intent to compare endpoints between treatment cohorts. Patients will undergo EUS and biopsy at baseline and after 3 cycles of neoadjuvant combination chemotherapy as part of the SBRT fiducial marker placement procedure. Biopsy samples will be utilized to assess molecular study endpoints. The planned biopsies performed by EUS are mandatory for study enrollment. In addition, endoscopic elastography will be performed in a subset of patient to assess dynamic changes in stromal characteristics in response to chemotherapy. Serum and plasma will be obtained at baseline, upon completion of the 3 cycles of neoadjuvant chemotherapy, prior to and upon completion of postoperative chemotherapy to assess exploratory biomarkers. Macropinocytosis will be analyzed on tissue from surgical specimens. There is no intent to compare endpoints between treatment arms.



EUS = Biopsy and Biomarker, fiducial markers will be placed at second EUS



Study Population:

Inclusion Criteria:

1. Histologically confirmed resectable or borderline resectable pancreatic adenocarcinoma. Pathology Report Form
2. No evidence of distant metastasis representing stage IV metastatic disease.
3. R-PDAC: No evidence of distant metastasis and tumor mass showing no extension to superior mesenteric artery (SMA) and hepatic artery. There must be clear fat plane between SMA and celiac axis. Patent superior mesenteric vein (SMV/portal vein (PV) with no distortion of venous architecture. Please refer to 2014 NCCN PDAC Guidelines.
4. B-RPDAC: defined as localized PDAC with 1 or more of the following features: "a) an interface between the primary tumor and superior mesenteric vein (SMV)-portal vein (PV) measuring 180^{o} or greater of the circumference of the vein wall, and/or b) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction and/or c) short-segment interface of any degree between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction and/or d) an interface

between the tumor and SMA or celiac trunk measuring less than 180^{o} of the circumference of the artery wall."[44] Please refer to 2014 NCCN PDAC Guidelines.

5. Age > 18 years old
6. ECOG performance status of 0 or 1
7. Patients must have adequate bone marrow function:
   - Platelets >100,000 cells/mm3
   - Hemoglobin > 9.0g/dL
   - Absolute Neutrophil Count $\geq$ 1,500 cells/mm^3
8. Patients must have adequate liver function:
   - AST and ALT $\leq$ 2.5 X upper limit of normal
   - Alkaline phosphatase $\leq$ 2.5 X upper limit of normal
   - Total bilirubin $\leq$ 1.5 mg/dL
9. Patients must have adequate renal function: creatinine $\leq$1.5 mg/dL is recommended; however, institutional norms are acceptable. Creatinine within institutional limits of normal or creatinine clearance (CrCl) > 50 mL/min calculated using the Cockcroft-Gault equation.
10. Women of childbearing potential and sexually active males must use an effective contraception method during treatment and for three months after completing treatment.
11. Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential.
12. Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE v. 4.03).
13. Ability to understand and willingness to sign a written informed consent.

Exclusion Criteria:

1. Patients with locally advanced surgically unresectable PDAC.
2. Patients with evidence of distant metastatic PDAC.
3. Prior chemotherapy or radiation therapy of any kind for treatment of pancreas adenocarcinoma.
4. Prior major surgery within 4 weeks of starting study drug administration.
5. Patient unable or not willing to perform all study related biopsies and blood draws for exploratory endpoints will not be enrolled on study, as all study related procedures are mandatory.
6. Concomitant treatment with full dose warfarin (coumadin) is NOT allowed. However, treatment with low molecular weight heparin (LMWH) (such as enoxaparin or dalteparin) or rivaroxaban is allowed. Patients on full dose warfarin (coumadin) must be transitioned to either LMWH or rivaroxaban prior to administration of any study related drugs.

7. Recent or ongoing clinically significant gastrointestinal disorder (e.g., malabsorption, bleeding, inflammation, emesis, diarrhea >grade 1).
8. Patients with clinically significant cardiac disease (e.g. congestive heart failure New York Heart Association Class III or IV (see Appendix A), symptomatic coronary artery disease and cardiac arrhythmias not well controlled with medication), or myocardial infarction within the previous six months.
9. Serious, uncontrolled, concurrent infection(s).
10. Pregnant or breastfeeding women. Positive pregnancy test within 7 days of starting treatment.
11. Treatment for other carcinomas within the last five years, except cured non-melanoma skin and treated in-situ cervical cancer.
12. Participation in any investigational drug study within 4 weeks preceding the start of study treatment.
13. Patients with external biliary drains.

Statistical Analysis:

Statistical Rationale:

This Phase II study is designed to test the feasibility and safety of a new preoperative regimen for patients with R-PDAC and BR-PDAC. The primary objective of the trial is to estimate the rate of R0 resections. All patients entered into each cohort will be included in the estimates of R0 resection rates (intent to treat) and progression-free survival, Overall survival will also be summarized. Specific molecular properties of the patient's tumor that are thought to relate to therapeutic efficacy will be analyzed and correlated with clinical outcomes. The trial will also be monitored for grade III/IV hematologic toxicity.

Assumptions: In the R-PDAC cohort, the trial will be considered to be successful if 81.6% or greater of R-PDAC patients entered on the trial have R0 resections; for the BR-PDAC cohort, the trial will be considered successful if R0 resection rate for this group of patients is ≥ 42%. See sample size and study design below. Target designs are Simon two-stage optimal phase II designs with 80% power and alpha of 0.05.

Primary Analysis:

The primary endpoint is the exact 95% confidence intervals for each cohort R0 resection rates by cohort. Secondary endpoints include Kaplan Meier curves for PFS and overall survival by cohort. Changes over time in biologic correlates using mixed effects models within and across cohorts to take into account incomplete longitudinal data.

Sample Size:

R-PDAC: 20 patients. This is based on a Simon optimal 2 stage design to test the null hypothesis that the rate of R0 resection rate is ≤50% versus the alternative that the R0 resection rate is ≥81.6%. If the regimen is not effective, there is a 2% probability of concluding that it is (target α =0.05). If the

regimen is actually effective, there is a 15% probability of concluding that it is not (target power = 80%). Based on this 2-stage design, if the regimen is tested on 9 patients in the first stage, if 4 or fewer patients go on to R0 resection, the trial be terminated at the end of the first stage. With a total of 20 patients, the regimen would be accepted for further study if 15 or more R0 resections are observed in the total group of 20 patients.

BR-PDAC: 30 patients. This is based on a Simon optimal 2-stage Phase II design to test the null hypothesis that the R0 resection rate is ≤20% versus the alternative that the R0 resection rate is ≥ 42%, if the regimen is not effective there is a 0.05 probability of concluding that it is (target α=0.05). If the regimen is actually effective, there is a 20% probability of concluding that it is not (power = 91%, target power =80%). Based on this 2-stage design, if the regimen is tested on 13 patients in the first stage, if 3 or fewer patients go on to R0 resection, the trial will be terminated. With a total of 30 patients, the regimen would be accepted for further study if or more R0 resections are observed in the total group of 30 patients.[45]

Primary Endpoint:

- R0 resection rates for patients with R-PDAC and BR-PDAC.

Secondary Endpoints:

- To assess safety and feasibility of perioperative therapy with neoadjuvant gemcitabine and nab-paclitaxel (nab-paclitaxel®) chemotherapy followed by stereotactic radiotherapy before surgery in addition to adjuvant of gemcitabine and nab-paclitaxel.
- To assess objective response rate to neoadjuvant chemotherapy and chemotherapy + radiotherapy.
- To determine the R0 response rate in patients able to undergo surgical resection of pancreas adenocarcinoma.
- To estimate the overall survival rate (OS) for all patients enrolled on this trial
- To estimate the median progression-free survival (PFS) for all patients enrolled on this trial
- To estimate the median disease-free survival (DFS) for all patients enrolled on this trial
- To evaluate if histological response after neoadjuvant chemoradiotherapy is related to response to treatment and/or PFS and/or OS
- To estimate the rate of patients not receiving surgical resection due to neoadjuvant therapy related adverse events.

Exploratory Objectives:

- To correlate post therapeutic macropinocytosis with other exploratory markers and estimates of clinical outcomes.
- To correlate pathologic response rate after preoperative therapy with DFS and PFS stratified by ability to undergo surgery.
- To correlate dynamic changes in stromal elasticity associated with chemotherapy administration and clinical outcomes.
- To correlate change in serum CA19.9 and CEA levels with clinical outcomes.
- To correlate basal and dynamic changes in biomarkers of tissue SPARC, SMAD4 deletion, circulating DNA analysis of KRAS and gene expression analysis with clinical outcomes.

List of Abbreviations and Definitions of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Aminotransferase (SGOT)
β-hCG	Beta - human chorionic gonadotropin (hCG)
BR-PDAC	Borderline Resectable Pancreas Ductal Adenocarcinoma
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CMH	Cochran-Mantel-Haenszel
CONKO	Charite Onkologie
CrEL	Cremophor-EL
CRF	Case Report Form
CR	Complete Response
CRT	Chemoradiation Therapy
CT	Computed Tomography
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-Free Survival
DHHS	Department of Health and Human Services
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee

DVT	Deep Vein Thrombosis
DY	Diagnostic Yield
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal Growth Factor
EMT	Epidermal-Mesenchymal Transition
EOS	End of Study Treatment
ES	Endosonographer
ESPAC	European Study Group for Pancreatic Cancer
EUS	Endoscopic Ultrasound
EUS-FNA	Endoscopic Ultrasound Fine-Needle Aspiration
EUS-FNB	Endoscopic Ultrasound Fine-Needle Biopsy
EUS-TA	Endoscopic Ultrasound – Guided Tissue Acquisition
5-FU	5-Fluorouracil
FDA	Food and Drug Administration
FOLFIRINOX	5-FU, folinic acid, irinotecan and oxaliplatin combination chemotherapy
GCP	Good Clinical Practice(s)
G-CSF	Granulocyte Colony-Stimulating Factor
GI	Gastrointestinal
GITSG	Gastrointestinal Study Group
Gy	Gray
HA	Human Albumin
hENT1	human equilibrative nucleoside transporter 1
Hgb	Hemoglobin
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry

IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous(ly)
IVRS	Interactive voice response system
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LAP-07	Locally Advanced Pancreas – 07 Clinical Trial
LD	Longest Diameter
LMWH	Low molecular weight heparin
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MR	Minor Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NA	Not Applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
ND	Not Done
NIH	National Institutes of Health
OCE	On-site cytopathologist evaluation
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDAC	Pancreas Ductal Adenocarcinoma
PE	Paraffin Embedded
PET	Positron-Emission Tomography
PFS	Progression-free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time

PTT	Partial Thromboplastin Time
PV	Portal Vein
RECIST	Response Evaluation Criteria in Solid Tumors
RI	Reconstruction Interval
ROS	Reactive Oxygen Species
R-PDAC	Resectable Pancreas Ductal Adenocarcinoma
RTOG	Radiation Therapy Oncology Group
PV	Portal Vein
RECIST	Response Evaluation Criteria in Solid Tumors
RI	Reconstruction Interval
ROS	Reactive Oxygen Species
R-PDAC	Resectable Pancreas Ductal Adenocarcinoma
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SD	Stable Disease
S.D.	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLD	Sum of Longest Diameters
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric Vein
SmPC	Summary of Product Characteristics
SPARC	Secreted Protein Acidic and Rich in Cysteine (osteonectin)
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
SUV	Standard Uptake Value
TTF	Time to Treatment Failure
UE	Unable to Evaluate
ULN	Upper Limit of Normal
US	United States

VEGF	Vascular Endothelial Cell Growth Factor
WBC	White Blood Cell
WHO	World Health Organization

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1.0 BACKGROUND

1.1 Pancreas Adenocarcinoma

Background. Pancreas Ductal Adenocarcinoma (PDAC) remains a devastating disease. Unfortunately upwards of 80% to 85% of patients diagnosed with this disease will have unresectable advanced disease at diagnosis.[2] This precludes the vast majority of patients from receiving the only curative therapy of surgical resection. Only approximately 20% of patients are candidates for resection of the cancer. Approximately eighty percent of patients that undergo surgical resection for this disease will develop disease recurrence.[2] As a result, the overall survival rate for this disease is less than 5% for all patients diagnosed with pancreas ductal adenocarcinoma. In recent years, there has been a significant improvement in the understanding of the genetics and biology of this disease. It is estimated that PDAC develops over a 20-year period with the clinical disease occurring in the last 2 to 3 years of the disease natural history.[46] Furthermore, there appears to be central founder mutations that are common to all foci of PDAC whereas, passenger mutations appear to be differentiated by the site of disease. Additional work demonstrates that pancreas cancer metastasis occurs as an early event in oncogenesis.[47] These results may underpin the clinical observation in some patients who develop distant disease early after surgical resection of the primary tumor. It also suggests that the majority of patients with resectable locally advanced disease possess a subclinical systemic component of their disease that is not treated by surgical resection. These are some of the factors that may account for the overall poor long-term survival associated with surgical resection of the disease.

Surgery. Surgical resection of PDAC is a technically challenging surgery that is associated with a high rate of morbidity and mortality in inexperienced centers.[48] However, in centers performing a large volume of these surgical procedures the surgery-related mortality rate is less than 3%, although complication remains a reality for a proportion of patients. Surgical resection for this disease can be accomplished by several surgical techniques depending on the location of the tumor within the pancreas. The approach to resect the pancreas head involves a pancreaticoduodenectomy (Whipple Procedure) in which the head of the pancreas along with the tumor, the common bile duct (choledochectomy), gall bladder and cystic duct (cholecystectomy), duodenum, proximal jejunum and regional lymph nodes are resected. Reconstructive surgery then follows, consisting of pancreaticojejunostomy, hepaticojejunostomy and a gastrojejunostomy. These procedures allow the digestive juices, bile and food to reach the gastrointestinal tract. This procedure has been modified in several ways over the course of time to include a pylorous sparing procedure as well of the introduction of minimally invasive techniques such as a laparoscopic approach or the implementation of robotic assistance. PDAC involving the body and tail of the pancreas generally are approached with a distal pancreatectomy with splenectomy. A small minority of patients will undergo a total pancreatectomy to resect a pancreas tumor.

The complexity of the surgical approach as well as the peri-pancreatic anatomy requires a deliberate approach to identify patients that may be surgical candidates. **Resectable PDAC** is defined as patients having no evidence of distant metastasis and tumor mass showing no extension to superior mesenteric artery (SMA) and hepatic artery. There must be a clearly defined fat plane between SMA and celiac axis. A patent superior mesenteric vein (SMV) / portal vein (PV) individually or at the SMV/PV confluence with no distortion of venous architecture is an additional requirement. Locally advanced disease is characterized as either **Borderline Resectable PDAC** or **Unresectable PDAC**. The importance of this designation is that patients with BR-PDAC are treated on a curative intent paradigm with possibility of undergoing surgical resection in conjunction with perioperative therapy, whilst those deemed unresectable are destined for palliative therapy. The definition of true borderline resectable disease remains controversial. Katz et al published a definition to be incorporated into clinical trial standardization that has been adopted by the Intergroup pilot study (Alliance A021101) as well as the National Comprehensive Cancer Network (NCCN) Pancreatic Cancer Guidelines of 2014.[44]

In this protocol, **BR-PDAC** is defined as localized PDAC with 1 or more of the following features: a) an interface between the primary tumor and superior mesenteric vein (SMV)-portal vein (PV) measuring 180^{o} or greater of the circumference of the vein wall, and/or b) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction and/or c) short-segment interface of any degree between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction and/or d) an interface between the tumor and SMA or celiac trunk measuring less than 180^{o} of the circumference of the artery wall. The goal of surgical resection for this disease is to achieve R0 resection without any evidence of microscopic disease involving the surgical margins. The natural history of the disease requires that all fit patients receive perioperative therapy; however, the appropriate perioperative remains controversial at this time and remains an active area of investigation. Central radiologic review by Dr. Alex Megibow at New York University will be used to determine the eligibility and stratification of identified patients for study participation.

Perioperative Therapies. The primary controversial issues regarding perioperative therapy for pancreas ductal adenocarcinoma revolve around the timing of initiation of said therapy as well as defining the appropriate therapeutic modalities to be utilized in this setting. Some groups have advocated for adjuvant therapy, whilst others have supported the use of neoadjuvant therapy. The historical benefit of adjuvant therapy has been the removal of the tumor at an early stage in the absence of distant metastases and at a time when the patient is likely to be at an ultimate fitness level to withstand the surgery-associated morbidity. Unfortunately, the enthusiasm for this approach has waned of late due to the high rate of both local and distant recurrence. In contrast, neoadjuvant therapy affords the opportunity administer systemic therapy early in the treatment paradigm after identification of the primary tumors. Additionally, neoadjuvant therapy can identify those patients that would not benefit from surgical resection due to rapid disease recurrence. Indeed, approximately 30% to 40% of patients who initiate neoadjuvant therapy with the serial administration of chemotherapy and chemoradiation therapy discontinue therapy prior to surgical resection.[49] The relative high attrition rate is due to a number of reasons including local progression, development of distant metastases, treatment-related toxicity and physical decompensation. Those patients who complete neoadjuvant therapy and went onto to have surgical resection of their tumor tend to have a superior outcome to those patients receiving adjuvant therapy.[50]

The role of perioperative chemotherapy alone or with the addition of radiation has also been a point of contention amongst a variety of research groups. These arguments have persisted largely because of the ineffective chemotherapy options available to these patients. Gemcitabine has remained the standard-of-care for this disease since a randomized trial demonstrated an overall survival benefit over 5-fluorouracil (5-FU) in patients with metastatic pancreas adenocarcinoma.[51] Postoperative adjuvant therapy with chemotherapy alone has been shown to improve overall survival. The Charite Onkologie Clinical (CONKO-001) trial evaluated 6 cycles of adjuvant gemcitabine versus observation, demonstrating favorable associated survival of 22.8 months in comparison to 20.2 months in the observation arm.[52] The long-term results of this trial demonstrate persistent benefit for chemotherapy with a 5-year overall survival of 20.7% compared to 10.4% for patients not receiving adjuvant therapy.[53] Although single-agent gemcitabine has been the standard of care for stage IV PDAC patients, the ESPAC-3 trial tested 5-fluorouracil versus gemcitabine in the postoperative adjuvant setting for PDAC patients. Overall survival was statistically the same for each agent.[6]

A large series of therapeutic trials combining other cytotoxic chemotherapy agents, as well as biologic agents with gemcitabine have been completed in attempt to demonstrate a survival benefit over gemcitabine in the metastatic disease setting to no avail. Recently two combination chemotherapy regimens have demonstrated improved overall survival in comparison to gemcitabine in the metastatic disease setting. Both the combination of infusional 5-FU, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) as well as the combination of gemcitabine and nab-paclitaxel (Abraxane/Nab-paclitaxel®) have demonstrated an improved median overall survival over gemcitabine of 11.7 and 8.5

months, respectively in comparison to 6.5 and 6.7 months, respectively for gemcitabine.[10,12] The clinically significant impact of these observations is bore out by the reduction in rate of death of 43% and 28%, respectively associated with FOLFIRINOX and gemcitabine combined with nab-paclitaxel relative to gemcitabine. Importantly when considering perioperative therapy, both regimens were associated with clinically significantly improved response rates and disease control rates in comparison to gemcitabine in the metastatic setting. Both therapies are overall tolerable but are associated with significant toxicities of bone marrow suppression and neuropathy, as well as GI toxicity and dehydration associated with FOLFIRINOX. As a result, it is incumbent upon clinical researchers to demonstrate the safety of these regimens in the perioperative setting for the treatment of potentially curable PDAC. The results of these clinical trials set the stage for the incorporation of effective combination chemotherapy into the perioperative setting for the management of PDAC.

In this trial, we have selected gemcitabine and nab-paclitaxel as the perioperative systemic regimen. This doublet is generally well tolerated initially with cumulative bone marrow and neurotoxicity as the usual dose-limiting toxicities. Gemcitabine and nab-paclitaxel can be administered to patients over 70 with less initial concern and less initial dose modification than FOLFIRINOX. The lead Principal Investigator (PI) at University of Colorado and the PI at New York University have had preliminary experience in this regimen with SBRT (see below) and have found the regimen safe. Finally, our interest in potential molecular biomarkers such as SPARC and macropinocytosis made us consider gemcitabine and nab-paclitaxel as more compelling in the perioperative setting.

