

TITLE: Randomized Phase II trial of Pre-Operative Gemcitabine and Nab-Paclitaxel with or with out Hydroxychloroquine (UPCI# 13-074)

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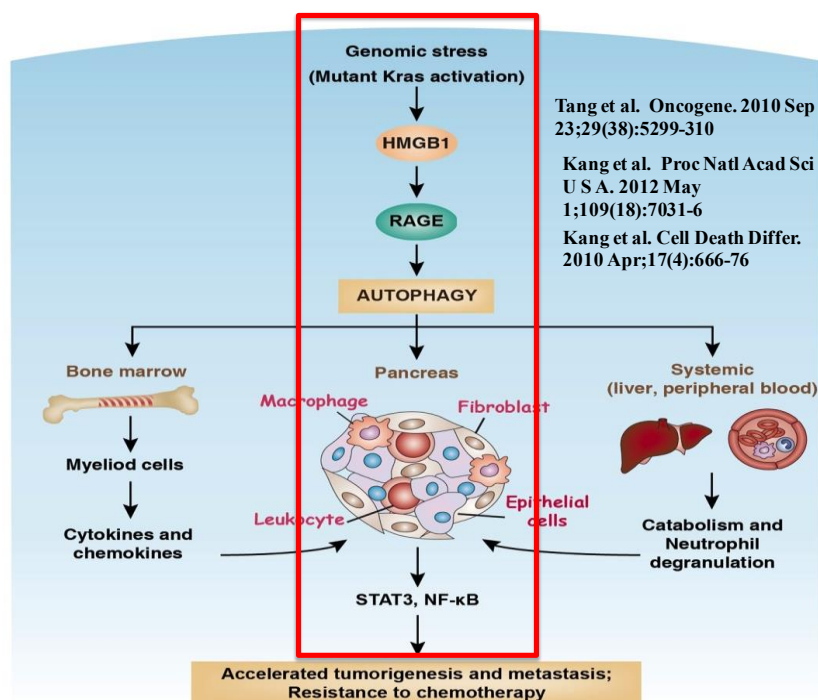
RESEARCH PROTOCOL ABSTRACT

This is a randomized phase II trial that will examine the ability of the hydroxychloroquine to improve the clinical activity of a pre-operative regimen of gemcitabine and nab-paclitaxel in subjects with potentially resectable adenocarcinoma of the pancreas. Eligible subjects will receive 2 cycles of gemcitabine and nab-paclitaxel (1000mg/m² & 125mg/m² – day 1, 8, 15) with or without hydroxychloroquine (1200mg/day) followed by surgical resection. Primary endpoint will be histologic response as graded by Evans criteria. The Secondary endpoint will be CA19-9 response. Pre and post treatment tissue biopsies will be obtained to assess for levels of autophagy in tumor, liver and peripheral blood.

1.0 BACKGROUND AND SIGNIFICANCE

Adenocarcinoma of the exocrine pancreas (pancreatic ductal adenocarcinoma, PDA)

Pancreatic cancer is a major unsolved public health problem in the United States, with approximately 42,000 new cases in the year 2012, making it the tenth most common malignancy in adult men and ninth in women. It ranks as the fourth



leading cause of cancer deaths; accounting for 5-6 % of all cancer related deaths in the United States, in 2008. Five-year survival is less than 5% for all stages. Currently, the only potentially curative therapy is surgical resection. Nonetheless, a vast majority of patients who undergo surgical resection will derive no therapeutic benefit. Survival of patients who undergo surgical resection followed by adjuvant radio-chemotherapy for localized non-metastatic adenocarcinoma of the pancreas is at best 15% at 5 years, and the median disease free survival is 10-13 months. This uniformly poor prognosis even in the earliest stage disease with best treatment modalities underscores the need for radical rethinking of our approach to pancreatic cancer. There is a critical need for identification of novel pathways with biological activity to improve outcomes in this disease. We have accumulated a large body of preclinical and clinical data suggesting that ancient

metabolic stress response of autophagy plays a major role in the pathogenesis of this disease. In this proposal we will directly examine several aspects of this hypothesis in human subjects. (Figure 1.) [1-7]

Inhibition of autophagy with chloroquine enhances apoptosis and response to chemotherapy in animal models. The finding that autophagy is critical mediator of DAMP induced tumor cell survival lead us to investigate this pathway as a target. Chloroquine (CQ) and its derivatives such as HCQ are synthetic 4-aminoquinolines that have been used for 60 years in humans for malaria prophylaxis and play a role in the treatment of patients with rheumatoid arthritis, and human immunodeficiency virus (HIV). They are inexpensive orally available drugs with a large therapeutic index. Chloroquine blocks acidification of the lysosome, thus inhibiting the last step in autophagy. Evidence in mouse models and human cancer cell lines suggest CQ may have significant anti-tumor activity by inhibiting autophagy induced by cancer therapy. [8-10] Yang et al have demonstrated significant responses in a xenograft model to single agent CQ[8]. Our own findings confirm that pharmacologic inhibition of autophagy with chloroquine enhances the effects of gemcitabine in an orthotopic transplantable model using two distinct murine pancreatic tumors (manuscript in preparation.) Consistent with our previous observations, the enhanced anti-tumor effect associated with autophagy inhibition resulted in substantially more apoptosis measured by TUNEL staining in treated tumors when compared with chemotherapy alone. Moreover, our

preliminary clinical experience with hydroxychloroquine and gemcitabine demonstrates substantial promise. In this submission we will directly examine the ability of the autophagy inhibitor hydroxychloroquine to improve the clinical efficacy of chemotherapy in human tumors. We will correlate levels of autophagy, STAT3/IL-6 signaling and apoptosis with histologic response in resected tumor treated with chemotherapy alone or chemotherapy and hydroxychloroquine.

Combination of gemcitabine and the autophagy inhibitor hydroxychloroquine demonstrates promising clinical activity in human subjects. Based on the above findings we launched and have accrued 30/40 subjects to a Phase I/II trial examining pre-operative gemcitabine (GC) in combination with oral hydroxychloroquine in the treatment of high-risk pancreatic adenocarcinoma. (UPCI09-122; NCT01128296; <http://clinicaltrials.gov/show/NCT01128296>). Eligibility was limited to only those patients predicted to have limited survival advantage of surgical resection[11]. Fixed dose rate gemcitabine (1500mg/m²) was administered every two weeks for two doses. HCQ (200mg/day-1200mg/day) was

administered 48 hours prior to the first dose of gemcitabine and continued for 31 consecutive days until day of surgery. Toxicity was evaluated based on National Cancer Institute criteria. Response to treatment was assessed by decrease in CA19-9 levels and PET CT. Two weeks after the last dose gemcitabine, patients underwent pancreatectomy. Twenty-two patients have completed treatment, 17 at the maximum dose of HCQ (1200 mg/day). (Table 1) There were no dose limiting toxicities. All patients underwent surgical resection with an R0 resection rate of 86%. Of these first 22 subjects, 100% were able to undergo resection with 86% R0 (margin negative) which compares very favorably to our previous experience with this population of high risk subjects at our own institution (53% resection and 33% R0, p<0.01) [11]. Next 13 /19 (68%) of patients with elevated pretreatment levels had a greater than 50% decrease in CA19-9 following the single cycle of gemcitabine based

PT#	Gender	Age	HCQ (mg/day)	Ca 199			T	N	Margin
				Pre	Post	%↓			
1	M	46	200	91	70	23.1	3	1	R0
2	M	62	400	126	133	-5.6	3	1	R0
3	M	56	600	2	0.8	NA	3	1	R0
4	M	68	800	67	22	67.2	3	1	R0
5	F	71	1000	1112	30	97.3	3	0	R0
6	F	51	1200	10643	28292	-165.8	3	1	R0
7	F	75	1200	<0.8	<0.8	0	3	0	R0
8	M	62	1200	37	1.4	96.2	3	1	R0
9	M	56	1200	109	10	90.9	3	0	R0
10	F	52	1200	261	43.7	83.3	3	1	R1
11	M	66	1200	60	12.7	79.9	2	0	R0
12	F	64	1200	35	6.9	80.3	3	1	R0
13	F	62	1200	86	11.9	86.2	2	1	R1
14	F	73	1200	3	2.2	NA	3	1	R0
15	M	79	1200	2386	431	81.9	3	1	R0
16	M	67	1200	274	882	-221.9	3	1	R1
17	F	61	1200	1092	2272	-108.1	3	1	R0
18	F	78	1200	126	6.4	94.9	2	1	R0
19	M	81	1200	384	211.6	45	3	0	R0
20	M	82	1200	1192	1140	4.4	3	1	R0
21	F	55	1200	10064	2538.6	74.8	3	1	R0
22	M	65	1200	3010	433	85.6	2	0	R0