1.2 Radiation Therapy for Pancreas Cancer

1.2.1 Chemoradiation Therapy (CRT)

The role of conventional combined chemotherapy and radiation (chemoradiation therapy, CRT) in the treatment of pancreas ductal adenocarcinoma remains controversial. Support for this therapeutic modality in the adjuvant setting was initially demonstrated in 1985 by the Gastrointestinal Tumor Study Group (GITSG).[14] A total of 43 patients were randomized to receive adjuvant chemoradiation with split course radiation and 5FU compared to observation. Patients receiving CRT had a median survival rate of 20 months compared to 11 months for those in observation. This was also associated with an improved 2-year survival of 42% versus 15% for those receiving CRT. The role of conventional CRT was further evaluated in the European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial used a 2 x 2 design to test adjuvant chemotherapy alone versus CRT or observation. The results of this study were highly controversial with chemotherapy demonstrating improved survival over observation of 20 months versus 15 months. However, chemoradiation demonstrated an inferior survival rate of 16 months in comparison to 18 months for chemotherapy alone. This study has been widely criticized for the lack of uniformity in the radiation administration both in terms of the technical aspects of the split course radiation and the total dose administered between sites.[54]

Two additional studies have evaluated the role of adjuvant CRT in pancreas cancer therapy. The Radiation Therapy Oncology Group (RTOG) trial RTOG 9704 explored the role of adding systemic chemotherapy to CRT.[55] All patients received conventional external beam radiation therapy to 50.4 Gy combined with 5FU 250 mg/m^2 per day. Subsequently, patients were randomize to receive either 5FU or gemcitabine for one cycle prior to CRT and followed with 3 additional cycles post CRT. Ultimately, this study showed a non-statistically significant trend in survival favoring gemcitabine. The LAP-07 trial results have been released, once again demonstrating no advantage of CRT over chemotherapy in the adjuvant setting.[56] These results are likely a function of the fact that pancreas cancer is largely a systemic disease with most patients developing distant metastasis at the time of recurrence.

1.2.2 Stereotactic Body Radiation Therapy (SBRT)

The development of advanced imaging techniques has allowed for compensation for organ movement associated with respiration. The administration of stereotactic body radiation therapy (SBRT) to extracranial organs is now feasible due to these advancements. The early use of SBRT for the treatment of pancreas cancer utilized the administration of a single fraction of high dose radiation of 20-25 Gy.[57] This was associated with a marginal survival benefit and delayed gastrointestinal toxicity. Work by a number of investigators has now demonstrated that several dosimetric parameters are predictive of toxicity including V_{15} (volume receiving 15 Gy or greater) > 9.1 cc, V_{20} > 3.3 cc and V_{25} > 20 cc correlating with a 50% chance of intestinal toxicity.[15] D_{max} (Maximum dose received) D_{max} of 35 Gy and 38 Gy correlated with 5% and 10% rate of at least grade 3 GI toxicity. As a result of these observations, more modern studies have introduced multiple fractionation of dosing, as well as decreasing the total administered dose. Systemic chemotherapy has also been added to SBRT in an attempt to augment the survival benefit associated with SBRT.

The addition of 6 cycles of gemcitabine post SBRT of 24-36 Gy administered in 3 fractions resulted in a local control rate of 78% with low frequency of GI toxicity (14% grade 3) and a median survival of 14.3 months.[58] The use of neoadjuvant gemcitabine for 2 cycles followed by SBRT resulted in a local control rate of 85% and a median survival of 20 months without acute grade 3 toxicity and minimal delayed grade 3 toxicity.[59] SBRT has been integrated into the treatment cycle of gemcitabine to address the question of the necessity to delay the time between chemotherapy and SBRT administration. In this study, SBRT was administered on the typical rest week of gemcitabine during cycle 1 when dosed weekly for 3 weeks with 1 week of rest. The subsequent cycles of gemcitabine were administered without delay. No grade 3 toxicities were observed with this strategy; thereby, demonstrating that a delay is not required between chemotherapy administration and SBRT. Chuong et al introduced the concept of dose-painting to SBRT.[16] This strategy treats the tumor abutting the vessel with a higher dose (35-50 Gy) with the remainder of the tumor receiving 25-30 Gy over 5 fractions. This SBRT strategy administered after neoadjuvant gemcitabine, taxotere and capecitabine for patients with BR-PDAC resulted in a 77% treatment response rate. Ninety-seven percent of patients undergoing surgical resection attained an R0 resection with a pathologic complete response occurring 9% of patients. Patients completing surgical resection had a median survival of 19.3 months versus 12.3 months.

In summary, the use of radiation therapy in the management of PDAC remains controversial and remains under active investigation. Conventional chemoradiation therapy possesses marginal benefit in comparison to single agent chemotherapy in the adjuvant setting. This is likely due to the systemic nature of the disease. Delayed initiation of systemic chemotherapy as a result of time required to administer CRT and CRT associated toxicity represent additional factors resulting in the marginal benefit of CRT in the adjuvant setting. SBRT represent an efficient way to administer dose intense radiation therapy that does not delay chemotherapy administration. Patients with BR-PDAC or locally recurrent disease may benefit the most from SBRT due to its ability to achieve a tumor response. That said, the impact in terms of toxicity and efficacy of combining SBRT with modern combination chemotherapy in the perioperative setting for R-PDAC and BR-PDAC on R0 resection rate and survival remains to be defined.

1.3 Endoscopic Ultrasound (EUS)

1.3.1 Endoscopic Ultrasound (EUS) – Guided Tissue Acquisition

Endoscopic Ultrasound - Guided Tissue Acquisition (EUS-TA) by fine-needle aspiration (EUS-FNA) and fine-needle biopsy (EUS-FNB) has become an integral to the diagnosis and staging of gastrointestinal malignancies.[60] The common indications for EUS-TA include diagnosis and staging

of pancreaticobiliary, esophageal, gastric and rectal malignancies along with evaluation of GI subepithelial lesions and lymphadenopathy. The ideal EUS-TA technique needs to be safe, accurate and achieve a high diagnostic yield (DY).

The key relevant outcomes of EUS-TA include specimen adequacy, DY, accuracy, and adverse events. There are several limitations and technical challenges associated with this procedure. Low DY (false-negative diagnoses) is the most important pitfall with the potential to negatively impact patient outcomes by inappropriate patient care. A recent review reported a false-negative diagnoses rate of 4-45% in solid pancreatic masses, 21-53% in pancreatic cystic neoplasms, and 6-14% in lymph nodes.[61] This usually is a result of sampling errors [related to improper EUS-TA, errors in image recognition, experience of the endosonographer (ES) and lesion characteristics].[60-63] There are several variables that have been studied to optimize outcomes associated with EUS-TA. These include performance of EUS-FNA versus FNB, needle gauge, use of a stylet and suction, number of passes, sampling technique, presence of an on-site cytopathologist evaluation (OCE) during the procedure and the skill and experience of the ES and the cytopathologist.

A recent review of the literature by Wani et al to assess the technical aspects of EUS-TA to optimize EUS-TA for tissue acquisition has identified the following parameters to optimize the safety, accuracy and diagnostic yield of the procedures: the routine use of a stylet during EUS-FNA; the use of suction during EUS-FNA of a pancreas mass; the use of a 25-g needle is associated with a higher DY compared to 22-g needle in patients undergoing EUS-FNA of pancreas mass; the high-definition FNB needle (Echo Tip Procure™) is highly effective for acquisition of core specimens; the routine use of the “capillary” technique is preferable to standard suction and should be utilized for EUS-FNB for histologic specimens. This study will employ these parameters to optimally and safely administer repetitive EUS-TA to assess the dynamic change in tissue specific biomarkers to correlate with clinical outcome.

1.3.2 Endoscopic Elastography

Endoscopic elastography has been developed as a noninvasive method to characterize pancreas masses of benign and malignant etiologies. This technique utilizes real-time assessment of the tissue elasticity distribution calculation with subsequent representation in fundamental B-mode imagining. An Elastography Score ranging from 1 to 5 is assigned to the pancreas masses. Score 1 is a homogeneous soft mass (green) associated with normal pancreas. Score 2 remains a soft (green, yellow or red) mass that has become heterogeneic corresponding to fibrosis. Score 3 masses are hard (blue) with minimal heterogenicity that correspond to small early pancreas adenocarcinoma (< 25mm). Score 4 mass possess a hypoechoic core with green appearance surrounded by hard (blue) tissue, corresponding with hypervascular lesion such neuroendocrine tumor or pancreas metastasis. Score 5 is associated with advanced pancreas adenocarcinoma are primarily blue with a soft tissue (green, red) core. Dynamic changes in elastography characteristics of a pancreas may represent a novel modality to assess tumor response to therapy. Indeed Alvarez et al have now demonstrated that increased elasticity (decrease tumor stiffness) is associated with response to combination gemcitabine and nab-paclitaxel chemotherapy. This trial will gather preliminary data on the effects of preoperative chemotherapy on the Elastography Score on a cohort patients enrolled in the trial.

1.4 Molecular Objectives

Knowledge of appropriate molecular markers to guide therapy is essential for the development of appropriate modern cancer treatments. Such markers are needed, but lacking for patients with PDAC. The neoadjuvant setting is ideal to compare tissue obtained pre-therapy with post-therapy tissue from the primary pancreatic adenocarcinoma. For patients with PDAC, several intratumoral markers have been tested in attempt to serve as predictive biomarkers of therapeutic response with varying degrees of reproducibility. Attempts to link intratumoral SPARC evaluation with response to nab-paclitaxel

(Nab-paclitaxel®) also remain inconsistent. Recently, Commisso et al published data demonstrating the role "macropinocytosis" in KRAS-mutated cells, which may explain the efficacy nab-paclitaxel in KRAS mutant PDAC.[17]

SMAD4: The loss of function of the tumor suppressor gene SMAD4 (also known as Deletion in Pancreas Cancer 4 (DPC4)), occurs as a late event 50% of PDACs. SMAD4 forms a protein complex with receptor-specific SMADs to promote signal transduction of the transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP) pathways.[18,19] The loss of function of SMAD4 occurs either by a combination of loss of heterozygosity (LOH) or intragenic mutation.[20,21] The deletion of SMAD4 has been associated with a number of negative clinical implications. Deletion of SMAD4 predicts for a poorer prognosis in patients with surgically resected pancreas adenocarcinoma.[22,23] An evaluation of the relationship between SMAD4 deletion and site of recurrence failed to demonstrate a direct correlation between SMAD4 deletion and post-surgical recurrence site.[24] In contrast, an analysis of site of disease at the time of death utilizing a rapid autopsy program demonstrated the 70% of patients will die of distant metastasis, whilst 30% die of complications of locally aggressive disease. Seventy-five percent of patients with distant metastases harbored SMAD4 deletion analyzed by immunoassay in comparison to 22% of patients with local disease possessed a SMAD4 deletion.[25] A prospective evaluation of the predictive nature of SMAD4 deletion in patients receiving neoadjuvant therapy is yet to be completed. Hence, we will evaluate the basal and dynamic SMAD4 loss of function in tumors of patients.

Circulating DNA Analysis of KRAS: Mutations in KRAS is the most common genetic abnormality found pancreas adenocarcinoma tumors, occurring in upward of 95%.[26] KRAS is one of three human RAS genes (HRAS, NRAS and KRAS). These are 21 k-Da small GTPases that function to tranduce receptor mediated signals to activate the mitogen-activated protein kinase (MAP kinase, MAPK) pathway, amongst others.[27] Mutated KRAS proteins in pancreas cancer are a result of one of three single point mutations at residues G12, G13 and Q61. Oncogenic substitutions at G12 and G13 are activating mutations resulting in constitutive activation of Ras, which effectively results in receptor-independent stimulation downstream signal-regulating cellular functions such as increased proliferation, suppression of apoptosis, altered metabolism, metastasis and alterations of the tumor microenvironment.[28] Q61 point mutations interfere with GTP hydrolysis.[29] Recently it has been demonstrated that circulating DNA found in the peripheral blood possess representative genetic abnormalities originating from tumor DNA.[30] These cell-free fragments of DNA (cfDNA) are shed into the bloodstream by cells undergoing apoptosis or necrosis and the load of circulating cell-free DNA correlates with tumor staging and prognosis.[31] Techniques such as digital polymerase chain reaction, beads, emulsion, amplification and magnetics (BEAMing) or pyrophosphorylsis-activated polymerization (PAP) now allow for the enumeration of rare mutant variants in complex DNA mixtures.[32-34] This approach has been used to follow dynamic changes in colorectal cancers in response to multimodality therapy.[35] This observation supports the use of monitoring circulating tumor DNA a feasible biomarker of therapeutic response. The use of circulating DNA as a dynamic biomarker of therapeutic response in pancreas cancer is appealing due to the difficult nature of biopsying pancreas tumors repetitively over the course of therapy. Analysis of circulating DNA represents a minimally invasive way to evaluate therapeutic response in this patient population. Given the high frequency of KRAS mutations in pancreas adenocarcinoma, quantification of KRAS mutated circulating DNA in patients with a known existing KRAS mutation in the primary tumor may represent a feasible minimally invasive way to assess therapeutic response to therapy. Since all patients will be undergoing surgical resection of their pancreas tumor, a comparison between levels of KRAS mutation in circulating DNA with the primary tumor will be possible to assess the concordance between alterations in circulating DNA KRAS frequency with pathologic response to therapy.

Gene Expression and Mutational Analysis: Next generation sequencing allows for increased base coverage of a DNA sequence, as well as higher sample throughput. This technique also allows for

the sequencing of RNA transcripts, which facilitates the evaluation of alternative gene splicing, post-transcriptional modification, gene fusions and mutations. Ingenuity pathway analysis (IPA) can be utilized to analyze the resultant RNA-Seq data to allow for interpretation of the data in terms of genetic pathways. RNA-Seq will be performed from primary tumor samples obtained at baseline, completion of chemotherapy as well as from the resected tumor.[35] This strategy will provide insight into genetic pathways regulated in response to chemotherapy and radiation, respectively. The RNA-Seq pathway analysis data will be evaluated with respect to clinical outcomes of pathologic response and survival estimates.

SPARC: Secreted protein acid and rich in cysteine (SPARC) is frequently overexpressed in PDAC. SPARC both positively and negatively effects tumor growth properties. It has been shown to inhibit angiogenesis by inhibiting vascular endothelial growth factor (VEGF) function whilst, promoting epithelial-to-mesenchymal transition (EMT) and invasion through altering matrix metalloprotease expression.[36,37] These features are particularly intriguing in PDAC where SPARC overexpression in the stroma stands along with inhibition of angiogenesis and promotion of cancer cell invasion and metastasis. SPARC also binds albumin. In this context, intratumoral SPARC may serve as a cellular sink to enhance intratumoral accumulation and pharmacokinetic parameters of nab-paclitaxel. Von Hoff et al have suggested that the effect of nab-paclitaxel with gemcitabine may rest with the former agent's ability to reach the stroma and deplete SPARC.[11] Although SPARC expression in the stroma of metastatic tissues is not prognostic or predictive of response to nab-paclitaxel plus gemcitabine, it has been demonstrated that SPARC expression in primary pancreatic lesions is associated with poor prognosis and worse response to gemcitabine.[13,38,39] Therefore, the correlation of SPARC expression with response to therapy will be evaluated in the resected primary tumor using the IHC assay developed for the MPACT trial.

Macropinocytosis: Oncogenes such as Ras and its down-stream effector, BRAF, stimulate nutrient uptake by up regulation or translocation of nutrient transporters to the plasma membrane.[40] Macropinocytosis is an endocytic process that Ras-transformed cells utilize to internalize extracellular albumin. In turn, albumin serves as a rich source of amino acids that drive cancer cell metabolism upon its degradation in the lysosome.[41] In addition to its metabolic functionality, macropinocytosis has also been characterized as a drug delivery mechanism for various therapeutics, including nanoparticles. More recently, it has been shown that macropinocytosis occurs in an oncogenic Ras model of PDAC.[17] Indeed, fluorescent-labeled nab-paclitaxel is selectively internalized into oncogenic K-Ras-expressing pancreatic cancer cells through macropinocytosis.[42] The extent of macropinocytosis in cancer cell lines varies therefore, we propose to study whether macropinocytic uptake in human tumors is predictive of clinical outcomes associated with nab-paclitaxel and gemcitabine treatment. Fresh tumor specimens from patients will be analyzed on patients at NYU and in the laboratory of Dr. Dafna Bar-Sagi at NYU.

Stromal Elasticity: Pancreas ductal adenocarcinoma is characterized by the extensive deposition of desmoplastic stroma. The stroma functions to support the growth of the malignant pancreas cells. The dense stromal compartment results in an increase in intratumoral turgor pressure, which in turn collapses the tumor vasculature. This phenomenon impairs the intratumoral pharmacokinetic properties of chemotherapy. It has recently been demonstrated that the combination of gemcitabine and nab-paclitaxel denude the desmoplastic stroma resulting in increased intratumoral vasculature patency to promote increased chemotherapy intratumoral penetration.[11] The dynamic change in the stroma architecture can be measured both by immunohistochemical staining as well as by endoscopic ultrasound (EUS). Alvarez et al have utilized immunohistochemical analysis of type I collagen to demonstrate that nab-paclitaxel induces a reduced stromal content by the formation of low density collagen bundles comprised of disrupted and disorganized fibers.[43] Concordantly they observed a decrease in tumor stiffness (increased tumor elasticity) as measured by EUS elastography in tumors responding to combination therapy with gemcitabine and nab-paclitaxel.

1.5 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), and in accordance with Good Clinical Practice (GCP) standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB/IEC except where it may be necessary to eliminate an immediate hazard to a research patient. In such a case, the deviation will be reported to the IRB or IEC as soon as possible.

2.0 STUDY HYPOTHESIS AND OBJECTIVES

2.1 Overarching Hypothesis

Effective preoperative combination chemotherapy plus SBRT prior to surgery combined with effective postoperative combination chemotherapy will improve overall survival for patients with R-PDAC and BR-PDAC.

2.2 Study Objectives

2.2.1 Primary Objective

1. The primary efficacy objective of this study is to estimate the R0 resection rate in patients with resectable PDAC as well as those with borderline resectable PDAC independently in response to neoadjuvant sequential therapy of combination gemcitabine and nab-paclitaxel followed by SBRT.

2.2.2 Secondary Objectives

1. To assess safety and feasibility of perioperative therapy with neoadjuvant gemcitabine and nab-paclitaxel (nab-paclitaxel®) chemotherapy followed by stereotactic radiotherapy before surgery in addition to adjuvant of gemcitabine and nab-paclitaxel.

2. Estimation of objective response rate in response to neoadjuvant therapy.

3. Estimation of overall survival: overall survival, defined as the time from study treatment initiation until death from any cause.

4. Estimation of progression-free survival: progression-free survival (PFS), defined as the time from study treatment initiation to the first occurrence of documented disease progression, as determined by the PI review of tumor assessments using RECIST v1.1, or death from any cause during the study.

5. Estimation of disease-free survival: disease-free survival, defined as the time from first postoperative CT scan demonstrating no evidence of malignancy to the time of documented disease progression, as determined by the PI review of tumor assessments using RECIST v1.1, or death from any cause during the study.

6. Estimation of the histopathologic response rate to neoadjuvant therapy and correlate it to survival outcomes.

2.2.3 Exploratory Objectives

1. Correlate the post therapeutic macropinocytosis with other exploratory markers and estimates of clinical outcomes.

2. Correlate pathologic response after neoadjuvant therapy with PFS stratified by ability to undergo surgical resection.

3. Correlate dynamic changes in stromal elasticity associated with chemotherapy administration and clinical outcomes.

4. Correlate changes in serum CA19.9 and CEA levels in response to therapy will be correlated with outcomes.

5. To correlate basal and dynamic changes in biomarkers of tissue SPARC, SMAD4 deletion, circulating DNA analysis of KRAS and gene expression analysis with clinical outcomes.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically confirmed resectable or borderline resectable pancreatic adenocarcinoma. Pathology Report Form.

2. No evidence of distant metastasis representing stage IV metastatic disease.
3. R-PDAC: No evidence of distant metastasis and tumor mass showing no extension to superior mesenteric artery (SMA) and hepatic artery. There must be a clearly defined fat plane between SMA and celiac axis. Patent superior mesenteric vein (SMV/portal vein (PV) with no distortion of venous architecture. Please refer to 2014 NCCN PDAC Guidelines.
4. BR-PDAC: defined as localized PDAC with 1 or more of the following features: a) an interface between the primary tumor and superior mesenteric vein (SMV)-portal vein (PV) measuring 180^{o} or greater of the circumference of the vein wall, and/or b) short-segment occlusion of the SMV-PV with normal vein above and below the level of obstruction that is amenable to resection and venous reconstruction and/or c) short-segment interface of any degree between tumor and hepatic artery with normal artery proximal and distal to the interface that is amenable to resection and arterial reconstruction and/or d) an interface between the tumor and SMA or celiac trunk measuring less than 180^{o} of the circumference of the artery wall. Please refer to 2014 NCCN PDAC Guidelines.
5. Age > 18 years old
6. ECOG performance status of 0 or 1
7. Patients must have adequate bone marrow function:
   - Platelets >100,000 cells/mm3
   - Hemoglobin > 9.0 g/dL
   - Absolute Neutrophil Count $\geq$ 1,500 cells/mm^3

8. Patients must have adequate liver function:
   - AST and ALT $\leq$ 2.5 X upper limit of normal
   - Alkaline phosphatase $\leq$ 2.5 X upper limit of normal
   - Total bilirubin $\leq$ 1.5 mg/dL

9. Patients must have adequate renal function: creatinine $\leq$1.5 mg/dL is recommended; however, institutional norms are acceptable. Creatinine within institutional limits of normal or creatinine clearance (CrCl) > 50 mL/min calculated using the Cockcroft-Gault equation.

10. Women of childbearing potential and sexually active males must use an effective contraception method during treatment and for three months after completing treatment.
11. Negative serum or urine β-hCG pregnancy test at screening for patients of childbearing potential.
12. Patients must have < Grade 2 pre-existing peripheral neuropathy (per CTCAE 4.03).
13. Ability to understand and willingness to sign a written informed consent.