Table 1. Demographics and outcomes following treatment with gemcitabine/hydroxychloroquine in high risk pancreatic adenocarcinoma. Twenty-two patients have completed treatment, 17 at the maximum dose of HCQ (1200 mg/day). There were no dose limiting toxicities. 59% of patients had a > 50% decrease in Ca 19-9 following treatment. All patients underwent surgical resection with an R0 resection rate of 86%.

treatment. Moreover 11/22 (50%) had >75% decrease and 4/22 (18%) had >90% reduction in this tumor marker. This type of CA19-9 response rates following one cycle of gemcitabine based chemotherapy is much greater than any previous reports. [12, 13] These data, when compared to historical controls, suggest significant biologic activity of this regimen and support larger clinical trials such as this proposal.

Gemcitabine and albumin bound paclitaxel is more clinically active regimen than gemcitabine alone. Since the initiation of our clinical trial of gemcitabine and hydroxychloroquine; new clinical data demonstrates that the combination of gemcitabine and nab-paclitaxel bound protein bound particles (Abraxanetm) is more clinically active than gemcitabine alone. In response to this information we have also participated in a multi-center feasibility trial of preoperative gemcitabine/nab-paclitaxel: PCRT # 10-001 Celgene # ABX267-PA09US Subjects meeting NCCN criteria for potentially-resectable pancreatic cancer received 3 cycles of gemcitabine and nab-paclitaxel (1000mg/m² & 125mg/m² – day 1, 8, and 15) followed by surgical resection. The primary endpoint was grade III/IV pathological response in ≥ 30% of resected tumor specimens. The trial has accrued the anticipated 25 patients (10 Female: 15 Male) at four centers. Of fifteen patients that completed all 3 cycles, six required dose reduction. Five patients were unable to complete all 3 cycles of therapy due to serious adverse events (Grade 3 or 4 toxicities). To date, ten patients have undergone surgical resection (5- Pancreaticoduodenectomy, 5- Distal Pancreatectomy). All ten achieved negative surgical margins (R0 100%) and CA19-9 decrease from baseline (mean 181.7 U/ml) to end of therapy (mean 44.2 U/ml) was also noted. There were no unexpected postoperative complications. A ≥ 90% tumor necrosis (Grade III/IV) was seen in 3 patients, with 4 Grade 2, 1 Grade I, and 2 without effect. (Personal communication Ramesh Ramanathan). This trial supports the safety and

feasibility of preoperative therapy with gemcitabine and nab-paclitaxel with preliminary evidence of improved radiological and pathological response in resected tumor specimens.

1.5 We have completed accrual to this trial (Fig.1A). Toxicity has been equivalent between the two arms. The primary endpoint for this trial is the rate of grade II/IV histologic response as defined by Evans *et al*³³. Secondary endpoints are response of the tumor marker CA19-9 and ratio of positive lymph nodes in resected specimens. Analysis of this primary endpoint in subjects at 95 % accrual analysis demonstrates a significant increase in the number of subjects with increased Evans grade histopathologic response with the PGH regimen (Fisher's exact test $p=0.0039$) (Table I). The percent change in CA19-9 was significantly different between arms (Wilcoxon test $p=0.014$) (Fig.1B). Similarly, the number of involved lymph nodes is statistically different between the arms. We are in the process of examining the resected tissues for evidence of autophagy inhibition and apoptosis. Given that it appears that the experimental arm has increased response rate we now propose to extend accrual to this arm (Gem/Abraxane/hydroxychloroquine) in order to better establish biomarkers of response that will assist in design of the future therapeutic trials.

Rationale for dosing in proposed clinical trial. The proposed clinical trial is based on a large body of pre-clinical and clinical data (outlined above) that suggest that the combination of autophagy inhibition with effective systemic chemotherapy will result in substantial improvement in clinical response in subjects with PDA. Safety and promising biologic activity of preoperative gemcitabine/hydroxychloroquine and gemcitabine / nab-paclitaxel has been established through our two pilot trials. The combination of these three agents has not been specifically studied in the preoperative setting however it is currently being examined in metastatic disease in an ongoing phase 1 dose escalation trial at the University of Pennsylvania. No unexpected synergistic toxicities have been identified at the proposed dosing of this trial of 1200mg daily of hydroxychloroquine (personal communication Peter O'dwyer).

2.0 OBJECTIVES AND SPECIFIC AIMS

2.1. Primary Objective:

- To determine if inhibition of autophagy can improve the rate of grade III/IV histologic response to pre-operative gemcitabine/ nab-paclitaxel.
- Histological response validated scoring system by Evans[14]
 - Grade I: 1-9% tumor destruction
 - Grade II: 10 – 90%
 - Grade III: >90% tumor destruction
 - Grade IV: Absence of viable tumor cells

2.2. Secondary Objectives

- To determine if inhibition of autophagy can improve the rate CA19-9 response to pre-operative gemcitabine/ nab-paclitaxel.
- To determine if inhibition of autophagy can improve Rate of R0 resection and positive lymph node ratio

3.0 STUDY DESIGN AND METHOD

This will be an adaptive phase II, non-blinded, randomized, control trial. Patients with pancreatic ductal adenocarcinoma will be staged prior to protocol entry by standard of care testing including contrast-enhanced helical chest, abdomen, pelvis CT scan done using a pancreas mass protocol used to determine resectability and to rule out metastatic disease. If the patient has not already undergone an EUS biopsy for pathology confirmation this will be performed in screening. During the EUS biopsy for pathology confirmation an additional biopsy will be taken for research purposes. The pancreatic tumor biopsy will be processed and billed as standard of care. The biopsy of the liver will be for research purposes only. If the patient has had an EUS biopsy done with positive pathology finding for pancreatic cancer prior to screening, it will not be repeated. The investigator will request the archival sample from this biopsy for research purposes. Patients meeting NCCN criteria for potentially resectable or borderline resectable tumors will be eligible. Subjects will then receive 2 cycles of gemcitabine and nab-paclitaxel (1000mg/m² & 125mg/m² – day 1, 8, and 15) plus or minus hydroxychloroquine 1200mg qd from day 1 through the evening before surgery. Sixty participants will be randomized to gemcitabine + nab-paclitaxel versus gemcitabine + nab-paclitaxel + oral HCQ (1200mg PO daily) by means of response-adaptive randomization [15] based on Grade III/IV histologic response, as follows. The first twenty participants will be randomly assigned in a

1:1 ratio. Each participant's histologic response will be graded, where a Grade III/IV response will count as a positive response for the purpose of randomization. After the first twenty participants, random assignment to treatment will continue, but the probability of assignment to gemcitabine + nab-paclitaxel + HCQ will be proportional to $P(\pi_c < \pi_x | \text{responses})^{(n/2N)}$, where π_c and π_x are the estimated probabilities of response in the control and experimental arms given the current data, n is the number of observed patients and $N=60$. If there is strong evidence that one treatment is better than the other, this allocation will tend to favor the better arm, but if the responses in the arms are similar, the probabilities of allocation will remain close to 1:1. The operating characteristics of this allocation are presented in the statistical methods section of the protocol. After the last dose of gemcitabine and prior to surgery, subjects will undergo repeat CT scan. Surgical exploration and pancreatectomy will be performed if technically feasible and all toxicities have resolved. Pathologic specimens will undergo detailed histologic and immunohistochemical evaluations. Tissue specimens will be stored at -80°C for future correlative studies of autophagy and tumor response to protocol therapy. Six to ten weeks following completion of successful surgical removal of their tumor, subjects will be free to pursue standard of care adjuvant therapy options at the discretion of their treating physician

For this extended phase II we will accrue only to Arm A. All other study interventions will remain the same