3.2 Exclusion Criteria:

1. Patients with locally advanced surgically unresectable PDAC.
2. Patients with evidence of distant metastatic PDAC.
3. Prior chemotherapy or radiation therapy of any kind for treatment of pancreas adenocarcinoma.
4. Prior major surgery within 4 weeks of starting study drug administration.
5. Patient unable or not willing to perform all study related biopsies and blood draws for exploratory endpoints will not be enrolled on study as all study related procedures are mandatory.
6. Concomitant treatment with full dose warfarin (coumadin) is NOT allowed. However, treatment with low molecular weight heparin (LMWH) (such as enoxaparin or dalteparin) or rivaroxaban is allowed. Patients on full dose warfarin (coumadin) must be transitioned to either LMWH or rivaroxaban prior to administration of any study related drugs.
7. Recent or ongoing clinically significant gastrointestinal disorder (e.g., malabsorption, bleeding, inflammation, emesis, diarrhea >grade 1).
8. Patients with clinically significant cardiac disease (New York Heart Association Classification III or IV (see Appendix A) and cardiac arrhythmias not well controlled with medication), or myocardial infarction within the previous six months.
9. Serious, uncontrolled, concurrent infection(s) requiring antibiotics.
10. Pregnant or breastfeeding women: positive pregnancy test within 7 days of starting treatment.
11. Treatment for other carcinomas within the last five years, except cured non-melanoma skin and treated in-situ cervical cancer.
12. Participation in any investigational drug study within 4 weeks preceding the start of study treatment.
13. Patients with external biliary drains.

4.0 STUDY DESIGN AND PLAN

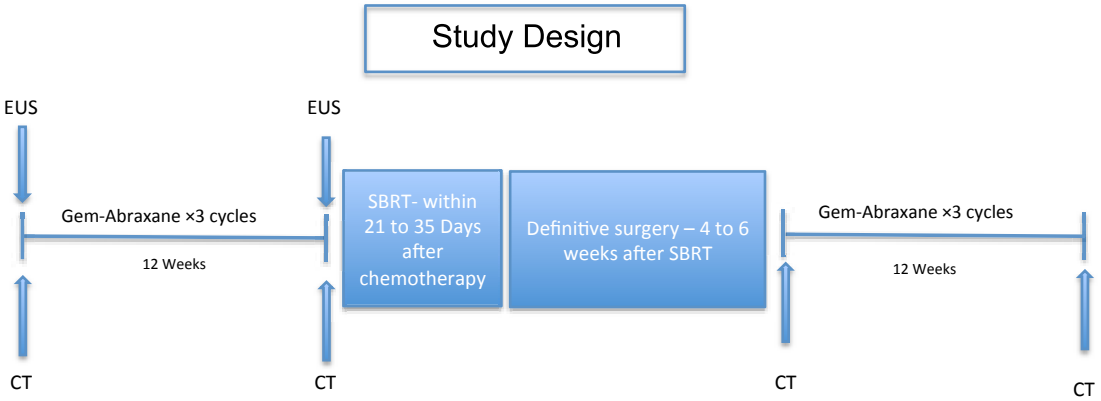
4.1 Study Design

The study is a multi-institutional, open-label phase II trial to assess the safety and obtain preliminary efficacy data for a new perioperative treatment regimen consisting of gemcitabine and nab-paclitaxel combined with SBRT in a sequential manner followed by surgical resection and adjuvant combination chemotherapy of gemcitabine and nab-paclitaxel for two independent patient cohorts: R-PDAC and BR-PDAC. The study will accrue 20 R-PDAC patients and 30 BR-PDAC patients

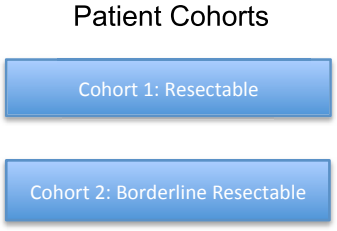
Patients will receive a total of 3 cycles of combination neoadjuvant chemotherapy followed by SBRT if restaging CT does not show evidence of metastatic disease. Upon completion of SBRT patients will receive definitive surgical resection. Subsequently, patients will receive 3 cycles of adjuvant combination chemotherapy, **Figure 1**. Each cycle of combination chemotherapy will be a total of 4 weeks. Gemcitabine and nab-paclitaxel will be administered according to the dosing schema utilized in the phase III MPACT study. Gemcitabine 1000 mg/m^2 IV (following nab-paclitaxel 125 mg/m^2) administered weekly for 3 weeks with one week off before the next cycle.

Patients will be evaluated for response at completion of the 3 cycles of neoadjuvant combination chemotherapy with CT scans of chest, abdomen and pelvis. Patients will undergo EUS and biopsy at baseline and upon completion of 3 cycles of neoadjuvant combination chemotherapy as part of SBRT fiducial marker placement procedure. The planned biopsies performed by EUS are mandatory for study enrollment. In addition, endoscopic elastography will be performed in a subset of patients to assess dynamic changes in stromal characteristics in response to neoadjuvant chemotherapy. Study endpoints will be evaluated independently for each study cohort. Serum and plasma will be obtained at baseline, upon completion of the 3 cycles of neoadjuvant chemotherapy, prior to and upon completion of postoperative chemotherapy to assess exploratory biomarkers. Macropinocytosis will be analyzed on tissue from surgical specimens. There is no intent to compare endpoints between treatment arms.

Following surgery, patients will undergo postoperative staging with CT scans of chest, abdomen and pelvis followed by administration of 3 cycles of adjuvant of gemcitabine and nab-paclitaxel. After completion of all post-operative chemotherapy, patients will undergo restaging with CT scan, CEA, CA19.9 serum biomarkers. The patient will subsequently be entered into surveillance with and followed with CT scan, CEA, CA19.9 serum biomarkers and physical exams at 3-month intervals to estimate overall survival, disease-free survival and progression-free survival for 2 years and then at a minimum 6-month intervals for the next 3 years to complete 5 years of follow up.



EUS = Biopsy and Biomarker, fiducial markers will be placed at second EUS



Gemcitabine 1000 mg/m^2 and nab-paclitaxel 125 mg/m^2 will be administered intravenously on days 1, 8 and 15 of a 28-day cycle in accordance to the dosing schedule in the completed phase III MPACT

study of this combination in patients with metastatic pancreas adenocarcinoma.[12] This regimen will be administered for a total of 3 cycles in the neoadjuvant (preoperative) and adjuvant (postoperative) settings. Patient will undergo restaging CT scan upon completion of combination chemotherapy. Patients will undergo EUS and biopsy at baseline and upon completion of 3 cycles of neoadjuvant combination chemotherapy as part of SBRT fiducial marker placement procedure.

SBRT will commence 21 days and no longer than 35 days after completion of the third cycle of neoadjuvant chemotherapy. The rationale of this therapy is to deliver highly conformal radiation at higher fractional doses than conventional radiation. The planned radiation dose per fraction will range from 5 Gy to 12 Gy per fraction depending on approximation of radiation field to adjacent bowel. This will result in the total delivered radiation dose ranging from 24 to 36 Gy.

Surgery will take place between four and six weeks after SBRT is complete. Adjuvant chemotherapy will be administered six to 12 weeks after surgery. A restaging CT scan will be obtained prior to initiating adjuvant chemotherapy to assess for evidence of disease recurrence.

In the post-therapy follow-up period, patients will be followed every three months with follow-up physical exam, serum CEA/CA19.9 and CT scans for two years. Follow-up after two years will occur at least every six months with physical exam, serum CEA/CA19.9 and CT scans at 6-month intervals for the next 3 years to complete 5 years of follow up.

Disease status will be assessed using RECIST version 1.1. In this trial, accrual will be halted after 10 patients are entered to analyze safety following the entire protocol. If more than three of the first 10 patients experience preoperative toxicity that prevents surgery, the trial will be halted. If more than 20% of the patients taken to surgery die of treatment-related complications, the trial will be halted. The determination to continue therapy will be made in concert with the PIs from each institution participating in this trial.

4.2 Study Chemotherapy Administration

4.2.1 Nab-paclitaxel (Abraxane®)

4.2.1.1 Nab-paclitaxel Product and Storage

Nab-paclitaxel 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. Nab-paclitaxel 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.

Nab-paclitaxel vials must be stored in original cartons at controlled 20°C–25°C. Vials must be retained in the original cartons to protect from bright light. For further details, see the Nab-paclitaxel Prescribing Information or Summary of Product Characteristics. Nab-paclitaxel is free of solvents. The active agent in nab-paclitaxel is paclitaxel.

4.2.1.2 Premedication

Patients do not require premedication prior to nab-paclitaxel administration, as hypersensitivity reactions are not expected, though initial antiemetic prophylaxis is recommended due to administration of gemcitabine following nab-paclitaxel treatment.

If a hypersensitivity reaction occurs, the infusion should be stopped and not restarted. If felt to be in the patient's best interests, at the PI's discretion, treatment may continue on subsequent cycles using the premedication regimen the institution typically uses for Taxol.

4.2.1.3 Administration

Nab-paclitaxel must be administered immediately before gemcitabine administration. Nab-paclitaxel should be administered by IV infusion at a dose of 125 mg/m2 over 30 minutes on Days 1, 8, and 15 of every 28-day cycle according to institutional standard.

4.2.1.4 Drug Ordering and Storage

Nab-paclitaxel vials must be stored in original cartons at controlled 20°C–25°C. Vials must be retained in the original cartons to protect from bright light. For further details, see the Nab-paclitaxel Prescribing Information or Summary of Product Characteristics.

4.2.2 Gemcitabine

4.2.2.1 Description

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2´-deoxy-2´,2´-difluorocytidine monohydrochloride (-isomer). For further details, see the Gemcitabine Prescribing Information or Summary of Product Characteristics.

4.2.2.2 Premedication

Please see gemcitabine prescribing information for recommended premedication strategies.

4.2.2.3 Administration

Gemcitabine must be administered immediately after nab-paclitaxel. Gemcitabine should be administered by IV infusion at a dose of 1000 mg/m2 over 30 minutes on Days 1, 8 and 15 of every 28-day cycle according to institutional standard.

4.2.2.4 Drug Ordering and Storage

Gemcitabine will be obtained commercially. Gemcitabine must be stored at 20°C–25°C. For further details, see the Gemcitabine Prescribing Information or Summary of Product Characteristics.

4.2.2.5 Regimen

Patients will be treated on an outpatient basis with nab-paclitaxel plus gemcitabine.

Patients receiving nab-paclitaxel plus gemcitabine will receive nab-paclitaxel 125 mg/m^2 as a 30- to 40-minute infusion (maximum infusion time not to exceed 40 minutes) followed by 1000 mg/m^2 gemcitabine as a 30- to 40-minute infusion (maximum 40 minutes) weekly for 3 weeks followed by a week of rest. Patients will receive 3 cycles in total as neoadjuvant therapy. The patients will receive an additional 3 cycles of the combination chemotherapy as adjuvant therapy post-surgical resection of pancreas ductal adenocarcinoma (see Table 1).

Table 1: Drug Dosing Schedule

Week	1	2	3	4	5	6	7	8	9	10	11	12
Nab-paclitaxel/Gemcitabine	Cycle 1-3											
	X	X	X	-	X	X	X	-	X	X	X	-

Supportive care per the institution's normal standard of care including concomitant medications can be provided at the PI's discretion (see Section 4.2).

4.3 Rules for Dose Omission and Schedule Modification

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 8 is administered as per cycle calendar if counts and chemistries permit. NOTE: The same applies to any intracycle dose of Cycle 1 of gemcitabine single agent (Days 8, 15, 22, 29, 36, 43): the cycle continues with 1 dose not given.

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.).

NOTE: The maximum delay between a missed scheduled dose and the next one (whichever dose was missed) should not be longer than 14 days (except for peripheral neuropathy; see Section 4.3.2.3).

4.3.1 Administration of Study Drug to Patients with Abnormal Hepatic Function

Study drug should only be administered if hepatic function is within the parameters established in the eligibility criteria. Hepatic toxicity from taxanes may occur but it is uncommon. Therefore, hepatic dysfunction that occurs while the patient is on study should prompt an evaluation to determine the cause, including the possibility of progressive metastatic disease and hepatotoxicity from concurrent medications.

4.3.2 Dose Modification Tables

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

Two levels of dose modifications are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction of either study drug, further treatment should be discontinued. Any further dose modification requires prior Celgene approval.

Table 2: Dose Levels

Dose Level	Nab-paclitaxel Dose (mg/m^2)[A]	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 Table 3 and Table 4 for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity, respectively. Please refer to Table 5 and Table 6 for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.
B. A maximum of 2 dose level reductions are allowed.

Patients experiencing study drug-related toxicities that require a delay in scheduled nab-paclitaxel or gemcitabine dosing for 21 days will be discontinued from further treatment in this study (except for peripheral neuropathy; see Section 4.3.2.3). When a dose reduction is required, no dose re- escalation will be permitted for the duration of study treatment (with the exception mentioned in Table 5, namely: on Day 15, re-escalation with granulocyte-colony stimulating factor (G-CSF) support is permitted, after a previous dose reduction on Day 8 of the same cycle).

4.3.2.1 Dose Modifications at Day 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of nab-paclitaxel and gemcitabine may be adjusted as detailed in Table 3 and Table 4 as presented below:

Table 3: Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

Treatment day counts and toxicity			
ANC		**Platelets**	**Timing**
$\geq 1.5 \times 10^9$/L	And	$\geq 100 \times 10^9$/L	Treat on time
$<1.5 \times 10^9$/L	Or	$<100 \times 10^9$/L	Delay by 1 week intervals until recovery

Key: ANC = Absolute neutrophil count.

Table 4: Dose Modifications for Day 1 of Each Cycle (Non-Hematologic Toxicity)

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Gemcitabine and Nab-paclitaxel dose this cycle**
Grade 0, 1 or 2 toxicity	Same as Day 1 of previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and nab-paclitaxel should both be reduced to next lower dose level)
Grade 3 toxicity[A]	Decrease gemcitabine and nab-paclitaxel to next lower dose level[A]
Grade 4 toxicity[BA, B]	Off protocol treatment[B]
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

Key: CTCAE = Common terminology criteria for adverse events.

A. If the toxicity only affects neuropathy, then only Nab-paclitaxel should be reduced (please see Section 4.3.2.3).
B. Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or a symptomatic, will be exempt from this requirement (please see Section 4.3.2.5).

4.3.2.2 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 5.

Table 5: Dose Modifications Due to Hematologic Toxicity

Day 8 Blood Counts	Day 8 nab-paclitaxel	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 nab-paclitaxel	Day 15 Gemcitabine	Any Day nab-paclitaxel	Any Day Gemcitabine
ANC >1000 And Platelets ≥75,000	100%	100%	ANC >1000 and Platelets ≥75,000	100%	100%		
			ANC 500-1000 or Platelets 50,000-74,999	Full Dose (treat on time) + G-CSF[A]	Full Dose (treat on time) + G-CSF[A]		
			ANC <500 or Platelets <50,000	Hold + G-CSF[A]	Hold + G-CSF[A]		
ANC 500- 1000[a,c] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	ANC >1000 and Platelets ≥75,000	Return to Previous Dose level (treat on time) + G-CSF[A]	Return to Previous Dose Level (treat on time) + G-CSF[A]		
			ANC 500-1000 or Platelets 50,000-74,999	Same Dose (as Day 8, treat on time) + G-CSF[A]	Same Dose (as Day 8, treat on time) + G-CSF[A]		
			ANC <500 or Platelets <50,000	Hold + G-CSF[A]	Hold + G-CSF[A]		
ANC <500[b] or Platelets <50,000	Hold	Hold	ANC >1000 and Platelets ≥75,000	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[A]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[A]		
			ANC 500-1000 or Platelets 50,000-74,999	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[A]	Decrease Day 8 dose by 1 level (treat on time) + G-CSF[A]		

Day 8 Blood Counts	Day 8 Nab-paclitaxel	Day 8 Gemcitabine	Day 15 Blood Counts	Day 15 Nab-paclitaxel	Day 15 Gemcitabine	Any Day Nab-paclitaxel	Any Day Gemcitabine
			ANC <500 or Platelets <50,000	Hold + G-CSF[A]	Hold + G-CSF[A]		
Febrile Neutropenia (Grade 3 or 4)[C]						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 dose level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)[B]						Decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	Decrease 2 dose levels (to 600 mg/m^2) and do not re-escalate throughout the rest of treatment.

Abbreviations: ANC = Absolute neutrophil count; G-CSF = Granulocyte colony stimulating factor.

A. G-CSF is optional if descent only affects platelets.
B. If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.
C. Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.

Note: for Gemcitabine Cycle 1 (of 8 weeks duration), intracycle dose modifications should be managed by either holding the dose, or reducing the dose, at the physician's discretion and based on the nature and severity of the hematologic toxicity. For doses held, the criteria specified in Section 4.2.3.2 should be followed. For dose reductions, the criteria specified for Day 8 gemcitabine in Table 5 should be followed. For subsequent (weekly x 3 every 4 weeks) gemcitabine monotherapy cycles, Table 5 criteria for both Days 8 and 15 apply.

Dose modifications may also be made for non-hematological toxicity within a cycle as specified in Table 6.

Table 6: Dose Modifications for Non-Hematological Toxicity within a Cycle

CTCAE Grade	Percent of Day 1 Nab-paclitaxel and Gemcitabine Dose
0-2 (and Grade 3 nausea/vomiting and alopecia)	100%[A]
3 (except nausea/vomiting and alopecia)	Hold either one or both drugs to ≤Grade 1. Then resume treatment at the next lower dose level.
4	Hold[B,C]

Abbreviations: CTCAE = Common terminology criteria for adverse events.
A. Except for cutaneous toxicity.
B. 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.
C. Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.2.5).

4.3.2.3 Peripheral Neuropathy

Nab-paclitaxel should be withheld in patients who experience ≥ Grade 3 sensory neuropathy. Treatment may be resumed at the next lower dose level (see Table 2) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, study drug should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2; see Table 2) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 1. Note: the PI may elect to dose modify for Grade 3 sensory neuropathy.

4.3.2.4 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reactions to nab-paclitaxel should not be re-challenged.

4.3.2.5 Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

4.3.2.6 Colony Stimulating Factor Administration

Colony stimulating factors may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC <500 cells/μL (as per Table 7). Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

G-CSF Administration

For QW study drug administration administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per PI/institution's standard of care) 24 hours after chemotherapy and hold 48 hours prior to the next dose

Table 7: Use of G-CSF and Dose reductions for Hematologic Toxicity

Adverse Event	Occurrence	Action to be Taken
ANC < 500 cells/mm^3 (nadir count) with neutropenic fever > 38° OR Delay of next cycle due to persistent neutropenia (ANC < 1500 cells/mm^3) OR For patients on weekly treatment whose next treatment within the cycle (Day 8 or Day 15) is omitted due to persistent neutropenia (ANC < 1000 cells/mm^3). OR Neutropenia < 500 cells/mm^3 for > 1 week	Any Occurrence	At the first occurrence of a hematological toxicity (as outlined in the Adverse Event column), the same dose is maintained and G-CSF is given as outlined below. In the event that a hematological toxicity re-occurs in the face of G-CSF, dose reduction to the next lower level will be required for subsequent cycles once ANC is ≥ 1500 cells/mm^3. If G-CSF is given concurrently with weekly NAB-PACLITAXEL, administration may begin the day after NAB-PACLITAXEL is given and should stop at least 48 hours prior to when NAB-PACLITAXEL is given the following week.
Thrombocytopenia Grade 3 or Grade 4*	1st Occurrence	Dose reduction to next lower level
	Recurrence	Dose reduction to next lower level

*See NCI Toxicity Criteria Scale for definition of Grade 3 and Grade 4 events.

4.3.2.7 Other Toxicities

If toxicities are ≥ grade 3, except for anemia, treatment should be withheld until resolution to ≤ grade 1 or baseline if baseline was greater than grade 1, then reinstituted, if medically appropriate, at the next lower dose level (see Table 2).

4.3.2.8 Pulmonary Toxicity

There are case reports in the literature of an interstitial pulmonary inflammation or fibrosis thought to be secondary to gemcitabine. If the patient develops dyspnea with a bilateral infiltrate not due to

infection or tumor with a 10% drop in O_2 saturation, they may come off study. This condition has been treated successfully in some cases with high dose steroids. The pulse oximeter test for O_2 saturation should be done every third cycle. Compare it to the O_2 saturation level taken at the initial visit.

Interstitial pneumonitis has been observed in ~1% during nab-paclitaxel monotherapy and in ~1% during combination treatment with nab-paclitaxel and carboplatin. However, the risk has been higher for the combination of nab-paclitaxel with gemcitabine. Pneumonitis has been reported at a rate of 4% with the use of nab-paclitaxel in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis. After ruling out infectious etiology, and upon making a diagnosis of pneumonitis, permanently discontinue treatment with nab-paclitaxel and gemcitabine and promptly initiate appropriate treatment and supportive measures.

Prevention, Surveillance and Management of Interstitial Pneumonitis

a. Before starting treatment with nab-paclitaxel candidates should be evaluated for familial, environmental or occupational exposure to opportunistic pathogens: do not enroll patients with a history of slowly progressive dyspnea and unproductive cough, or pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis or multiple allergies.

b. During treatment with nab-paclitaxel episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and computed tomography (CT) scans (normal or high resolution) may be indicated to look for infiltrates ground-glass opacities or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.

c. Infections should be ruled out with routine microbiological and/or immunologic methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.

d. Upon a diagnosis of interstitial pneumonitis nab-paclitaxel should be permanently discontinued. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

4.3.2.9 Sepsis

Sepsis has been reported in less than 1% during monotherapy and fatalities attributed to these events have been rare. However, the risk was appreciably higher in patients with advanced or metastatic pancreatic cancer receiving nab-paclitaxel in combination with gemcitabine with a rate of 5% in patients in patients with or without neutropenia receiving nab-paclitaxel combined with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. The increased risk of sepsis in the setting of advanced or metastatic cancer in combination with gemcitabine could be managed with prophylactic antibiotic treatment in febrile patients (regardless of neutrophil count) and dose reduction, and with G-CSF treatment in neutropenic patients. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold nab-paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500, then

resume treatment at reduced dose levels.

4.4 Concomitant Medications

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the PI. Concurrent treatment with bisphosphonates is allowed. Erythropoietin and G-CSF may be administered at the discretion of the PI, consistent with institutional guidelines.

4.5 Discontinuation

A patient may voluntarily discontinue study participation at any time. The PI may also, at his/her discretion discontinue the patient's study participation at any time. In the event of discontinuation, the patient should return to the study site as soon as feasible to have the EOS assessments performed and the appropriate follow-up evaluations should occur. Patients must discontinue study treatment if any of the following occurs:

- Progressive disease with evidence of distant metastasis as determined by CT scans or MRIs. CA19-9 will not be used to determine disease progression or as a criterion for patient withdrawal from the study.
- Development of toxicity that is unacceptable in the opinion of the PI.
- Patient develops moderate to severe pulmonary embolism.
- Patient declines to continue therapy (ie, withdraws consent).
- If following the second dose reduction there is a recurrence of Grade 4 neutropenia, or any other Grade 3 or 4 hematologic toxicity or non-myelosuppressive AE, unless per the PI there is evidence of continuing benefit to the patient that outweighs the risk of recurrent toxicity, and after consultation with the Celgene.
- Patient does not experience resolution of Grade 4 neutropenia within 21 days, despite uninterrupted G-CSF treatment.
- Initiation of other anticancer therapy.
- In the PI's judgment, it is in the patient's best interest to discontinue the study treatment.

Responders and stable disease patients may continue on study treatment unless they develop an unacceptable toxicity.

Patients who discontinue study treatment secondary to a laboratory abnormality or adverse event should be followed as outlined in Section 6.10.

Patients who discontinue study treatment or active participation in the study should still be followed up for safety, disease progression and OS as described in Section 6.10, Section 6.11, and Section 6.12, respectively. Only if a patient withdraws consent for any further follow-up or contact should he or she be discontinued from the study.

5.0 DETAILED DESCRIPTION OF STUDY DRUG MANAGEMENT AND ADMINISTRATION

5.1 Nab-paclitaxel

5.1.1 Packaging, Labeling, and Storage of Study Drug

Availability

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.

Storage and Stability

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

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

Stability of Reconstituted Suspension in the Vial

Reconstituted nab-paclitaxel should be used immediately, but may be refrigerated at 2 ºC to 8 ºC (36 ºF to 46 ºF) for a maximum of 4 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 25 ºC) and lighting conditions for up to 4 hours.

Study Medication Administration

Nab-paclitaxel is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line filter is not recommended.

Reconstitution and use of Nab-paclitaxel (*ABRAXANE*)

1. Calculate the patient's body surface area (BSA) at the beginning of the study and if the weight changes by > 10% by using the Hosteler BSA formula.
2. Calculate the total dose (in mg) to be administered by:
   - **Total Dose (mg) = BSA x (study dose mg/m2)**
3. Calculate the total number of vials required by:

$$\textbf{Total Number of Vials} = \frac{\textbf{Total Dose (mg)}}{\textbf{100 (mg/vial)}}$$

Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Aseptically, reconstitute each ABRAXANE vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - Once the injection is complete, allow the vial to sit for a **minimum of 5 (five) minutes** to ensure proper wetting of the lyophilized cake/powder.
   - **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. Avoid generation of foam. Rapid agitation or shaking will result in foaming.
   - If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
   - Each ml of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/ml suspension required for the patient:
   - **Dosing volume (ml) = Total dose (mg) / 5 (mg/ml)**
8. The reconstituted suspension should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed.
9. Once the exact volume of reconstituted ABRAXANE has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted ABRAXANE suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
11. Administer the calculated dosing volume of reconstituted ABRAXANE suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.

5.2 Gemcitabine

5.2.1 Packaging, Labeling, and Storage of Study Drug

Description

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of gemcitabine, please see the gemcitabine package insert.

Formulation

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in in-vivo and in vitro tumors. **Gemcitabine is approved for the treatment of patients with pancreatic cancer and will be obtained commercially and relabeled as clinical supplies.** Gemcitabine should be stored, reconstituted and administered according to the manufacturer's recommendation.

Instructions for Storing Gemcitabine

Store unopened vials per the gemcitabine product label. Preparation and administration of gemcitabine should be per the gemcitabine package insert.

Instructions for Use/Handling of Gemcitabine

Use/handling of gemcitabine should be per the gemcitabine package insert.

5.3 Endocopic Ultrasound Procedures

5.3.1 Endoscopic Ultrasound

Many patients with suspected pancreatic cancer will undergo endoscopic ultrasound (EUS) examinations and EUS-guided fine-needle aspiration/biopsy (EUS-FNA/FNB) as indicated to confirm the diagnosis of pancreatic adenocarcinoma. Procedures will be performed by experienced endosonographers; each having performed >1000 cases. The curvilinear array echoendoscopes (GF-UC140P or GF-UCT140, Olympus) will be used and the procedures will be performed with the patients in the left lateral position or prone position under moderate-deep sedation with midazolam/fentanyl and/or intravenous propofol. The location (head, genu, body and tail of pancreas), size, shape, margins (regular, irregular, well defined, poorly defined) and echogenicity of the lesions will be recorded. In addition, endosonographers will document evaluation for vascular invasion. This evaluation will be standardized among all endosonographers and documented in a case report form. After localizing the lesion, a 22 or 25-guage needle (EUS N-3/ProCore Biopsy Needle, Cook Medical, Winston Salem, N.C.) will be used for FNA/FNB under EUS guidance. The use of a stylet and suction during the procedure will be at the discretion of the endosonographer. It is routine practice to perform these procedures in the presence of an on-site cytopathologist in the endoscopy unit to render an opinion regarding adequacy of the specimen and preliminary diagnosis of the aspirate.

5.3.2 Cytopathologic assessment and final diagnosis

Each procedure will be performed with a cytopathologist or cytotechnologist in the room. After each pass, the sample from the needle will be expressed using a 10 mL air-filled syringe onto a glass slide until no further material could be expressed. Then using another glass slide the sample will be spread out to make two slides. These slides will be numbered according to the number of the pass. One slide will be air dried and stained with Diff-Quik stain for immediate on-site interpretation. The other slide will be fixed in alcohol (95% ethanol) and stained later with Papanicolaou stain. The residual contents of the needle after every pass will be flushed with 5-10 ml of sterile saline solution into the Saccomano or cytolyte solution. After flushing the needle, the exterior of the needle will be wiped with sterile gauze soaked in saline solution to reduce cross contamination between the passes. The on-site evaluation of smears will be performed to assess cellular adequacy and to assess the need for any additional passes. The overall number of passes will be at the discretion of

the endosonographer as clinically indicated. Based on institutional experience and published literature, four EUS-FNA passes are required to confirm the diagnosis of malignancy. Two additional EUS-FNA/FNB passes will be made and collected for biomarker studies. Experienced cytopathologists will evaluate cytology slides. The slides for each pass were assessed using strict predefined criteria for the following: cellularity, adequacy of specimen, contamination, amount of blood, and diagnosis. The final diagnosis of malignancy will be made by reviewing all the slides prepared from the lesion and the cell block. The results will be entered in a case report form and then transferred to a database.

5.3.3 Elastography

Endoscopic elastography has been developed as a noninvasive method to characterize pancreas masses of benign and malignant etiologies. This technique utilizes real-time assessment of the tissue elasticity distribution calculation with subsequent representation in fundamental B-mode imagining. An Elastography Score ranging from 1 to 5 is assigned to the pancreas masses. Score 1 is a homogeneous soft mass (green) associated with normal pancreas. Score 2 remains a soft (green, yellow or red) mass that has become heterogeneic corresponding to fibrosis. Score 3 masses are hard (blue) with minimal heterogenicity that correspond to small early pancreas adenocarcinoma (< 25mm). Score 4 mass possess a hypoechoic core with green appearance surrounded by hard (blue) tissue, corresponding with hypervascular lesion such neuroendocrine tumor or pancreas metastasis. Score 5 is associated with advanced pancreas adenocarcinoma are primarily blue with a soft tissue (green, red) core. Dynamic changes in elastography characteristics of a pancreas may represent a novel modality to assess tumor response to therapy. Indeed Alvarez et al have now demonstrated that increased elasticity (decrease tumor stiffness) is associated with response to combination gemcitabine and nab-paclitaxel chemotherapy. This trial will gather preliminary data on the effects of preoperative chemotherapy on the Elastography Score of selected patients enrolled in the trial.

5.3.4 Fiducial markers placement

After completion of three cycles of gemcitabine and nab-paclitaxel in 12 weeks, repeat EUS will be performed. The protocol described above will be used to evaluate the pancreatic lesion. In addition, two EUS-FNA/FNB biopsies will be obtained and specimens will be collected for biomarker studies. After EUS-FNA/FNB, fiducial markers will be placed by experienced endosonographers using a 19-gauge EUS-FNA needle (Cook Endoscopy, Winston-Salem, NC). Traditional fiducials (gold/carbon measuring 5 mm in length, 0.8 mm in diameter) will be used for this study. Fiducial marker placement involves first backloading the FNA needle with one fiducial marker at a time. The stylet of the EUS needle is withdrawn approximately 2-3 cm and the fiducial is backloaded into the needle tip by using sterile techniques. The needle tip of the EUS needle is then sealed with sterile bone wax to prevent unintended loss of the fiducial while advancing the needle through the therapeutic channel of the echoendoscope. The needle will then be inserted into the target lesion under EUS guidance. The stylet of the EUS needle will be advanced to maximal insertion, thus pushing the fiducial out of the needle and into the lesion. The EUS needle will then be withdrawn from the echoendoscope and reloaded with a new fiducial, and the technique will be repeated until a total of three fiducials are placed into the lesion in different planes. The goal will be to provide ample distance and angulation for image guided radiation therapy. The use of fluoroscopy will be at the discretion of the endosonographer. Intraprocedural intravenous antibiotics (Unasyn 3 gm or ciprofloxacin 400 mg) will be administered prophylactically in all patients. Technical difficulty and success along with the number of fiducials placed will be documented in a case report form.

5.4 SBRT

5.4.1 Radiation Schedule

Patients will undergo CT simulation within 2 weeks of completion of chemotherapy and no more than 3 weeks prior to the first SBRT fraction. SBRT will be started between 3-5 weeks of completion of chemotherapy.

5.4.2 Radiation Simulation

Prior to simulation patients will undergo endoscopic fiducial marker placement (as described above.) Simulation will occur at least 1 day following fiducial placement to allow settling of the markers. Ideally, 3 fiducial markers will be placed in the pancreatic tumor. In the event of fiducial migration, the migrated fiducial will not be used if the marker position does not allow for accurate localization. A treatment planning CT scan preferably with IV contrast (unless contraindicated) and oral contrast (20 minutes before CT to opacify the duodenum) will be required to define clinical and planning target volumes and the critical organs at risk (OAR). The treatment planning CT will be acquired with the subject set up in the same position as for daily treatments. 4-dimensional CT (4D-CT) simulation tracking respiratory motion will be performed. Target volumes will be contoured based on the maximum tumor excursion, for example on maximum intensity projection image. Normal structures will be contoured based on average image intensity projection image.

Each subject will be positioned in the supine position. A stereotactic body frame will be used to minimize set-up variability. Abdominal compression may be used at the discretion of the treating physician. Oral and intravenous contrast agents are recommended but not required. The CT scan of the abdomen should start at or above the mid-thoracic spine and continue through the mid-lumbar spine. All tissues to be irradiated must be included in the CT scan. CT scan thickness should ideally be 1.0 – 3.0 mm through the region that contains the target volumes. It is advised that extreme gastric filling not be present at the time of the planning CT scan. The target volumes and normal tissues must be outlined on all CT slices in which the structures exist.

5.4.3 Radiation Planning

The definition of volumes will be in accordance with the ICRU Report #50 and 62: The Gross Tumor Volume (GTV) is the extent of disease based on available diagnostic imaging (including PET/CT) and CT simulation images. The Clinical Target Volume (CTV) is the gross tumor volume plus areas considered to contain microscopic disease. Elective lymph node regions will not be included in the CTV. The Internal Target Volume (ITV) includes the CTV with a margin to account for physiological patient movements (mostly breathing motion), based on the maximum tumor excursion on 4D-CT. The Planning Target Volume (PTV) will provide a margin around the ITV to compensate for the variability of treatment set up. Ideally a 2mm margin in all directions around the ITV will define the PTV as long as not prohibitive for the OAR. To maintain OAR constraints, the PTV may be cropped back from the duodenum and stomach. The treatment plan used for each subject will be based on an analysis of the volumetric dose including dose-volume histogram (DVH) analyses of the PTV and critical normal structures. DVHs must be generated for all critical normal structures and the unspecified tissues.

Megavoltage equipment is required with effective photon energies ≥ 6 MV. Treatment may be delivered with Image Guided Intensity Modulated Radiation Therapy (IMRT) or Image Guided Volumetric Modulated Arc Therapy (VMAT).

Target Dose
The prescribed dose to the PTV will be 33Gy. The dose per fraction will be 6.6Gy. Treatment will be prescribed such that 95-100% of the PTV receives the prescription dose.

OAR Constraints

Duodenum (contoured 1cm above and below the PTV): V15 Gy < 9cc; V20 Gy < 3cc; V33 Gy < 1cc
Proximal Stomach: V15 Gy < 9cc; V20 Gy < 3cc; V33 Gy < 1cc
Kidneys: V12 Gy < 75%
Liver: V12 Gy ≤ 50%
Spinal Cord: Max Dose 8 Gy

5.4.4 Radiation Treatment Delivery

SBRT will be delivered over a total of 5 fractions delivered on 5 consecutive days, Monday through Friday over an elapsed time of 1-2 weeks. Occasionally, treatment breaks will be necessary due to patient tolerance, weather, departmental schedule or treatment machine maintenance. These treatment breaks should be avoided if possible, but if they occur should be documented and reported. Daily target localization with kV and cone beam CT will be performed prior to radiation delivery, with adjustments in table position so that target volumes treated correspond to those planned to within 2 mm. Details of the administration of radiation therapy will be recorded as outlined in CRF in Appendix A.

5.4.5 Radiation Administration Minor Deviations And Major Deviations

1. Prescribed Dose

    a. Minor deviation: Less than 95% of the PTV receives at least 95% of the protocol specified dose.

    b. Major deviation: Less than 95% of the PTV receives at least 90% of the protocol specified dose.

2. Volume

    a. Minor deviation: Margins less than specified or fields excessively large as deemed by the study coordinator.

    b. Major deviation: Margins transect the GTV, CTV or ITV.

3. Treatment Interruptions

    a. No deviation: No unplanned treatment interruptions.

    b. Minor deviation: Unplanned treatment interruptions of 1-2 days.

    c. Major deviation: Unplanned treatment interruption of > 2 days.

5.5 Surgery

5.5.1 Definitive Surgical Resection

Diagnostic laparoscopy should involve simple laparoscopy to assess for small volume metastatic disease, which can be missed on conventional cross sectional imaging. Laparoscopy should include general assessment of abdominal cavity to include liver, peritoneal surfaces and extra pancreatic sites. Any suspicious implants should be biopsied. Cytologic washings will not be acquired due to its unclear significance in disease outcome.

Pancreatic resections (pancreaticodudenectomy for uncinate and head lesions, distal pancreatectomy +/- splenectomy for neck, body and tail lesions) will be performed in either an open or minimally invasive manner. For pancreaticoduodenectomy patients, either classic or pylorus-preserving pancreaticoduodenectomy may be performed. Surgical drains and enteral tubes (e.g. gastrostomy and/or jejunostomy tubes) may be placed at the discretion of the operating surgeon. Exploration of the peritoneal cavity, laparoscopically or open, should include evaluation for radiologically occult macroscopic peritoneal or hepatic metastases. Biopsy proof of any metastatic disease (by frozen section assessment) is required prior to aborting planned procedure. Cytologic washings are not to be performed. Regional adenopathy is not a contraindication to resection if in the normal resection field for the planned operation. For pancreaticoduodenectomy operations, the retroperitoneal dissection along the medial edge of the uncinate process and the right lateral border of the superior mesenteric artery is the retroperitoneal margin to be inked and assessed by pathology for classification of R0 or R1 resections. If gross disease is left behind the procedure is deemed an R2 resection.

All soft tissue to the patients right of the superior mesenteric artery (SMA) should be removed. This requires exposure and dissection along the right lateral border of the SMA. For distal pancreatectomy operations, dissection should continue lateral to the celiac axis and include the retroperitoneal tissues to the patients left of the celiac axis. Vascular resections (venous, and hepatic arterial) should be performed when indicated to achieve resection of all gross disease but not SMA resections, which have poor survival outcomes.[64] Frozen section evaluation of the pancreatic parenchymal bile duct margins should be performed intraoperatively. In the event of a positive frozen section margin, further resection in an effort to achieve microscopically negative margins should be performed if possible. The retroperitoneal SMA margin should be evaluated on permanent section.

5.5.2 Specimen Orientation

The surgeon should ensure that the specimen is oriented for the surgical pathologist especially identifying the retroperitoneal SMA margin. In addition, pancreatic parenchymal margin, bile duct margin and if appropriate vascular resection margins need to be properly marked. It is advisable for the operating surgeon to personally orient the specimen with the pancreatic pathologist upon removing the specimen and before fixation.

5.5.3 Operative Note

The operative report should contain:

1. A section detailing the operative findings with respect to the extent of disease and the primary tumor anatomy

2. A comment on the status of resection (R0/R1 (all gross disease resected) vs R2 (gross disease left behind). When the final pathology is available, an addendum should be dictated to further clarify R0 or R1 resection.

The definitions for the resection classification that should be utilized in operative notes include:

R0 – Macroscopically complete tumor removal with negative microscopic surgical margins

(bile duct, pancreatic parenchyma, and SMA margins)

R1 – Macroscopically complete tumor removal with any positive microscopic surgical margin

(bile duct, pancreatic parenchyma, or SMA margins)

R2 – Macroscopically *incomplete* tumor removal with known or suspected residual gross disease.

6.0 MEASUREMENTS AND EVALUATIONS

6.1 General Considerations

Informed consent will be obtained prior to any study procedures being performed. Each participant will be given a copy of the signed ICF. The ICF must be approved by an Institutional Review Board (IRB)/Ethics Committee (EC) and by a Celgene or other sponsor-nominated representative.

A complete medical history (including specific information regarding any prior anthracycline- related cardiac abnormality) and physical examination will be conducted on each patient for a review of systems and determination of any concurrent symptoms or conditions prior to the first dose of study drug.

Routine study evaluations will be conducted to monitor for existing adverse events and the development of new adverse events. Study site personnel will ask patients the following questions:

6.1.1 Have you had any (other) medical problems since your last study visit?

6.1.2 Have you taken any new prescribed or over-the-counter medicines or herbal/vitamin preparations, other than those given to you for this study, since your last study visit?

6.1.3 Have any new procedures been performed since your last study visit?

In addition, patients are to be encouraged to call the site to report any unexpected symptoms or problems they encounter between study visits.

Medical symptoms or conditions present at or before study drug administration that manifest with the same intensity or frequency subsequent to study drug administration do not need to be recorded as adverse events in the CRF. However, any pre-existing condition that presents with increased intensity or increased frequency following study drug administration, or any exacerbation of an event that is present at the time of study drug administration, should be considered an adverse event. All adverse events occurring from initial dosing through study end, inclusive, should be followed as outlined in Section 6.10. All adverse events must be completely and promptly recorded in the patient's source document (e.g., patient hospital records, patient clinic charts, and laboratory reports) and on the CRF (see Section 6.10). Note that individual signs/symptoms should not be recorded in the CRF as adverse events. If a unifying diagnosis is known, it is the diagnosis that should be recorded as the adverse event.

Clinically significant laboratory abnormalities present at the Baseline visit will be recorded as pretreatment signs and symptoms. After study treatment administration, laboratory abnormalities

will not be recorded as adverse events unless considered clinically significant by the PI, and clinically significant laboratory abnormalities will not be recorded as serious adverse events unless the event meets the definition of serious.