4.0 HUMAN SUBJECTS

4.0 Subject Selection ~~The study is powered to have 30 evaluable subjects in each arm this multiple institution study. The goal for subject accrual is 60 evaluable subjects, 30 to each arm of the trial. Because the randomization process is not 1:1 and there is attrition, there may be slightly more than 30 subjects accrued to one arm in order to get to the required number of evaluable subjects. A subject is deemed evaluable if they have received at least one cycle of chemotherapy and at least 80% of the expected HCQ dose and they undergo successful surgical extirpation their disease. The racial, gender, and ethnic characteristics of the proposed subject population reflect the demographics of Pittsburgh and the surrounding area and/or the subject population of the University of Pittsburgh Medical Center. We shall attempt to recruit subjects in proportion to these demographics. No exclusion criteria shall be based on race, ethnicity, or gender.~~

For this extended phase II we will accrue only to Arm A. All other study interventions will remain the same

4.1 Inclusion Criteria

- Subjects with biopsy-proven potentially resectable or borderline adenocarcinoma of the pancreas as determined by NCCN criteria
- Karnofsky performance status of 70-100%
- No active second malignancy except for basal cell carcinoma of the skin
- Patient has adequate biological parameters as demonstrated by the following blood counts at screening (obtained ≤ 14 days prior to randomization)
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$;
 - Platelet count $\geq 100,000/\text{mm}^3$ ($100 \times 10^9/\text{L}$);
 - Hemoglobin (Hgb) ≥ 9 g/dL.
- Patient has the following blood chemistry levels at Baseline (obtained ≤ 14 days prior to randomization):
 - AST (SGOT), ALT (SGPT) $\leq 2.5 \times$ upper limit of normal range (ULN)
 - Total bilirubin $\leq 1.5 \times \text{ULN}$
 - Serum Creatinine $\leq 1.5 \text{ mg/dl}$ OR calculated creatinine clearance ≥ 50 for those patients with creatinine greater than 1.5
 - PT WNL $\pm 15\%$

- PTT WNL+/- 15 %
- Age >18 years.
- Patient must be able to swallow enteral medications with no requirement for a feeding tube. Patient's must not have intractable nausea or vomiting which prohibits the patient from oral medications
- Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

- Subjects deemed surgically unresectable or subjects unwilling to undergo surgical resection.
- Subjects who have received chemotherapy within 12 months prior to randomization.
- Prior use of radiotherapy or investigational agents for pancreatic cancer.
- Any evidence of metastasis to distant organs (liver, lung, peritoneum).
- Symptomatic evidence of gastric outlet obstruction
- Inability to adhere to study and/or follow-up procedures
- History of allergic reactions or hypersensitivity to the study drugs (hydroxychloroquine, gemcitabine, nab-Paclitaxel).
- The effects of HCQ, gemcitabine, and nab-Paclitaxel on the developing human fetus are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. All females of childbearing potential (please refer to ECOG's definition in section 5.1) must have a blood test or urine study within two weeks prior to randomization to rule out pregnancy. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately. If a man impregnates a woman while participating in this study, he should inform his treating physician immediately as well.
- Because patients with immune deficiency are at increased risk of lethal infections when treated with bone marrow-suppressive therapy, known HIV-positive patients are excluded from the study. For patients receiving combination anti-retroviral therapy, the potential impact of pharmacokinetic interactions with HCQ and gemcitabine is unknown. Appropriate studies may be undertaken in patients with HIV and those receiving combination anti-retroviral therapy in the future. Given the low incidence of HIV infection in this population; Screening for HIV status will not be performed
- Due to the risk of disease exacerbation, patients with porphyria are ineligible.
- Patients with psoriasis are ineligible unless the disease is well controlled and they are under the care of a specialist who agrees to monitor the patient for exacerbations.
- Patients requiring the use of enzyme-inducing anti-epileptic medication that includes: phenytoin, carbamazepine, phenobarbital, primidone or oxcarbazepine are excluded.
- Patients with previously documented macular degeneration or diabetic retinopathy are excluded.
- Baseline EKG with QTc >470 msec (including subjects on medication). Subjects with ventricular pacemaker for whom QT interval is not measurable will be eligible on a case-by-case basis.
- Patient with a history of interstitial lung disease, history of slowly progressive dyspnea, sarcoidosis, silicosis, idiopathic pulmonary fibrosis or pulmonary hypersensitivity pneumonitis
- Patient with known active infection with HIV, Hepatitis B or Hepatitis C