Each PI is responsible for assessing the clinical significance of all abnormal laboratory values using the NCI CTCAE Scale version 4.03 (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf), where applicable). It is also the responsibility of the PI to assess the clinical significance of all abnormal laboratory values as defined by the list of normal values provided by the local laboratory. All abnormal laboratory tests that are judged to be at least possibly drug related, or clinically relevant abnormal laboratory tests of uncertain causality, must be repeated. Any abnormal values that persist should be followed at the discretion of the PI. In some cases, significant changes within the range of normal values will require similar judgment.

6.2 Central Laboratory and Central Imaging

Central laboratory, central imaging, and central SPARC and other molecular biomarkers testing will be utilized for this study.

6.2.1 Central Imaging

Dr. Alec Megibow, based at New York University, will act as a central imaging reviewer and will provide an independent review of disease categorization in terms of resectable versus borderline resectable disease. Patient treatment cohort allocation will be based on this central review of screening radiologic imaging (CT or MRI). Turnaround time for patient allocation will be within 24 hours of electronic receipt of the pertinent images. Dr. Justin Ream at New York University will be a back-up reviewer if Dr. Megibow is not available. The central imaging reviewer will also assess response and progression to therapy for all patients enrolled into the study in a blinded fashion that is independent of institutional evaluation assessment of therapeutic response. Prospective collection of all on-study CT/MRI scans for all patients enrolled in the study will be included as part of the review.

Films or electronic copies should be collected by the investigative sites and sent to the central image reader. Complete details regarding image handling and submission can be found in the Radiology Technical Manuals (Appendix B).

Patients who are discontinued from treatment in the absence of disease progression (e.g., patients removed for unacceptable toxicity or patient/PI discretion) should undergo repeat imaging and tumor response assessments until disease progression is documented. CT scans should be continually performed into follow-up every 12 weeks (at any time during that week), regardless of regimen.

If a patient starts a new anti-cancer therapy prior to disease progression, then repeat imaging and tumor response assessments should be discontinued.

6.2.2 Central Laboratory.

An overview of the schedule of study assessment is provided in Study Calendar, Table 8.

The laboratory of Colin Weekes will serve as central laboratory for sample processing to obtain molecular objectives. Batched samples will be processed according to procedures outlined on the specimen collection forms. Individual sites will be provided with necessary kits for initial on-site processing and storage prior to batched samples being delivered to the central laboratory. Samples are not to be shipped on Fridays.

Macropinocytosis assay will be performed on pancreatic specimens obtained only at New York University due to assay requirements to perform the assay on fresh samples. The macropinocytosis assay will be performed in the laboratory of Dafna Bar-Sagi, Ph.D. according to procedures published by Commisso et. al.[61]

6.3 Table 8: Study Calendar

Assessment		NeoAdjuvant Chemotherapy												SBRT	Surgery	Adjuvant Chemotherapy												Surv.[17]	EOS[18]
		Cycle 1				Cycle 2				Cycle 3						Cycle 1				Cycle 2				Cycle 3					
		Days				Days				Days										Days				Days					
	Baseline	1	8	15	22	1	8	15	22	1	8	15	22			1	8	15	22	1	8	15	22	1	8	15	22		
Informed Consent[1]	X																												
Informed Consent[2]	X																												
Medical History[3]	X																											X	X
Physical Exam[4]	X	X											X	X	X	X												X	X	X
Toxicity Evaluation[5]		X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight[6]	X	X	X	X		X	X	X		X	X	X				X	X	X		X	X	X		X	X	X			X
BSA Calculations[6]	X	X	X	X		X	X	X		X	X	X				X	X	X		X	X	X		X	X	X			
Prior/Concomitant Medication[7]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent Procedures	X	X				X				X						X				X				X					X
Peripheral Neuropathy Evaluation[3]	X	X				X				X						X				X				X					X
Vital Signs[3,9]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG[3,10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12 lead)[3]	X																												
Urinalysis[3]	X	X				X				X						X				X				X					
Serum β-HCG[3]	X																												
Chemistry Panel[3,11]	X	X				X				X						X				X				X				X	X
CBC[3.12]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT, PTT[3]	X																												
Serum CA19.9[3,13]	X	X				X				X			X			X				X				X			X	X	X
Serum CEA[3,13]	X	X				X				X			X			X				X				X			X	X	X
Plasma Biomarker[3,13]	X												X			X											X		X
CT Scan[3,14]	X[14]												X[14]			X[14]											X[14]	X[14]	X[14]
Radiology Review	X													X		X											X	X	X
EUS	X[2]													X[2]															
SBRT[15]														X[15]															
Surgery[16]															X[16]														

Chemotherapy		X	X	X		X	X	X		X	X	X				X	X	X		X	X	X		X	X	X			
Biopsy	X[2]													X[2]															

1. Informed Consent to be obtained for study participation. Must be performed within 21 days of the initiation of study related treatments on cycle 1 day 1.
2. Informed Consent to use diagnostic tumor biopsy specimens for molecular marker analysis. Must be obtained within 1 week prior to performing initial tumor biopsy by endoscopic ultrasound. Consent for EUS procedure will be obtained within 1 week of procedure as per standard operating procedure within respective endoscopic laboratory. Elastography will be performed in patients consenting to this procedure at institutions possessing facilities to perform the endoscopic assay.
3. Medical History. This will be performed as part of screening evaluation for study participation within 21 days of study initiation. This will also include all procedures and labs associated with screening evaluation.
4. Physical exam. This will be performed as part of screening evaluation for study participation within 21 days of study initiation and on days of response assessment. Response assessment can occur $\pm$ 7 days of cycle 3 day 28 of "Neoadjuvant Chemotherapy" and "Adjuvant Chemotherapy".
5. Toxicity Examination. Unless otherwise specified, visits are to be performed within $\pm$ 2 days of planned visit date.
6. Body Surface Area (BSA) Calculation. Height and weight will be obtained on dates of chemotherapy administration for purposes of BSA calculation for chemotherapy dosing.
7. Prior/Concomitant Medications. Medications and vitamins/supplements that the patient is taking in addition to study medications will be reviewed at each time point of either physical examination or toxicity examination.
8. Peripheral Neuropathy. Sensory neuropathy will be assessed at baseline. Preexisting peripheral neuropathy at baseline must be $\leq$ grade 1 according to CTCAE version 4.0. This will be assessed on days of study drug administration prior to dosing.
9. Vital Signs. Will be assessed at baseline and prior to study drug administration and with every physical examination or toxicity examination.
10. ECOG Performance Status. Must be 0 or 1 at time of study enrollment. Will be assessed prior to study drug administration and with every physical examination or toxicity examination
11. Chemistry Panel (CMP). Will be assessed at baseline, at day 1 of each chemotherapy cycles as well as response assessments and end of study visits. Baseline examination can occur within 21 days of cycle 1 day 1. Serum chemistry panel includes: Sodium (Na), Potassium (K), Bicarbonate (CO_2), Chloride (Cl), Blood Urea Nitrogen (BUN), Creatinine (Cr), Serum Glucose, Alkaline Phosphatase (Alk Phos), Total Bilirubin (TBili), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Total Protein (TP) and Albumin (Alb).
12. Complete Blood Count (CBC). Will be assessed at baseline and at each day of chemotherapy administration as well as response assessments and end of study visits. Baseline examination can occur within 21 days of cycle 1 day 1. The CBC includes: Total white blood cells (WBC), Hematocrit (Hct), Hemoglobin (Hgb), Platelet Count (Plt), white blood cell count differential to allow for calculation of Absolute Neutrophil Count (ANC).
13. Serum Tumor Markers and Biomarkers. CEA and CA19.9 and plasma biomarkers will be assessed at baseline, cycle 1 day 1 of "Adjuvant Chemotherapy" and at completion of cycle 3 day 28 of both "Neoadjuvant Chemotherapy" and "Adjuvant Chemotherapy" and at end of study visit. Baseline examination can occur within 21 days of cycle 1 day 1. CEA and CA19.9 will also be assessed as part of the surveillance evaluation.
14. Radiologic Imaging. CT scan of chest, abdomen and pelvis with oral and intravenous (IV) contrast is preferred imaging modality for radiologic evaluation cancer burden and therapeutic response. Magnetic Resonance Imaging (MRI) is an acceptable alternative for those patients with a contraindication for CT IV contrast. These assessments will be obtained within 21 days of cycle 1 day 1 of study treatment and again at cycle 3 day 28 of "Neoadjuvant Chemotherapy" and within 1 week prior of cycle 1 day 1 and cycle 3 day 29 of "Adjuvant Chemotherapy". Patients in the surveillance component of the clinical trial will have CT scan at 12 week intervals. All radiologic images will undergo central review for allocation of treatment cohort, assessment of response to therapy and on study cancer staging.
15. Stereotactic Body Radiation Therapy (SBRT). SBRT will be initiated between weeks 3 and 5 from last dose of chemotherapy administered during cycle 3 of "Neoadjuvant Chemotherapy". Patients will have physical examination and toxicity evaluation as dictated per the standard operating procedures of Radiation Oncology Department administering SBRT.
16. Surgical Resection of Primary Pancreas Ductal Adenocarcinoma.
17. Surveillance examination. Patients who have completed all therapy will enter into surveillance phase of clinical trial. Patients will be evaluated at 12-week intervals for 2 years. Those patients that survive beyond 2 years beyond completion of all therapy will undergo surveillance examination at 6-month intervals, unless clinical circumstances warrant more frequent examinations. Surveillance examination will include medical history, physical examination,

ECOG performance status assessment, concomitant medication reconciliation and laboratory evaluation to include CMP, CBC, CEA and CA19.9. Radiologic imaging will be obtained within 1 week prior to surveillance examination.

18. End of Study (EOS) Examination. EOS examination will occur within 30 days of patients who do not complete the treatment phase of the clinical trial due to either disease progression or study-related toxicity. EOS examination will include medical history, physical examination, ECOG performance status assessment, concomitant medication reconciliation and laboratory evaluation to include CMP, CBC, CEA, CA19.9 and plasma biomarker.

6.4 Baseline Evaluations

Baseline evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤21 days prior to initiating of therapy (see Section 6.5). Any questions regarding patient eligibility should be directed to the Criterium-nominated Project Manager or designee for review Lead PI Dr. Colin Weekes or PI for Translational Science, Dr. Lawrence Leichman and written approval.

The following clinical evaluations will be performed at Baseline after informed consent has been obtained:

- Medical history (including specific information regarding any prior therapy and cardiac abnormality);
- Physical examination;
- Height and weight assessment;
- Urinalysis (a urine dipstick may be used);
- Prior medication evaluation;
- Vital signs;
- ECOG performance status score.
- Serum β-HCG pregnancy test (for women of childbearing-potential only) will be conducted within 72-hours prior to first study drug administration (negative results required for study drug administration);
- ECG (12 lead);
- Clinical chemistry panel (to include, but not limited to, sodium, potassium, chloride, glucose, BUN, alkaline phosphatase, AST/SGOT, ALT/SGPT, serum albumin, and total bilirubin and creatinine);
- CBC, differential and platelet count;
- PT, PTT coagulation studies (local lab results allowed to confirm patient eligibility);
- CEA and CA19.9 and plasma biomarkers;
- CT scan (or MRI if patient is allergic to contrast agent) within 14 days prior to Cycle 1 Day 1;
- Peripheral Neuropathy Assessment;
- Consent to use diagnostic tumor biopsy (archival tissue) for molecular marker analysis.

The PI will account for all patients who are screened for this study. Although CRFs will not be completed for patients who fail screening, source documents will be reviewed by the Criterium-designated study monitor for completion and accuracy. All appropriate CRF pages must be completed for enrolled patients.

6.5 Treatment Phase Evaluations

All Baseline testing must be completed within 21 days of initiating therapy. Following completion of Baseline testing, patients will receive study-mandated treatment. Patients should return within 3 days to begin Cycle 1 of study drug dosing. Unless otherwise specified, visits where response assessments are not performed must occur within ± 2 days of the planned visit date. CT scans should be performed at Baseline (within 21 days prior to Cycle 1 Day 1), Cycle 3 Day 28 of neoadjuvant chemotherapy, Cycle 1 Day 1 of adjuvant chemotherapy, Cycle 3 Day 28 of adjuvant chemotherapy and every 12 weeks during the surveillance phase (at any time during that week), and EOS. CT scans may be obtained within 7 days prior of scheduled day during the treatment phase and for unscheduled imaging studies outlined in Section 6.7.

If the PI suspects a drug-related toxicity, an extra-unscheduled visit with additional laboratory tests may be performed. Nab-paclitaxel and gemcitabine should be administered as specified in Section 4.2.The same mode of imaging for target lesions must be used at Baseline and throughout the study. CT image preparation will follow the specifications provided in the RECIST response guidelines.

6.6 Molecular Marker Analyses

In those cases where tumor samples from patients treated on study are available and informed consent has been obtained, paraffin-embedded (PE) tumor blocks or newly sectioned, unstained slides will be sent for immunohistochemistry (IHC) analysis. Immunohistochemical stains will include, but not be limited to, SPARC and hENT1 and will be performed in a central, Clinical Laboratory Improvement Amendments (CLIA) - approved laboratory. All tissue samples will be run blinded with respect to the treatment assignment and to the patient response to treatment. It is preferred that fixed tissue samples from patients are shipped as PE blocks so that slides from each specimen can be generated at the central testing laboratory for IHC analysis. However, in cases where PE blocks may not be released from the custody of the site, the sections may be prepared at the site. At least 10 slides (1 section per slide) should be prepared using super frost plus slides and left to AIR DRY. Thickness of the sections should be at 4-5 micron. Specimen collection kits, including super frost plus slides and return shipping containers, will be provided by the central laboratory to each of the specimen collection sites.

Serum CA19-9 and Plasma biomarker. Blood samples for the evaluation of the CA19-9 and molecular biomarkers will be collected on Day 1 of each chemotherapy cycles with a maximum of 6 cycles including both neoadjuvant and adjuvant combination chemotherapy for both treatment arms. CA19-9 and SPARC are further discussed in Section 8.3.5. Plasma molecular biomarkers will be obtained at baseline, within 1 week of cycle 3 day 28 of neoadjuvant chemotherapy, cycle 1 day 1 of adjuvant chemotherapy and within 1 week of cycle 3 of day 28 of adjuvant chemotherapy.

Macropinocytosis Analysis.

6.7 Day 1 Assessments

The following assessments will be performed on Day 1 of each treatment cycle:

- Physical examination;
- Height and Weight assessment;
- BSA calculations (Day 1 of Cycle 1, and recalculated per the site's standard of care, or if body weight changes by more than 10%);
- Urinalysis (a urine dipstick may be used);
- Concomitant medication evaluation;
- Concurrent procedures;
- Peripheral Neuropathy Assessment;
- Vital signs (prior to dosing);
- ECOG Performance Score
- Clinical chemistry panel;
- CBC, differential and platelet count;
- Adverse event evaluation;
- Serum CA19-9 and CEA (Day 1 of each chemotherapy cycles with a maximum of 6 cycles including both neoadjuvant and adjuvant combination chemotherapy);

Day 1 evaluations for Cycle 1 may be omitted if Baseline evaluations are performed within 72 hours of Cycle 1, Day 1.

6.8 Efficacy Response Assessments

The following efficacy response assessments will be performed:

CT scans should be performed at Baseline (within 14 days prior to Cycle 1 Day 1), Cycle 3 Day 28 of neoadjuvant chemotherapy, Cycle 1 Day 1 of adjuvant chemotherapy, Cycle 3 Day 28 of adjuvant chemotherapy and every 12 weeks during the surveillance phase (at any time during that week), and EOS (if required per the defined study imaging schedule).

6.9 Per Cycle Evaluations

On Days 8 and 15 of each cycle, the following assessments will be performed:

- Height and Weight Assessments
- BSA calculations
- Concomitant medication evaluation;
- Vital signs (prior to dosing);
- ECOG Performance Status

- CBC, differential and platelet count;
- Adverse event evaluation.

The following assessments will be performed during the rest week of each cycle:

- Concomitant medication evaluation;
- Vital signs;
- ECOG Performance Status
- CBC, differential and platelet count;
- Adverse event evaluation.

6.10 End-of-Study (EOS) Evaluations

An EOS evaluation should be performed for all patients who end treatment. The following procedures will be completed at the EOS Visit:

- Physical examination;
- Height and Weight assessment;
- Concomitant medication evaluation;
- Concurrent procedures;
- Peripheral Neuropathy Assessment;
- Vital signs;
- ECOG Performance Status
- Clinical chemistry panel;
- CBC, differential and platelet count;
- CA19.9, CEA and plasma biomarker
- CT scan (or MRI if patient is allergic to contrast agent) only if required per the defined study imaging schedule;
- Adverse event evaluation.

The PI must follow all SAEs observed during the study until these events have resolved, the patient is lost to follow-up, or the events are otherwise explained. The PI should report these SAEs in accordance with the procedures described in Section 7. Clinical laboratory tests may be repeated during the post-treatment period if clinically indicated.

6.11 Follow-up for Adverse Events

Any AE or SAE whose onset occurred between the signing of the informed consent form to 30 days after the last dose of study drug or EOS (whichever is later) will be collected. The PI should report SAEs in accordance with the procedure described in Section 7.

Adverse event follow-up will be conducted as follows:

- Non-serious adverse events, other than neuropathy, will be followed for 30 days after the patient's last dose of study drug.
- Neuropathy will be followed until improvement to Grade 1 occurs, or at least 3 months have elapsed without improvement or worsening, or the patient initiates any other anticancer therapy during follow-up. For patients taking nab-paclitaxel and gemcitabine, if nab-paclitaxel is discontinued but gemcitabine is continued, this should be considered as continuation of the study regimen and AE follow-up should continue.
- All serious adverse events (regardless of relationship to study drug) will be followed until resolution.

Clinical laboratory tests may be repeated during follow-up if clinically indicated.

Follow-up evaluations include studies necessary to document the resolution or persistence of any unresolved AEs and could include:

- Physical examination, weight;
- Concomitant medication evaluation;
- Concurrent procedures;
- Vital signs;
- ECOG performance status score. Only one observer is required at these time points;
- CBC, differential, platelet count, and clinical chemistries;
- Peripheral neuropathy assessment (physician).

6.12 Follow-up for Disease Progression

Patients who are discontinued from treatment in the absence of disease progression (e.g., patients removed for unacceptable toxicity or patient/PI discretion) should undergo repeat imaging and tumor response assessments until disease progression is documented. Imaging studies (CT scans) should be continually performed into follow-up every 8 weeks (at any time during that week), regardless of regimen. It is recommended that subsequent therapy not be instituted until disease progression is documented.

If a patient starts a new anti-cancer therapy prior to disease progression, then repeat imaging and tumor response assessments should be discontinued. For patients taking nab-paclitaxel and gemcitabine, if nab-paclitaxel is discontinued but gemcitabine is continued, this should be considered as continuation of the study regimen and imaging should continue.

6.13 Follow-up for Overall Survival

Post-study, overall survival status will be monitored on a monthly basis for 6 months and then every 3 months thereafter until death, the study closes or 3 years have elapsed since subject discontinuation from treatment. This evaluation may be by record review and/or

telephone contact with the patient's treating physician.

7.0 ADVERSE EVENTS MANAGEMENT GUIDELINES

7.1 Background

These adverse event management guidelines are intended to ensure the safety of each patient while attempting to characterize the safety and tolerability of the test products. **In agreeing to the provisions of this protocol, the PI accepts all legal responsibilities for prompt notification of SAEs to Celgene Drug Safety. Celgene in turn will be responsible for reporting the SAEs to the appropriate regulatory authorities.**

Adverse events occurring during the study will be graded according to the NCI CTCAE Scale, where applicable. Adverse events that are not included on the toxicity scale will be designated as Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening, and Grade 5 = death.

The PI should evaluate all adverse events and should make an immediate effort to determine their etiology. Adverse events that are determined *not* to be possibly, probably, or definitely related to study drug may not require further evaluation but will need to be recorded on the CRFs. Study medications may be interrupted for an adverse event at the discretion of the PI. Patients requiring toxicity management should be assessed and evaluated at least weekly as indicated by the severity of the event.

7.2 Definition of an Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient receiving a marketed pharmaceutical product or in a patient who is participating on a clinical trial who is receiving an investigational or non-investigational pharmaceutical agent. **The AE does not necessarily have a causal relationship with the patient's treatment.** Therefore, an adverse event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. In cancer clinical trials, many AEs are in fact related to progression of the patient's underlying malignancy.

An adverse event includes:

7.2.1 An exacerbation of a pre-existing illness;

7.2.2 An increase in frequency or intensity of a pre-existing episodic event or condition;

7.2.3 A condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;

7.2.4 Continuously persistent disease or symptoms that were present at Baseline and worsen following the start of the study.

An adverse event does not include:

7.2.5 A medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); however, the condition that leads to the procedure **is** an

adverse event.

[Procedures that occur during the trial should be recorded on the Concurrent Procedure CRF];

7.2.6 Pre-existing diseases, conditions, or laboratory abnormalities present or detected at the start of the study that do not worsen;

7.2.7 Hospitalizations or procedures that are done for elective purposes not related to an untoward medical occurrence (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);

7.2.8 The disease being studied or signs/symptoms associated with the disease;

7.2.9 Overdose of study drug without any clinical signs or symptoms.

7.3 Definition of a Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined as any untoward medical occurrence at any dose that:

7.3.1 Is **fatal**;

7.3.2 Is **life-threatening** (defined as an immediate risk of death from the event as it occurred);

7.3.3 **Results** in persistent or significant disability or incapacity**;**

7.3.4 Requires **in-patient hospitalization or prolongs an existing hospitalization.** (Exception: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an adverse event. NOTE: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious);

7.3.5 **Is a congenital anomaly/birth defect in the offspring of a patient who received medication;**

7.3.6 Conditions not included in the above definitions that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above unless clearly related to the patient's underlying disease.

The PI should exercise medical and scientific judgment when deciding whether expedited reporting is appropriate in other situations not strictly meeting the criteria outlined above. Examples of important medical events which may also meet the definition of a SAE include: intensive treatment in an emergency room or at home for a reversible condition that did not result in hospitalization (e.g., allergic bronchospasm or convulsions), certain laboratory abnormalities (eg, blood dyscrasias), or development of drug dependency or drug abuse. If there is any question, please consult the relevant Medical Monitor.

7.4 Timeline for Consideration of AE/SAE Reporting Requirements

The PI is responsible for recording, reporting and following **all** adverse events, ***regardless of causality,*** observed during the study period, starting with signing of the informed consent form and ending at the time the patient goes off study or 30 days after patient's last dose of study drug and those made known to the PI at any time thereafter that are suspected of being related to investigational product, whichever is later. Events occurring within 30 days prior to study drug administration should be recorded as pre-treatment

signs and symptoms.

7.5 Lack of Efficacy is not considered an AE or SAE

"Lack of efficacy" (progressive disease) is not considered an adverse event and therefore should not be captured as an adverse event or serious adverse event.

7.6 Laboratory Results as Serious Adverse Events

According to the NCI CTCAE system of adverse event grading, laboratory values of Grade 3 or 4 are described as "severe" or "life-threatening." For example, an absolute neutrophil count (ANC) <500/mm^3 would meet laboratory criteria as Grade 4 ("life-threatening"). This description is not always synonymous with the assessment of the "serious" criteria of an AE as "life-threatening". In order for adverse events to be considered serious by "life-threatening"
criteria, it must be medically judged as possessing "an immediate risk of death from the event as it occurred," not because of the theoretical potential for life-threatening consequences. In the case of a neutrophil count <500/mm^3, the AE would be captured as an AE of Grade 4
neutropenia, but it would not automatically be considered a SAE unless the investigational physician determined this represented an immediately life-threatening event for the patient or another serious criterion was met. Specifically, uncomplicated Grade 4 neutropenia should not be reported as a SAE. Neutropenia associated with fever, infection, or hospitalization should be reported as a SAE.

7.7 Patient Reporting of AEs and SAEs

Patients are to be encouraged to call the site to report any unexpected symptoms or problems they encounter between office visits. These events should be considered in the same fashion as if they had been reported at a scheduled office visit. At each scheduled office visit, after the patient has had an opportunity to spontaneously mention any problems, the site Investigator should inquire about adverse events by asking the following standard questions:

7.7.1 Have you had any (other) medical problems since your last clinic visit?

7.7.2 Have you taken any new prescribed or over-the-counter medicines or herbal/vitamin preparations, other than those given to you in this study, since your last visit/assessment?

7.7.3 Have any new procedures been performed since your last study visit?

7.8 Investigator Reporting of AEs and SAEs

The PI or designee must completely and promptly record each adverse event in the source documentation and in the appropriate CRF, regardless of relationship to study drug as determined by the PI. **The PI must assess AE/SAE causality for any patients treated at his/her site.** The PI should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the PI should report the diagnosis, not the symptoms, as the adverse event.

Clinically significant laboratory abnormalities present at the Baseline visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, laboratory

abnormalities will not be recorded as adverse events unless considered clinically significant by the PI, and clinically significant laboratory abnormalities will not be recorded as serious AEs unless the event meets the definition of serious.

AEs and SAEs should be reported on the appropriate CRFs. Any AE that meets a criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. **In addition, all SAEs must be reported to Celgene Drug Safety within 24 hours of the PI's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.** This instruction pertains to initial SAE report as well as any follow-up reports.

The PI is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time of initial study drug administration to 30 days after the last dose of IP, and those made known to the PI at any time thereafter that are suspected of being related to IP.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

7.8.1 Additional Investigator Responsibilities on Follow-up of SAEs

The PI and supporting personnel responsible for patient care should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include extra clinical laboratory tests, discharge summary, physical examinations or consulting an appropriate specialist. Celgene Drug Safety may also request the PI to conduct supplemental assessments. The results of any additional assessments conducted must be reported to Celgene Drug Safety. If a patient dies during participation in the study and an autopsy is performed, a copy of the report must be submitted to Celgene Drug Safety. **If during the follow-up period for a SAE, a patient dies due to another event unrelated to the SAE being followed, the event causing the death will be reported as a separate SAE.**

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (e.g. missing causality assessment) may be handled by phone.

Report of Adverse Events to the Institutional Review Board

The PI is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Principal Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators

brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.
If this is a multicenter trial, suggest including language indicating that participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to Celgene and the primary study site, and the primary site will be responsible for reporting to FDA.

Adverse event updates/IND safety reports

Criterium Inc. shall notify the PI via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The PI shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The PI must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g., probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The PI is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present. The PI is responsible for reporting adverse events to Celgene as described below.

7.8.2 IRB/EC Notification of SAEs

The PI is responsible for promptly notifying the IRB/EC of the SAE, including any follow-up information, occurring at his/her site and any SAE regulatory reports and Investigational New Drug Safety Reports that he/she receives from Celgene Drug Safety (see Section 7.8 for Guidelines for Reporting Adverse Events).

7.8.3 Expedited Reporting by Principal Investigator to Celgene

Serious adverse events (SAE) are defined above. The PI 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-CL-PANC-AGICC-004253) 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.

7.8.4 Sponsor Notification of Post-Study SAEs

The PI should notify Celgene of any death or SAE occurring after a patient has withdrawn from the study, when such death or SAE may reasonably be related to the medication used in the study. However, PIs are not obligated to actively seek adverse events in former study participants.

7.9 Pregnancy

7.9.1 Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 30 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form or approved equivalent form.

The PI will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the site Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the PI's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard

to causality, as SAEs. In addition, any infant death after 28 days that the PI suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the PI's knowledge of the event using the SAE Report Form, or approved equivalent form.

7.9.2 Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the PI, and the pregnant female partner should be advised to call their healthcare provider immediately.

7.10 Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Criterium Inc. will determine the expectedness of events suspected of being related to study medication based on the Investigator Brochure for nab-paclitaxel and clinical experience with gemcitabine.

Criterium Contact Information:

Lawrence Reiter, PhD
Director, Clinical Operations & Quality Assurance
Tel: 416-277-9630
Fax: 518-583-0384
Office: 518-583-0095

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 STATISTICAL METHODS

8.1 Statistical Considerations

8.1.1 Brief Statistical Rationale:

This is a Phase II study with two primary aims: 1) to estimate the rate of R0 resection in each of the two cohorts separately; 2) to test the feasibility and safety of a new preoperative regimen for patients with R-PDAC and BR-PDAC. All patients entered into each cohort will be included in the estimates of R0 resection rates (intent to treat). Secondary objectives include estimation of Progression-free survival and Overall Survival in each cohort (strata). Outcomes will be examined in relation to the correlative biomarkers for each patient's tumor. The trial will also be monitored for grade III/IV hematologic toxicity. Although dose reductions for chemotherapy are written into the protocol, as part of their charter, the Steering Committee will develop criteria for safety evaluation for all portions of

the clinical trial (chemotherapy, SBRT and surgery).

In the R-PDAC cohort, the trial will be considered to be successful if 81.6% or greater of R- PDAC patients entered on the trial have R0 resections; for the BR-PDAC cohort, the trial will be considered successful if 42% of patients or greater have a R0 resection. See sample size and study design below. Each of the designs is a Simon optimal two stage phase II design with 80% power and alpha of 0.05.

8.1.2 Sample Size

R-PDAC: 20 patients. This is based on a Simon optimal 2 stage design to test the null hypothesis that the rate of R0 resection rate is ≤50% versus the alternative that the R0 resection rate is ≥81.6%. If the regimen is not effective, there is a 2% probability of concluding that it is (target α =0.05). If the regimen is actually effective, there is a 15% probability of concluding that it is not (target power = 80%). Based on this 2-stage design, if the regimen is tested on 9 patients in the first stage, if 4 or fewer patients go on to R0 resection, the trial be terminated at the end of the first stage. With a total of 20 patients, the regimen would be accepted for further study if 15 or more R0 resections are observed in the total group of 20 patients.

BR-PDAC: 30 patients. This is based on a Simon optimal 2-stage Phase II design to test the null hypothesis that the R0 resection rate is ≤20% versus the alternative that the R0 resection rate is ≥ 42%, if the regimen is not effective there is a 0.05 probability of concluding that it is (target α=0.05). If the regimen is actually effective, there is a 20% probability of concluding that it is not (power = 80%, target power =80%). Based on this 2-stage design, if the regimen is tested on 13 patients in the first stage, if 3 or fewer patients go on to R0 resection, the trial will be terminated. With a total of 30 patients, the regimen would be accepted for further study if 10 or more R0 resections are observed in the total group of 30 patients. [Calculations from PASS 2014, NCSS, J. Hintze, Kaysville, Ut] [45]

8.1.3 Statistical Analysis

Within each cohort, patient and disease characteristics will be summarized using descriptive statistics (means, standard deviations, medians, etc.) for continuous variables and frequency distributions for qualitative variables. Each of the biomarkers measured at the pretreatment biopsy (e.g., SPARC and collagen deposition) will be described similarly in each cohort. Macropinocytosis activity will be summarized in a similar manner. For the primary endpoint of R0 resection, resection rates for each cohort will be estimated with exact 95% confidence intervals at the completion of the trial.

Biomarkers and R0 Resection Rates. To evaluate the influence of the biomarker levels and other characteristics on R0 resection rates in each cohort, logistic regression models will be used to evaluate the role of each of these biomarkers individually and in combination in predicting response to treatment. Further, the association between R0 resection (yes/no) and macropinocytosis activity will be estimated using odds ratios. From these analyses, we will estimate the odds of R0 resection as a function of each of the biomarkers alone, macropinocytosis alone, or in combination as well as the area under the curve (AUC) for the Receiver Operating Characteristic Curve (ROC). From the ROC curves associated with each of these biomarkers (univariate analyses and multivariable analyses), we can estimate the sensitivity and specificity for various cut-points of each of the

biomarkers individually and in combination with 95% confidence intervals. To frame these analyses, for a single biomarker (e.g., macropinocytosis activity), we can detect an odds ratio of 2.8 if the observed R0 rate is 50% for a one standard deviation change above the mean activity with 58 patients in the BRPDAC cohort (3.5 in the 20 patient RPDAC cohort). [Calculations from PASS 2014, NCSS, J. Hintze, Kaysville, Ut].[45] The contributions of additional biomarkers to classification of R0 resection will be evaluated by the increases in AUC for the ROC curves in each cohort. We note that to be useful, the AUC should be at least 75%. Two-sided z tests will be used to test the increases in AUC with additional biomarkers. Validation studies will be undertaken if these initial studies support the utility of these biomarkers to predict response to the chemotherapy regimen. *Safety.* All adverse experiences will be summarized within cohort by body system and grade. Summary tables will be provided that indicate the proportions of patients with one or more specified AEs in these classes.

Other Endpoints. Progression-free survival and survival will be estimated separately for each cohort of patients with Kaplan Meier curves and estimates of median survival with 95% confidence intervals. Exploratory analyses will be undertaken to evaluate the prediction of PFS and OS based on measured biomarkers using Cox regression methods with a strategy similar to that used above for response prediction with logistic regression methods.

8.2 Population Analysis

All efficacy analyses will be based on the ITT population. Unless otherwise specified, the treated population includes all who received at least 1 dose of study drug, will be the analysis population for all safety/ tolerability analyses. In addition, overall-survival, progression-free survival and disease-free survival analysis will be stratified based upon the ability to have tumor resection or resection outcome (R0 or no-R0).

8.3 Demographics and Baseline Characteristics

Patient characteristics including demographics, disease duration and extent at Baseline, and relevant medical history will be summarized for the purpose of characterizing the patient population and establishing baseline comparability of the treatment regimens.

8.4 Patient Disposition

Patient disposition including reason for discontinuation of therapy will be summarized by treatment regimen. Patient disposition also will be summarized by study site.

8.5 Prior and Concomitant Medications

All concomitant medications and prior medications taken within 30 days of first study drug administration will be coded to therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Classification. The incidence of prior and concomitant medication usage will be summarized by therapeutic drug class and generic drug names.

8.6 Endpoints

8.6.1 Safety Endpoints

Safety endpoints include AEs, SAEs, physical examination, vital signs, clinical laboratory testing and ADA testing. Safety endpoints will be analyzed using the safety population.

Adverse Events

All reported AEs will be mapped to standard coding terms of the MedDRA, grouped by system organ class and preferred terms and tabulated by dose groups. The incidence of AEs in each dose group will be tabulated by seriousness, severity, and relationship to study drug. The incidence of DLTs will be summarized by dose group.

ECOG Performance Status and Physical Examination

ECOG performance status and physical examination data at baseline and follow-up will be listed by patient for each dose group.

8.6.2 Efficacy Endpoints

Efficacy endpoints include R0 rate, overall survival, disease-free survival, progression-free survival and tumor marker CA 19-9. Efficacy endpoints will be analyzed using the ITT Population.

8.6.3 Exploratory Endpoints

Exploratory endpoints include blood biomarkers, tumor biomarkers and endoscopic elastography (optional). These endpoints will be analyzed using the ITT Population. The correlation of predictive biomarkers with efficacy endpoints for study treatment will be explored.

8.7 Criteria for Enrollment Termination

Enrollment will be terminated when the predetermined number of patients has completed treatment on study.

8.8 Efficacy Assessments

Patients will undergo tumor assessments as outlined in Section 4.1.

Any evaluable and measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. The Investigator, as well as Central Reviewer will assess response per RECIST v1.1 for patients with measurable disease (see Appendix C). Tumor assessments should generally be performed during the last week of cycles in which they are required, before the start of treatment in the next cycle. Tumor assessments may also be performed at any time if progressive disease is suspected.

Screening assessments should include CT scans of the chest and abdomen. Spiral CT or MRI may be performed instead. A bone scan is required to assess for bone metastases. CT scan of the pelvis and/or brain scan (CT or magnetic resonance imaging [MRI]) should be performed if clinically indicated. For subsequent tumor assessments, the same

imaging methods used at screening must be used for each patient to assess disease documented at baseline. Other methods of assessment of measurable disease may be used per RECIST v1.1. Assessments of the tumor marker CA 19-9 should be performed on the same schedule as imaging studies. Radiographic assessment should be the main source in determining the treatment benefit and tumor progression in this study.

Survival data including the date of death and the cause of death will be collected.

8.9 Independent Data Monitoring Committee

Monitoring and Oversight

The Lead Principal Investigator (Lead PI) will be responsible for overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of the Lead PI receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site's investigators and staff at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The Lead PI will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

As the sponsor-investigator in this multi-site trial, the Lead PI is responsible for organizing and conducting monthly teleconferences with all participating sites. The Lead PI will also be responsible for including data from all of the participating sites within the overall trial's six month DSM report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations

from the DSMC's six month review to their IRB of record at the time of continuing review.

Quality Control and Quality Assurance

Site monitoring visits will be performed by the Lead PI's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. After the CRFs are received by the Lead PI's authorized representative, they will be reviewed for safety information, legibility, completeness, accuracy and logical consistency. The data will be entered into a database. Additional computer programs that identify selected Protocol deviations, out-of-range data, and other data errors may be used to help monitor the study. As necessary, requests for clarification or correction will be sent to the appropriate Investigator.

Independent auditors from the Lead PI's authorized representative will be allowed by the Investigator to audit previously monitored data. In addition, audits may be conducted at any time by appropriate regulatory authorities.

Steering Committee

The conduct of this trial will be overseen by a Steering Committee, presided by the Lead PI and representative PIs from the individual sites participating in this multi-center study. Functions of the Steering Committee include, but are not limited to, assessing reports provided on compliance with the protocol by participating sites, monitoring patient enrollment, and evaluating the appropriateness of continuing or stopping the study.

The Steering Committee will meet periodically by teleconference to discuss the progress of the study, as well as based on need. The Steering Committee meetings shall include the Lead PI or his designee and require two-thirds of its constituency to be present in order to approve recommendations affecting the study. Note: the Steering Committee is separate from the independent Data Monitoring Committee described in Section 8.5.

9.0 REGULATORY CONSIDERATIONS

9.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRB/EC charged with this responsibility. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by Celgene prior to submission to the IRB/EC. The PI will forward to Celgene or sponsor-nominated designee a copy of the IRB/EC's approval of this protocol, any amendments informed consent form, and any modifications to the informed consent, based on the US Food and Drug Administration (FDA) regulations set forth in 21 Code of Federal Regulations (CFR) 56, as well as those of the applicable regulatory bodies in all other participating countries outside of the US.

In addition, the PI will be responsible for forwarding to Celgene or sponsor-nominated designee a description of the IRB/EC board members (including profession and affiliation) or a US Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA

and other appropriate regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB/EC for informational purposes.

Clinical supplies will not be shipped to the clinical site until IRB/EC approval is obtained for the protocol and the informed consent form. Any existing amendments, informed consent, and photocopies of the approved documents must be received by Celgene or other sponsor- nominated designee prior to drug shipment.

The PI will be responsible for obtaining annual approval/renewal of the IRB/EC throughout the duration of the study. Copies of the PI's reports and the IRB/EC's continuance of approval must be sent to Celgene.

9.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), Guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, and in full compliance with the World Medical Association Declaration of Helsinki and its most recent amendments.

9.2.1 Informed Consent

Written informed consent of the patient to participate in the study must be obtained and documented by the PI in accordance with the FDA Regulations set forth in 21 CFR 50 as well as the applicable regulatory bodies in all other participating countries outside the United States.

The PI must provide the patient with a copy of the consent form, which is in a language understandable to the patient. Written consent should be obtained before any protocol-required procedures are performed, including any procedure not part of normal patient care (e.g., withdrawal of current medications).

9.3 Confidentiality

The PI and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other information (hereinafter collectively "information") disclosed to the PI or other study personnel. Such information shall remain the confidential and proprietary property of Celgene, and shall be disclosed only to the PI or other designated study personnel. The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the PI or other study personnel; and,
- information after such time that it is disclosed to the PI by a third party entitled to disclose such information.

In order to comply with the applicable privacy laws, the PI will ensure that the patient consents to the use of data by Celgene and its designees for the purposes of regulatory submissions, study publications and drug approval.

In compliance with ICH GCP Guidelines, it is required that the PI and institution permit

authorized representatives of the company, of the regulatory agency(s), and the IRB/EC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The PI is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

9.4 Publication

Data from any individual center must not be published or presented until the complete multicenter study has been published or presented in full. Any subsequent publications should refer to the published multicenter findings.

9.5 Investigator Documentation

9.5.1 Form FDA 1572

This study meets all of the requirements for exemption from the IND regulations. An IND is not required to conduct this investigation and a fully executed Form FDA 1572 is also not required. Alternately, the PI will provide Celgene with a listing of principal and sub-investigators and all updates when applicable.

9.5.2 Curriculum Vitae

The PI must provide Celgene with his/her current dated curriculum vitae and a current dated curriculum vitae for each sub-Investigator listed on the study. Current dated curriculum vitae is defined as updated within 2 years of study start up.

9.5.3 Financial Disclosure

The PI and Sub-Investigator(s) must complete a Clinical Investigator Financial Certification/Disclosure Statement to report financial interests and arrangements that may be of concern to FDA in accordance with 21 CFR 54.

9.5.4 Records Retention

Essential documents must be retained by the PIs for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The PI must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

9.5.4.1 Signed informed consent documents for all subjects;

9.5.4.2 Subject identification code list, screening log (if applicable), and enrollment log;

9.5.4.3 Record of all communications between the PI and the IRB/EC;

9.5.4.4 Composition of the IRB/EC;

9.5.4.5 Record of all communications between the PI, Celgene, and their authorized representative(s);

9.5.4.6 List of Sub-investigators and other appropriately qualified persons to whom the PI has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;

9.5.4.7 Copies of CRFs (if paper) and of documentation of corrections for all subjects;

9.5.4.8 IP accountability records;

9.5.4.9 Record of any body fluids or tissue samples retained;

9.5.4.10 All other source documents (subject records, hospital records, laboratory records, etc.);

9.5.4.11 All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The PI must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The PI must obtain approval in writing from Celgene prior to destruction of any records. If the PI is unable to meet this obligation, the PI must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. PI/Institution should take measures to prevent accidental or premature destruction of these documents.

9.5.5 Protocol Deviations

Apart from the regulatory requirements, it is vital to the success of the study that the PI adheres to the details of the protocol and thus holds to a minimum the number of cases, which may be later classified as “incomplete,” “unusable,” or “not evaluable.”