5.0 CLINICAL AND LABORATORY EVALUATIONS *(see Study Calendar, Appendix E):*

5.1 Screening Evaluations

5.1.1 ~~The following are required~~ ≤28 days prior to randomization, ~~unless otherwise specified~~

- Review of medical history
- Physical examination
- Height
- Vital signs
- Weight
- Performance status assessed by the KPS scale (see Appendix A).

- Review of concomitant medications with particular attention to enzyme-inducing anti-epileptic medication that includes: phenytoin, carbamazepine, phenobarbital, primidone or oxcarbazepine-*within 14 days prior to randomization.*
- Serum Chemistry to include: total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, bicarbonate, chloride, BUN, Cr, glucose, calcium-*within 14 days prior to randomization.*
- CBC, differential, platelets *within 14 days prior to randomization.*
- PT, PTT *within 14 days prior to randomization.*
- Serum CA-19-9
- Serum Pregnancy test for women of child-bearing potential as defined by ECOG. *Within 14 days prior to randomization.*
 - *ECOG defines a female of childbearing potential as any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:*
 - *Has not undergone a hysterectomy or bilateral oophorectomy; or*
 - *Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).*
- CT Contrast-enhanced or Spectral CT scan, pancreas mass (protocol helical CT scan) of chest, abdomen, liver
- Endoscopic ultrasound for assessing tumor invasion of vascular structures if CT findings of unresectability are equivocal.
 - *This is standard of care for subjects. Examples of unresectability at the time of study entry include: soft tissue involvement of the superior mesenteric artery, celiac artery, common/proper hepatic artery, aorta, inferior vena cava, or portomesenteric venous occlusion. If the subject has not undergone standard of care EUS prior to study enrollment then in addition to biopsy of the tumor (SOC) an additional random biopsy of the liver will be performed for assessment of autophagy.*
 - *If the subject has already undergone EUS prior to study enrollment a second EUS will not be performed but the cell blocks from this EUS study will be obtained for research purposes and the liver biopsies will be omitted.*
- Electrocardiogram (EKG)
- Research labs within 14 days of randomization

5.2 Treatment Phase Evaluations

Once deemed eligible, patients will be assigned to either the gemcitabine and **Nab-Paclitaxel** alone or with hydroxychloroquine. Please refer to the study calendar for the schedule of events. Unless otherwise specified, all visits must occur within ± 3 days of the planned visit date. Waivers to accommodate holidays, vacations, and other scheduling problems may be granted by the Principal Investigator upon request of the treating physician. If the Investigator suspects a drug-related toxicity, an extra, unscheduled visit with additional laboratory tests should be performed as clinically needed

Refer to Appendix D for dosing parameters/modifications for Gemcitabine and **Nab-Paclitaxel**. No dose modifications are allowed for hydroxychloroquine.

5.3 Prior to Chemotherapy Dosing on Cycle 1 (Arm A: Day 3)

- Physical examination to include evaluation for peripheral neuropathy.
- KPS performance status
- BSA calculation and weight (recalculated per the site's standard of care, or if body weight changes by more than 10%)
- Concomitant medications evaluation
- Vital signs
- Adverse event evaluation
- CBC, differential, and platelet counts

- Serum Chemistry to include: total bilirubin, AST, ALT, alkaline, phosphatase, sodium, potassium, bicarbonate, chloride, BUN, Cr, glucose, calcium
- Serum CA19-9

5.4 Prior to Dosing on Cycle 1 (Arm A: Day 10 and 17)

- KPS performance status
 - Concomitant medications evaluation
 - Vital signs
 - Adverse event evaluation
 - CBC, differential, and platelet count
 - CMP
-
- **Prior to Dosing on Cycle 2 (Arm A)** Physical examination to include evaluation for peripheral neuropathy
 - KPS performance status
 - BSA calculation and weight
 - Concomitant medications evaluation
 - Vital signs
 - Adverse event evaluation
 - CBC, differential, and platelet counts
 - Comprehensive Metabolic Panel (CMP), Serum CA19-9

5.5 Prior to Dosing on Cycle 2 (Arm A)

- **KPS performance status**
- Concomitant medications evaluation
- Vital signs
- Adverse event evaluation
- CBC, differential, and platelet count
- CMP

5.6 Surgery Evaluation (Arm A)

Laboratory and clinical evaluations will be performed to assess AEs and patients will be evaluated for surgery. The following evaluations will be performed ≤ 5 business days (+1 day) prior to surgery.