10.0 APPENDICES

Appendix A: New York Heart Association Classification
Appendix B: Radiology Technical Manual
Appendix C: RECIST CRITERIA 1.1

Appendix A: New York Heart Association Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Appendix B: Radiology Technical Manual

1. Imaging:

Every attempt should be made to assure that imaging studies used for determination of eligibility for this protocol are obtained with a "pancreas protocol". While the details of this will vary from site to site, important components are given below. Please note, that MOST sites will easily meet these requirements.

a. CT

1. CTs should be performed on a multidetector scanner with 16 slice capability as a minimum requirement.

2. All scans MUST be IV contrast enhanced

3. 2-phase acquisition is preferable with images taken during a "pancreatic parenchymal" phase (approximately 40 seconds following initiation of contrast bolus) and a portal venous phase (approximately 70-80 seconds following initiation of contrast bolus).

b. MRI

1. Studies should be obtained using a phased array body coil

2. IV gadolinium gradient recalled echo sequences through the liver and pancreas should be obtained during arterial, early portal venous, and portal venous phases.

3. Other sequences will be obtained including some form of T2 weighted sequence, non contrast T1 sequences. Most sites will acquire diffusion weighted images. MRCP sequences are NOT a requirement for determining resectability.

*For patients who present with imaging studies not performed at participating sites, eligibility will be at the discretion of the PI. Every attempt will be made to avoid having the patient repeat the study; however, this may not be possible in all cases.

2. Transferring of Images.

Images should be collected on a CD. For CT studies, please ask your technologists to include the "THIN SECTION" data as well as the conventional reconstructed images. The thin sections are important to visualize the vascular structures, which are critical for determining resectability status. MRI studies, by virtue of the way in which they are acquired, do NOT require additional thin section images to be sent.

For research purposes, please also include the site radiologist's report on the study. The CD should be anonymized and named for the site and the sequence of the study sent (e.g. NYU_1, NYU_2…NYU_n). Reports should have names redacted. Once the

CD is created, please use overnight mail (labels will be provided) and send to:

Alec J. Megibow, MD, MPH
Department of Radiology, NYU-Langone Medical Center
550 First Avenue, ROOM HCC 232
New York, NY 10016

3. Image interpretation

Determination of protocol eligibility will be based on 2014 NCCN guidelines for resectability. The central PI will communicate to the site PIs with a simple email stating that the patient is eligible or ineligible. If the site disputes the central PI determination, a more detailed analysis of the case will be sent to the site. Please be certain that the site's PI email address is included with the packet in which the CD is sent.

Appendix C: RECIST CRITERIA 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference

ELIGIBILITY

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable Disease – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable Lesions – lesions that can be accurately measured in at least one dimension with the minimum size of:

  - 10 mm by CT scan or MRI (no less than double the slice thickness and a minimum of 10 mm).
  - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
  - 15 mm for nodal disease in short axis
  - 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)
  - Malignant lymph node: 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up only the short axis is to be followed.

  Non-Measurable Lesions – all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geq$10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques, and nodal disease that is 10 to <15 mm in short axis.

Special Considerations Regarding Lesion Measurability: Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- 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 as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Measurement of Lesions

- All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

Methods of Measurement

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and at each subsequent response assessment. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- CT is the best currently available and reproducible method to measure target lesions selected for response assessment. The CT scan slice thickness should be 5 mm or less. When the CT scans have a slice thickness that is greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. Eisenhauer et al. (2009) for more details concerning the use of CT scan and MRI.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- Ultrasound (US) should not be used to measure tumor lesions. The utilization of endoscopy and laparoscopy for objective tumor evaluations is not advised.

- FDG-PET can be used to determine a new lesion if the lesion was absent at baseline on FDG PET.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two 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) and be representative of all involved organs, but in addition should lend themselves accurate repeated measurements.

- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added to the sum.

- If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded at 0 mm.

- If extranodal target lesions fragment, the LDs of the fragmented portions are added in the sum. If targets lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.

- For a patient with SD or PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion is considered PD.

- New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor. If a new lesion is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed from the date of the first scan.

- All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each or in rare case unequivocal progression should be noted at each subsequent response assessment.

RESPONSE CRITERIA

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph node (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. The appearance of one or more new lesions is also considered progression.
* 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.

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 (i.e., <10 mm short axis)
* 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):	Unequivocal progression of the existing non-target lesions. The appearance of one or more new lesions is also considered progressive disease.

Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the PI should prevail.

Evaluation of Overall Response

The overall response is assessed according to the following table.

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status. If described in the clinical protocol, FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

Confirmation

Confirmation of PR or CR to deem either one the 'best overall response' is only needed in non-randomized trials if response is the primary endpoint.

REPORTING OF RESULTS

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) inevaluable for response: specify reason such as early death from malignant disease, early death from toxicity, tumor assessments not repeated/incomplete, or other (specify)

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Consent and Authorization Form

Principal Investigator: **Wells A. Messersmith, MD, FACP**
COMIRB No: **15-0150**
Version Date: **January 4, 2021**
Study Title: **Perioperative Therapy for Resectable and Borderline Resectable Pancreatic Adenocarcinoma with Molecular Correlates**

You are being asked to be in a research study. This form provides you with information about the study. A member of the research team will describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part.

Why is this study being done?

This study plans to learn more about pancreatic cancer. We will study the safety and effectiveness of a new treatment for patients with a type of pancreatic cancer called operable and borderline operable pancreatic ductal adenocarcinoma. This treatment is a combined chemotherapy and radiation therapy. The treatment will be given to patients before they have surgery (preoperative) and again after they have surgery (postoperative).

We hope to learn how well this combination of chemotherapy and radiation therapy works to shrink tumors before surgery. This way, the tumors can be safely and more completely removed during surgery. Patients in this study have operable, non-metastatic (no spread to other organs) pancreatic adenocarcinoma. The main goal of this study is to find out the rate at which surgery may remove all visible cancer from the study patients. The study researchers will look at the harm that this treatment might cause patients. The researchers will also look at the tumor markers of the disease found in tumor tissue and blood samples.

Standard treatment therapies that are used to treat patients with pancreatic cancer include surgery, chemotherapy, and radiation therapy. Generally, surgery comes first, followed by chemotherapy and radiation. In this study, patients will first be given a combination of two chemotherapy drugs that are intended to help stop the growth and spread of cancer. Next, they will receive radiation, then have their surgery, and again receive the combination chemotherapy. In this study receiving chemotherapy before and after surgery is considered investigational.

The two chemotherapy drugs are nab-paclitaxel (abraxane) and gemcitabine (gemzar). These drugs will be given through a vein (intravenously, or "IV"). **Throughout the rest of this form, when these drugs are referenced by themselves they will be called "abraxane" and "gemcitabine". When referenced together in combination use they will be called the "study drugs".**

Abraxane has been approved by the United States Food and Drug Administration (FDA) for the treatment of advanced, inoperable pancreatic cancer that has spread to other organs. However, the use of abraxane to treat patients whose pancreatic cancer can be removed by surgery (resectable or operable) or partly removed by surgery (borderline resectable or borderline operable) is considered "investigational". This means this study drug has not been approved by the FDA for this use.

Gemcitabine has been approved by the FDA for the treatment of all pancreatic cancer at all stages and is not considered investigational.

You are being asked to be in this research study because we are only studying this treatment in patients who have not yet been treated for pancreatic cancer, and whose disease is non-metastatic. Your doctor has reviewed your computerized tomography (CT) or Magnetic Resonance Images (MRI) and believes you are eligible to take part in this study.

Other people in this study

Up to 15 people from your area will participate in the study.

Up to 50 people around the country will be in the study. Two patient groups (cohorts) will be taking part in this study:

- *Up to 20 people will be in Cohort 1: Resectable (Operable) tumors*
  In general "resectable" pancreatic cancers are those which can be removed because they do not touch major blood vessels.
- *Up to 30 people will be in Cohort 2: Borderline Resectable (Borderline Operable) tumors*
  "Borderline resectable" generally includes those which touch the major arteries and/or veins that take blood to or from the pancreas or its surrounding tissues.

What happens if I join this study?

If you join the study, you will be asked to sign this consent form before you receive any study related tests or procedures. Some of these procedures are the same as you would receive as standard of care treatment even if you did not participate in this trial.

There are three parts to this study:

1. Screening (before the study)
2. Treatment
3. After Treatment Follow-up

Below is a general description of these three parts of this study, including which therapies, tests, and procedures will be given and when. It is also an overview of what will be expected of you if you decide to take part in this study.

1. SCREENING

Once you sign this consent form the following will be done to see if you can be in this study. In the next section "Study Procedures" will give a description of these and other procedures you can expect to have if you take part in this study.

- Medical History
- Physical exam
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review of medications (those you are allergic to or taking including, vitamins, herbs or over-the-counter medications)
- Review of other medical procedures you may be having done
- Peripheral neuropathy evaluation

- Vital signs
- ECOG performance status
- ECG
- Urine test
- Blood tests (including a complete blood count (CBC), a complete chemistry panel (CMP), serum pregnancy, coagulation, and tumor markers known as serum CA19-9, serum CEA, and a plasma biomarker.
- CT with contrast or MRI (chest, abdomen and pelvis)
- Radiology review
- Endoscopic Ultrasound (EUS) with diagnostic tumor biopsy. You will sign a separate consent form when you have this procedure. Tumor tissue that is taken during this procedure and not needed for your diagnosis and standard treatment would normally be thrown away, but we will use this left-over tumor tissue in this study to do a molecular tumor analysis (this may also include looking to see if the tumor tissue is hard or soft).
- Archived tumor tissue

2. TREATMENT

The study treatment consists of:

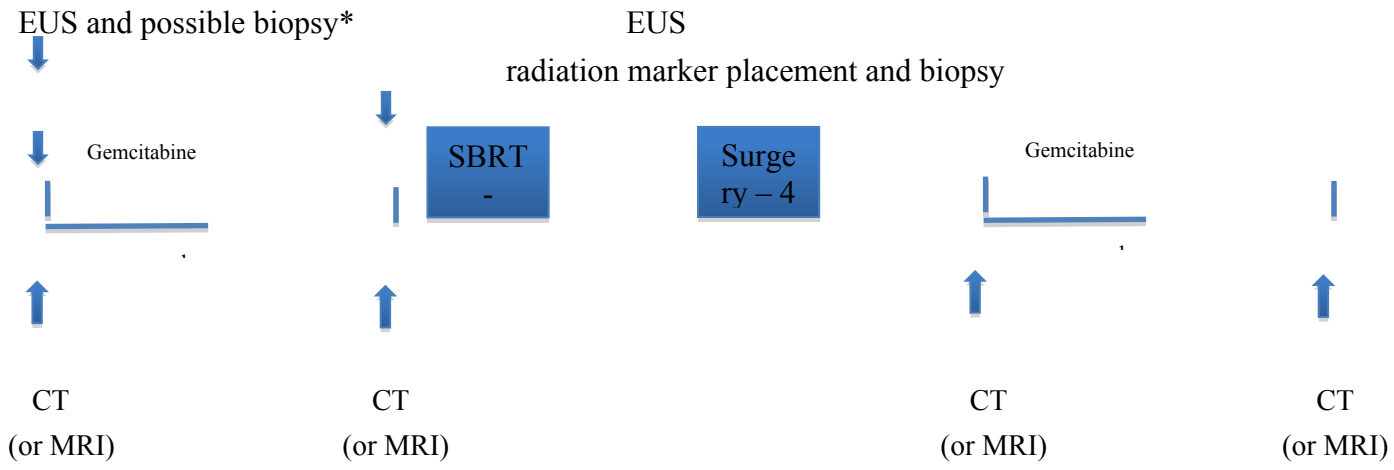
- 3 months (12 weeks) of chemotherapy (the study drugs)
- 5 days of Stereotactic Body Radiation Therapy (SBRT)
- surgery (4 to 6 weeks after SBRT) to remove any operable cancerous tumors
- 3 months (12 weeks) of chemotherapy.

The chemotherapy you receive before your operation and after your operation will be the same.

A. STUDY DESIGN

Below is a chart that shows the order in which procedures will take place in this study. Below the chart is a description of each procedure, but in the chart some of the procedures are show using abbreviations that mean the following:

EUS means an Endoscopic Ultrasound.
CT means a Computed Tomography Scan
MRI means a Magnetic Resonance Imaging Scan
SBRT means Stereotactic Body Radiation



B. STUDY PROCEDURES

Archived Tumor Tissue

If you also had surgery in the past, you must allow us to request tumor tissue from your prior biopsy to be used for this study. We will contact the institution where you had your surgery and ask them to send us a portion of your tumor tissue that they have stored so that it may be used this research. We will also do molecular tumor testing on this tumor tissue.

Body Imaging Studies (CT or MRI)

Body imaging studies such as Computerized Tomography (CT) Scans and Magnetic Resonance Imagining (MRI) will be used to determine your eligibility for this trial. Your doctor will make the choice which test is appropriate for you. These tests are routine for patients with pancreas cancer. They will help determine if you are eligible for this study. They will also show the size of your tumor and whether the size changes during treatment. Since these are standard tests, your doctor and/or radiologist will describe this procedure including the side effects you might experience.

Blood Tests

We will take approximately 2 tablespoons of blood for a variety of tests to check your kidney and liver function and to look for tumor markers. A pregnancy test will also be done for women of childbearing potential.

ECOG performance status score

This is a scale used to assess how a patient's disease is progressing, and how the disease affects a patient's daily living abilities. It helps determine appropriate treatment and prognosis.

Electrocardiogram (ECG)

An ECG is a simple, noninvasive procedure that makes a recording of the electrical activity of the heart. Electrodes are placed on the skin of the chest and connected in a specific order to a machine. Output usually appears on a long scroll of paper that displays a printed graph.

Peripheral Neuropathy Assessment

When your medical history is reviewed, your doctor will also do an evaluation about peripheral neuropathy. This is numbness, tingling, pain, or lack of feeling in your arms, legs, hands, or feet. This is done to see how well you may tolerate the treatment.

Endoscopic ultrasound (EUS) and Diagnostic Tumor Biopsy

This is a minimally invasive procedure done to assess many things, including cancer of the pancreas. Under light sedation, an experienced, well trained physician will pass a thin flexible tube into your stomach and duodenum to visualize the pancreas and your tumor. It uses high-frequency sound waves to produce detailed images of the lining and walls of your digestive tract, chest, and nearby organs, such as the pancreas, liver, and lymph nodes. An EUS is a formal outpatient surgery that allows your doctor to sample (biopsy) tissue from your pancreatic tumor. This procedure will also include tumor marker testing. Your doctor will give you specific instructions to prepare for your EUS which may include asking you to:

- Fast before the EUS procedure, to make sure your stomach is empty.
- Stop taking certain medications, such as blood thinners. Blood thinners may increase your risk of bleeding if a biopsy is performed during EUS. If you have chronic conditions, such as diabetes or high blood pressure, your doctor will give you specific instructions about your medications.
- Plan ahead for your recovery, if you will be sedated before EUS. Most people who have EUS are given medication to relax them. You should arrange for someone to drive you home after the procedure.

This study requires 2 endoscopic evaluations of your pancreatic tumor. During the second evaluation, radiation markers (tiny gold seeds) will be placed to help guide your radiation oncologist for Stereotactic Body Radiation Therapy (SBRT). A doctor trained in analyzing biopsies (pathologist) will report the test results if you have fine-needle aspiration. Your doctors will discuss any important findings and next steps with you.

Molecular Marker Analysis

Molecular markers (also called biomarkers) are substances such as genetic material (DNA and RNA) and proteins found in blood and tumor tissue. These can show if a patient with cancer will or will not respond to a treatment. Currently, no such markers are available for patients with your type of pancreas cancer. In this study we will be testing your blood and tumor tissue (from your biopsy) before treatment is started and after chemotherapy is completed. The biopsy and the blood needed for this testing will be taken prior to the start of chemotherapy and prior to the start of SBRT (most likely at the time of radiation marker placement).

The intent of the treatment used in this study is to make your operation more successful, but the biopsies and blood draws for biomarker analysis will not be used to determine your treatment in this study. Instead they will be analyzed after all enrollment in this trial is complete. You will not receive the results of these analyses.

Chemotherapy (the Study Drugs)

Cancer chemotherapy is designed to safely kill tumor cells while doing less harm to normal cells. The next section of this consent form will tell you about the known side effects of the chemotherapy that you will receive. Chemotherapy prior to surgery is designed to kill both tumor cells in your pancreas and other invisible cells that might have escaped the pancreas to invade other parts of your body. This is called "preoperative chemotherapy."

In this trial you will receive two chemotherapeutic agents (two drugs) by intravenous (IV) infusion. These are gemcitabine and abraxane. These drugs are FDA approved to be given to patients with advanced pancreas cancer. However, they are not FDA approved to be given to patients before or after an operation for pancreas cancer. These drugs are given on the same day. This study visit procedure will last several hours so you can receive the drugs safely and with medication to prevent nausea or vomiting.

Gemcitabine is a type of chemotherapy known as anti-metabolites which prevents cells from making DNA, to stop cell growth and cause cells to die. You will receive gemcitabine through a tube in your vein (IV infusion) for 3 cycles before your surgery and for 3 cycles after your surgery. Each cycle will consist of an IV infusion each week for 3 consecutive weeks with one week off. The 3 cycles will take approximately 12 weeks.

Abraxane is paclitaxel bound to a protein called albumin. This allows the abraxane to be given without the other medicine, which lowers the risk of an allergic reaction. Abraxane is a type of chemotherapy drug known as a taxane. It works on cells when they undergo the part of cell division known as mitosis. Because cancer cells divide faster than normal cells, they are more likely than normal cells to be affected by this drug. In this study, abraxane will be given for 3 cycles before the surgery and for 3 cycles after the surgery. Each cycle will consist of an IV infusion each week for 3 consecutive weeks with one week off. The 3 cycles will take approximately 12 weeks. This is the same schedule we will use for gemcitabine.

Stereotactic Body Radiation Therapy (SBRT) and Radiation Marker Placement

Radiation Therapy
This is a standard of practice in the United States for many patients after they have had a successful operation for pancreatic cancer.

Stereotactic body radiation therapy (SBRT)
This is a type of radiation therapy in which a few high doses of radiation are delivered to small, well-defined tumors. The goal is to deliver a radiation dose that is high enough to kill the cancer, while minimizing exposure to healthy tissues and organs nearby. SBRT is typically used to treat small, early-stage tumors, or isolated recurrences or spread from various types of cancer. SBRT

has been used successfully to treat early-stage pancreatic cancer and metastatic cancers. SBRT begins with one or more sessions of treatment planning. This planning uses imaging (such as a CT scan, or MRI) to map the exact position of the tumor to be treated. These images are then used to create customized treatment plans. During treatment, high-level computerized devices point several radiation beams of different intensities at different angles, so that the radiation is directed precisely to the tumor.

SBRT Delivery: In this study, SBRT will be given 5 times, on 5 consecutive days.

Radiation Marker Placement
This is now considered **standard practice** to place radiation markers for a SBRT. Radiation markers are tiny gold seeds that are placed into the pancreas. The radiation markers will be placed during the second study EUS. A radiation marker is placed in the view of an image that is created when a CT or MRI imaging system is used. The radiation marker is used as a point of reference or measure to help doctors pinpoint the exact location of a tumor. The doctor will aim the radiation beam in the way that will concentrate its energy on the tumor and not the nearby tissue. This procedure will be performed under anesthesia and the doctor performing the procedure will discuss the risks with you and give you a separate consent form. The risks will also be discussed in the next section of this consent form.

Surgery

Surgery to remove a tumor offers the best chance for long-term control of all types of pancreatic cancer. If a tumor is able to be removed with surgery, it is called resectable.

Different types of surgery are performed depending on the location of the tumor within the pancreas:

- Whipple Procedure (Pancreaticoduodenectomy)
- Distal Pancreatectomy
- Total Pancreatectomy

The Whipple Procedure, or pancreaticoduodenectomy, is the most common surgery to remove tumors in the pancreas. In a standard Whipple procedure, the surgeon removes the head of the pancreas, the gallbladder, part of the duodenum (the uppermost portion of the small intestine), the pylorus (a small portion of the stomach), and the lymph nodes near the head of the pancreas. The surgeon then reconnects the rest of the pancreas and digestive organs so that pancreatic digestive enzymes, bile, and stomach contents will flow into the small intestine during digestion.

A distal pancreatectomy is generally performed if a tumor is located in the body or tail portion of the pancreas. The surgeon removes the body and tail of the pancreas, and sometimes the spleen. All other organs are left in place.

A total pancreatectomy is performed when the tumor is situated in such a way that requires the entire pancreas to be removed. It may also be performed when there are multiple tumors spread throughout the pancreas. Similar to a Whipple procedure, the gallbladder, part of the duodenum, the bottom portion of the stomach and local lymph nodes are removed along with the entire pancreas. The spleen may also be removed.

Within 2 months of surgery, you will begin postoperative chemotherapy using the same study drugs you received pre-operatively. Once again, you will have 3 cycles of chemotherapy. In each cycle, you will receive an IV infusion of the study drugs each week for three weeks with one week off.

When you finish the postoperative chemotherapy, the treatment portion of the study is done and you will be given a guide to follow-up examinations and studies.

The treatment portion of this study will take about 8 months. We will continue to follow up with you about every 12 weeks for 5 years.

C. STUDY VISITS

Preoperative Chemotherapy

Cycle 1, Day 1

- Physical exam
- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Review other medical procedures you may be having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Urine test
- Blood tests
- Chemotherapy infusion

Cycle 1, Day 8 and Day 15

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests
- Chemotherapy infusion

Cycle 1, Day 22

- Toxicity (adverse events) evaluation
- Review your medications

- Vital signs
- ECOG performance status
- Blood tests

Cycle 2, Day 1

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Review other medical procedures you may be having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Urine test
- Blood tests
- Chemotherapy infusion

Cycle 2, Day 8 and Day 15

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Blood tests
- Chemotherapy infusion

Cycle 2, Day 22

- Toxicity (adverse events) evaluation
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests

Cycle 3, Day 1

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Review other medical procedures you may be having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Urine test
- Blood tests
- Chemotherapy infusion

Cycle 3, Day 8 and Day 15

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests
- Chemotherapy infusion

Cycle 3, Day 22

- Physical exam
- Toxicity (adverse events) evaluation
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests – which will include tumor marker testing
- CT or MRI

Radiation (SBRT) and Surgery

SBRT

- Physical exam
- ECOG performance status
- Radiology review
- Endoscopic Ultrasound (EUS)
- SBRT
- Tumor biopsy

Surgery

- Physical exam
- ECOG performance status
- Surgery

Postoperative Chemotherapy

Cycle 1, Day 1

- Physical exam
- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Review other medical procedures you may be having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Urine test
- Blood tests – which will include tumor marker testing

- CT or MRI
- Chemotherapy infusion

Cycle 1, Day 8 and Day 15

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests
- Chemotherapy infusion

Cycle 1, Day 22

- Toxicity (adverse events) evaluation
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests

Cycle 2, Day 1

- Physical exam
- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Review other medical procedures you may be having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Urine test
- Blood tests
- Chemotherapy infusion

Cycle 2, Day 8 and Day 15

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests
- Chemotherapy infusion

Cycle 2, Day 22

- Toxicity (adverse events) evaluation
- Review your medications

- Vital signs
- ECOG performance status
- Blood tests

Cycle 3, Day 1

- Toxicity (adverse events) evaluation exam
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Review other medical procedures you may be having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Urine test
- Blood tests
- Chemotherapy infusion

Cycle 3, Day 8 and Day 15

- Toxicity (adverse events) evaluation
- Height and weight
- Body Surface Area calculation (for chemotherapy dosing)
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests
- Chemotherapy infusion

Cycle 3, Day 22 – End of Treatment

- Physical exam
- Toxicity (adverse events) evaluation
- Review your medications
- Vital signs
- ECOG performance status
- Blood tests – which will include tumor marker testing
- CT or MRI
- Radiology review

3. AFTER TREATMENT FOLLOW-UP

Surveillance Evaluations

If you complete all therapy you will enter into the surveillance phase of the study. We will evaluate you at least every 12 weeks (3 months) for 2 years. If your disease does not progress after 2 years, then we will evaluate you every 6 months. We will examine you more often if needed for clinical reasons.

Surveillance examination will include the following assessments:

- Medical History
- Physical Exam
- Toxicity (adverse events) evaluation
- Review your medications
- Height and weight
- Vital signs
- ECOG performance status
- Blood tests
- CT or MRI with radiology review within 1 week prior to this visit.

End-of-Study (EOS) Evaluations

An EOS evaluation will be performed for all subjects who end treatment after the surveillance period. The following procedures will be completed at the EOS Visit:

- Medical history
- Physical exam
- Toxicity (adverse events) evaluation
- Height and weight
- Review other medications you are taking
- Review other medical procedures you are having
- Peripheral neuropathy evaluation
- Vital signs
- ECOG performance status
- Blood tests - which will include tumor marker testing
- CT or MRI with radiology review

What are the possible discomforts or risks?

Discomforts you may experience while in this study include those listed below:

Risks from the Study Drugs

You may have side effects while you are in this study, but you will be carefully checked by the study doctor for any problems. There may be risks or side effects of the study drugs that are unknown at this time. You should tell the study doctor/ staff about anything that is bothering you or any side effects you have, even if you do not think they are related to the study drug.

Gemcitabine

Most Common Side Effects of Gemcitabine

- A decrease in white blood cells that fight infection. You may be more susceptible to bacterial infections.
- A decrease in platelets that assist in blood clotting. You may experience excess bruising or bleeding.
- A decrease in red cells (anemia) that carry oxygen to your tissues. This may cause fatigue or the sense of being tired.
- Overall fatigue may occur from the weekly IV infusions of gemcitabine

- Flu-like symptoms may occur. This includes headaches, muscle aches, fever with shivering.
- Mild swelling of your hands or feet.
- A skin rash over the chest and extremities, especially the legs may occur. It may cause itching.
- Nausea
- Diarrhea

Less Common Side Effects of Gemcitabine

- Muscle aches
- Vomiting
- Constipation
- Change in liver function tests that could cause jaundice (yellowing of the skin)
- Change in kidney function tests
- Excess protein in the urine
- Shortness of Breath

Rare but Serious Side Effects of Gemcitabine

- A severe skin reaction called Stevens-Johnson syndrome, a painful red or purplish rash that spreads and blisters causing the top layer of skin to die and shed
- Inflammation or scarring of the lung leading to shortness of breath and cough
- Kidney and liver failure
- Cardiac dysfunction such as heart attack, congestive heart failure (heart unable to pump enough blood throughout the body), and atrial fibrillation (problem with speed or rhythm of the heartbeat).

Abraxane

The following is a list of the most medically significant or most common side effects reported in completed studies considered to be related to abraxane. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/ therapy and some may never go away. The study doctor may alter the dosage regimen of abraxane (if allowed by the study) or give you medicines to help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

Very Common Side Effects of Abraxane
(a 10% or more chance that this will happen)

- Anemia (a decrease in the number of red blood cells, which may make you feel weak or tired)
- Low number of white blood cells with or without fever (that may make it easier to get infections). A decrease in the number of platelets, the cells that help your blood to clot (which may lead to unusual bleeding or bruising under the skin).
- Constipation
- Diarrhea
- Nausea

- Vomiting
- Stomach pain
- Pain, swelling, or sores on the inside of the mouth
- Neuropathy, a disorder of the nerves which can cause tingling or numbness, with weakness or decreased sensation or movement
- Dizziness
- Headache
- Feeling tired or weak
- Pain (including muscle, joints, bone, and chest pain)
- Swelling caused by fluid held in the tissues, especially of the ankles, feet, or fingers
- Fever
- Chills
- Decreased appetite
- Change in taste
- Weight loss
- Difficulty sleeping
- Depression
- Cough
- Shortness of breath
- Hair loss
- Rash, possibly red, bumpy, or generalized
- Itchiness
- Changes in nails, including discoloration or separation from nailbed
- Abnormal liver function test results
- Dehydration (loss of water and minerals in the body)
- Nosebleed
- Decreased potassium levels in the body

Common Side Effects of Abraxane
(between a 1% to less than 10% chance that this will happen)

- Bone marrow depression, which is a severe reduction of red or white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely
- Infections, including pneumonia or of the lung, mouth, gallbladder, urinary tract, nail, or hair follicle (which may be bacterial, fungal or viral)
- A very severe infection of the blood, which may include a decrease in blood pressure
- Inflammation of the lung passages
- Thickening, inflammation, or scarring in the lungs which may cause breathlessness or cough
- Inflammation of the bowel causing abdominal pain or diarrhea
- Blockage of the intestine
- Trouble swallowing
- Indigestion or upset stomach
- Abnormal chemistry or electrolyte blood test results
- Abnormal kidney function test results

- Acute kidney failure
- Blood in the urine
- Lack of muscle coordination
- Muscle weakness
- Anxiety
- Nasal congestion
- Mouth or throat pain
- Dry mouth, nose, and throat
- Coughing up blood or bloody sputum
- Blood clot in the lungs or in deep vein
- Fluid in the chest cavity
- Red or flushed skin
- Dry skin
- Hand-foot syndrome, involving reddening, swelling, numbness, and peeling of palms and soles of feet
- High blood pressure
- Low blood pressure
- A decrease in the heart's ability to pump blood to all parts of the body and possibly heart failure
- Faster heartbeat
- Watery eyes
- Changes in vision or blurry vision
- Infusion site reactions (described as discomfort, bleeding or bruising/ swelling at the needle site, and in some instances infection or leaking of IV fluid outside of blood vessel into the surrounding tissue
- Localized swelling due to buildup of lymph fluid

Uncommon Side Effects of Abraxane
(between a 0.1% to less than 1% chance that this will happen)

- Irregular or slow heartbeat
- Stopping of the heart
- Allergic reaction (may include skin inflammation, rash, trouble breathing, trouble speaking, fever), sometimes fatal
- Syndrome involving abnormal blood clotting with decreased platelets, bruising (including tiny red or purple spots under the skin), and possibly leading to blood clots
- Edema/ swelling and cyst formation of the macular area of the retina.
- Irritation and redness of the thin membrane covering the eye
- Inflammation of the cornea
- Too much fluid in the body
- Feeling unwell
- Sleepiness
- Scaly or peeling skin
- Potentially life-threatening allergic reaction of the skin and oral mucous membranes (may include lesions in the mouth, itching and blistering skin.
- Hives
- A loss of nerve function in the muscles of the face

Additional side effects observed during post-marketing surveillance of abraxane, not otherwise noted above include:

- Lack of movement in the vocal cords with possible voice changes
- Skin sensitivity to sunlight
- Potentially life-threatening allergic reaction (may include skin rash with skin blistering)
- Skin or tissue damage from prior radiation therapy can become damaged again, when a person receives chemotherapy after having had radiation therapy. This is referred to as radiation recall and may involve redness, peeling, pain, and swelling. Skin changes have been noted to range from mild redness to tissue death. Radiation recall may also occur in the lungs and other internal organs.

Elderly Subjects

- In subjects 65 years old or older with metastatic breast cancer who received abraxane monotherapy, a higher incidence of nose bleed, diarrhea, dehydration (loss of water and minerals in the body), feeling tired or weak and swelling caused by fluid held in the tissues, especially of the ankles, feet, or fingers has been reported.

Abraxane in Combination with Gemcitabine

- In subjects with metastatic pancreatic cancer, who received the combination of abraxane and gemcitabine, there may be an increase of blood infections. Contact your study doctor immediately if you develop a fever. Your study doctor will evaluate if your fever is an early sign of a serious infection, which may require treatment.
- A particular lung illness, known as pneumonitis (thickening, inflammation, or scarring in the lungs with breathlessness or cough) appears to occur more often (4%) when the two drugs are given together. This lung illness requires early detection and treatment as it may be life-threatening or even fatal. Therefore, it is important that you promptly tell your study doctor if you have worsening shortness of breath, difficulty breathing, fever, or a dry cough (not productive), for further evaluation and possible treatment.
- Acute renal or kidney failure and hemolytic uremic syndrome (a syndrome involving abnormal blood clotting, with decreased platelets, bruising including tiny red or purple spots under the skin, and possibly leading to blood clots) have been reported commonly and uncommonly, respectively, in combination of abraxane with gemcitabine.
- A very rare condition known as Posterior Reversible Encephalopathy Syndrome that causes leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your doctor if you have one or more of the following symptoms:
    - headache;
    - abnormal shaking of the body;
    - sleepiness;
    - increased blood pressure;
    - feeling confused;

- abnormal vision including loss of vision;
- loss of muscle control or muscle weakness, numbness, or tingling in extremities.

- A very rare condition known as Capillary Leak Syndrome that causes leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your study doctor if you have one or more of the following symptoms:
  - fatigue;
  - lightheadedness or fainting;
  - pain in arms, legs, stomach, or all over body;
  - swelling in face or body; difficulty breathing; low blood pressure.

Elderly Subjects

- In subjects 65 years old or older, who received abraxane and gemcitabine, a higher incidence of diarrhea, decreased appetite, dehydration (loss of water and minerals in the body) and of nose bleed has been reported compared to subjects less than 65 years old.
- In subjects 75 years old or older, a higher incidence of serious adverse reactions and adverse reactions leading to treatment discontinuation has been reported.

Risks of Having Blood Taken

In this study we will need to get about a half-cup of blood from you. We will get blood by putting a needle into one of your veins and letting the blood flow into a glass tube. You may feel some pain when the needle goes into your vein. A day or two later, you may have a small bruise where the needle went under the skin.

Risk of Pregnancy

Females:

Abraxane can cause harm to an unborn child if it is given to a pregnant woman. You cannot take part in this study if you are pregnant or breast-feeding. Because of the possible risks to an unborn child, if you are a female who can become pregnant, you will be asked to take a pregnancy test prior to starting study drug treatment and throughout your study participation.

If you decide to take part in this study, you should avoid becoming pregnant while receiving study medication. You must commit to abstinence from heterosexual contact, or agree to use medical doctor-approved contraception throughout the study without interruption, while receiving study medication or for a longer period if required by local regulations. If you become pregnant while receiving study medication, you must tell the study doctor right away. If this happens, the study medication will be discontinued. The study doctor will follow you and your pregnancy to completion.

Males:

If you have a partner of childbearing potential, you should avoid fathering a child while receiving study medication and for 6 months after your last dose of study medication. You must agree to complete abstinence from heterosexual contact or use a condom during

sexual contact with a female of childbearing potential while receiving study medication and within 6 months after your last dose of study medication. If your partner becomes pregnant while you are receiving study medication or within 6 months after you took your last dose of study medication, you must tell the study doctor right away.

The principal investigator may ask for your partner's permission to collect information about the outcome of her pregnancy and the health of her baby. You will be given a contact form to share with your partner. This form will allow her to reach out to the study team if she is interested in providing information about her pregnancy and the health of her baby. By sharing the contact form with your partner, your partner will become aware of your participation in this study.

Risks of loss of confidentiality:

There is a risk that people outside of the research team will see your research information. We will do all that we can to protect your information, but it cannot be guaranteed.

Other possible risks include:

While you take part in this study, you will have tests and procedures that are standard of care for your disease. These include CT scans, MRIs, endoscopic ultrasound (EUS) with diagnostic biopsy, and stereotactic body radiation therapy (SBRT). There are risks associated with these procedures. You should talk to your study doctor about any questions you may have about these risks.

The study may include risks that are unknown at this time.

What are the possible benefits of the study?

This study is designed for the researcher to learn more about pancreatic cancer. However, there is no guarantee that your health will improve if you join this study. Also, there could be risks to being in this study. If there are risks, these are described in the section describing the discomforts or risks.

Are there alternative treatments?

There may be other ways of treating your pancreatic cancer. Instead of taking part in this study:

- You may choose to receive treatment with another experimental therapy
- You may choose to receive treatment with another approved therapy
- You may choose to receive comfort/palliative care
- You could also choose to get no treatment at all

You should talk to your doctor about your choices. Make sure you understand all of your choices before you decide to take part in this study. You may leave this study and still have these other choices available to you.

Who is paying for this study?

Celgene Corporation is providing a grant of funding support for this research. Celgene Corporation manufactures abraxane. Dr. Wells Messersmith is the Investigator-Sponsor of this study. The research study will only pay for procedures not considered standard of care. This may include a biopsy, if the most recent biopsy you had before you start the study (at screening) was obtained outside the time allowed for this study. If this is the case, a research biopsy may be required.

Will I be paid for being in the study?

You will not be paid to be in the study.

Will I have to pay for anything?

You and/or your health insurance may be billed for the costs of medical care during this study, if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay. If you have health insurance, the cost of these services will be billed to your insurance company. If your insurance does not cover these costs, or you do not have insurance, these costs will be your responsibility.

Is my participation voluntary?

Taking part in this study is voluntary. You have the right to choose not to take part in this study. If you choose to take part, you have the right to stop at any time. If you refuse or decide to withdraw later, you will not lose any benefits or rights to which you are entitled.

If you leave this study, you will still receive your normal medical care. The only medical care that you will lose is the medical care you are getting as part of this study. You might be able to get that same kind of medical care outside of the study. Ask your study doctor.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them.

Can I be removed from this study?

The study doctor may decide to stop your participation without your permission if the study doctor thinks that being in the study may cause you harm, or for any other reason. Also, the sponsor may stop the study at any time.

What happens if I am injured or hurt during the study?

If you have an injury while you are in this study, you should call Dr. Messersmith immediately. His phone number is 303-724-0747 (clinic hours) or 720-848-0300 (24 hours).

We will arrange to get you medical care if you have an injury that is caused by this research. However, you or your insurance company will have to pay for that care.

Who do I call if I have questions?

The researcher carrying out this study is Wells A. Messersmith, MD. You may ask any questions you have now. If you have questions, concerns, or complaints later, you may call Dr. Messersmith at 303-724-0747 (clinic hours) or 720-848-0300 (24 hours). You will be given a copy of this form to keep.

You may have questions about your rights as someone in this study. You can call Dr. Messersmith with questions. You can also call the responsible Institutional Review Board (COMIRB). You can call them at 303-724-1055.

A description of this clinical trial will be available on http://www.clinicaltrials.gov as required by U.S. law. This Web site will not include information that can identify you. You can search this Web site at any time.

Who will see my research information?

The University of Colorado Denver (UCD) and its affiliated hospital(s) have rules to protect information about you. Federal and state laws including the Health Insurance Portability and Accountability Act (HIPAA) also protect your privacy. This part of the consent form tells you what information about you may be collected in this study and who might see or use it.

The institutions involved in this study include:

- University of Colorado Denver
- University of Colorado Hospital

We cannot do this study without your permission to see, use and give out your information. You do not have to give us this permission. If you do not, then you may not join this study.

We will see, use and disclose your information only as described in this form and in our Notice of Privacy Practices; however, people outside the UCD and its affiliate hospitals may not be covered by this obligation.

We will do everything we can to maintain the confidentiality of your personal information but confidentiality cannot be guaranteed.

The use and disclosure of your information has no time limit. You can cancel your permission to use and disclose your information at any time by writing to the study's Principal Investigator (PI), at the name and address listed below. If you do cancel your permission to use and disclose your information, your part in this study will end and no further information about you will be collected. Your cancellation would not affect information already collected in this study.

Wells A. Messersmith, MD
University of Colorado Cancer Center
12801 E. 17th Ave, RC-1 South, Room 8121
Mail Stop 8117
Aurora, Colorado 80045

Both the research records that identify you and the consent form signed by you may be looked at by others who have a legal right to see that information, such as:

- Federal offices such as the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) that protect research subjects like you
- People at the Colorado Multiple Institutional Review Board (COMIRB)
- The study doctor and the rest of the study team
- Celgene Corporation, who is the manufacturer of abraxane and the company providing a grant of funding support.
- Academic Gastrointestinal Cancer Consortium (AGICC)
- Officials at the institution where the research is conducted and officials at other institutions involved in this study who are in charge of making sure that we follow all of the rules for research

We might talk about this research study at meetings. We might also print the results of this research study in relevant journals. But we will always keep the names of the research subjects, like you, private.

You have the right to request access to your personal health information from the Investigator.

The investigator (or staff acting on behalf of the investigator) will use your information for the research outlined in this consent form. They will also make *all or some* **of the following health information about you collected in this study available to:**

- Criterium, Inc., a Contract Research Organization who is assisting with the management and monitoring of this study
- Other participating sites including:
    - Harvard Cancer Center
    - Mayo Clinic - Arizona
    - New York University
    - University of Arizona
    - University of Kansas

Information about you that will be seen, collected, used and disclosed in this study:

- Name and Demographic Information (age, sex, ethnicity, address, phone number, etc.).
- Your social security number
- Portions of your previous and current Medical Records that are relevant to this study, including but not limited to Diagnosis(es), History and Physical, laboratory or tumor tissue studies, radiology studies, procedure results
- Research Visit and Research Test records
- Tumor Tissue samples and the data with the samples.
- Billing or financial information

What happens to Data, Tumor Tissue, Blood and Specimens that are collected in this study?

Scientists at the University of Colorado Denver and the hospitals involved in this study work to find the causes and cures of disease. The data, tumor tissue, blood and specimens collected from you during this study are important to this study. If you join this study:

- The data, tumor tissue, blood, or other specimens given by you to the investigators for this research no longer belong to you.
- Both the investigators and Celgene Corporation may study your data, tumor tissue, blood, or other specimens collected from you.
- If data, tumor tissue, blood, or other specimens are in a form that identifies you, UCD or the hospitals involved in this study may use them for future research only with your consent or Institutional Review Board (IRB) approval.
- Any product or idea created by the researchers working on this study will not belong to you.
- There is no plan for you to receive any financial benefit from the creation, use or sale of such a product or idea.

[SIGNATURES ON NEXT PAGE]

Agreement to be in this study and use my data

I have read this paper about the study or it was read to me. I understand the possible risks and benefits of this study. I understand and authorize the access, use and disclosure of my information as stated in this form. I know that being in this study is voluntary. I choose to be in this study. I will get a signed and dated copy of this consent form.

Signature: _____ Date: _____

Print Name: _____

Consent form explained by: _____ Date: _____

Print Name: _____

Witness Signature: _____ Date: _____

Witness Print Name: _____

Witness of Subject Signature ☐
Witness of Consent Process ☐