- Physical examination
 - KPS performance status
 - Vital Signs
 - Spectral CT or CT Scan of chest, abdomen and pelvis
 - Adverse event evaluation
 - Concomitant medications evaluation
 - CBC, differential, and platelet counts
 - Research labs
 - Serum Chemistry to include: total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, bicarbonate, chloride, BUN, Cr, glucose, calcium
 - Serum CA19-9 level
 - PT/PTT
-
- **Surgery** (to occur no sooner than 2 weeks post last dose of chemotherapy and no longer than 6 weeks post-chemo) **(Arm A)** resection and tissue collection for research

- *If patient underwent liver biopsy in screening, at time of resection an additional random liver biopsy will be performed to monitor autophagy. This will not be done in those patient's that did not have a pretreatment liver biopsy.*

5.7 Four (4) Weeks Post Discharge From Hospital Stay (+/- 2 Weeks) (Arm A)

- Physical examination
- Weight
- Vital signs
- KPS performance status.
- Review of concomitant medications
- Clinical chemistry panel
- CBC, differential, platelets
- Research labs
- Serum CA19-9 level
- Adverse events evaluation - *The protocol will monitor and record post-operative complications. These will be recorded at time of post-operative outpatient visit. The study is not adequately powered to detect significant differences in the treatment regimens. Therefore no safety or stopping evaluations will be made on post-operative adverse events.*

5.8 Follow-Up Period (Arm A)

Following surgery, subjects will return to standard of care treatment by their treating doctor. Subjects' data will be collected from their medical records or phone calls every 4 months (+/- 2 weeks) to determine disease progression/recurrence and overall survival. If a subject is available, study labs for research will be collected every 4 months (+/- 2 weeks) for the first year. These are not mandatory collections.

6.0 STUDY MEDICATIONS AND PROCEDURES

6.1 Study Drug Management and Administration

- ~~Genzar will be prepared and administered per manufactures recommendations. For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Genzar please see the Package insert.~~
- ~~Nab-paclitaxel will be prepared and administered per manufactures recommendations. For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Nab-Paclitaxel, please see the Package insert.~~
- Hydroxychloroquine (Plaquenil® Sanofi Aventis) will be prepared and administered per manufactures recommendations. ~~For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Plaquenil, please see the Package insert.~~

~~Cycle 1 will be a 30 day cycle and Hydroxychloroquine (600mg PO BID) will be started on Day 1 (48 hours prior to the first dose of chemotherapy) and continued through the evening dose before surgery. Subjects will be treated on an outpatient basis with nab-Paclitaxel plus gemcitabine. Nab-Paclitaxel 125 mg/m² as a 30 minute infusion (+/- 10 Minutes) followed by gemcitabine 1000 mg/m² as a 30-minute infusion (+/- 10 Minutes) will be administered on Day 3, 10 and 17 of cycle 1.~~

~~Cycle 2 will start 30 days after the start of Hydroxychloroquine. Cycle 2 (day 31) will be a 28 day cycle. The nab Paclitaxel and gemcitabine will be given on days 1, 8, 15 of cycle 2. Surgery will take place no sooner than 2 weeks after day 15 of cycle 2. Surgery will not occur until recovery from any clinically significant toxicities but no later than 6 weeks post chemotherapy. Supportive care and anti-emetics per the treating physician discretion of care can be provided.~~

6.2 Hydroxychloroquine Administration

- Patients will self-administer HCQ every day starting at cycle 1 day 1 and continued through the evening dose the day before surgery.

- HCQ will be administered in divided doses (BID) of 600mg (3 capsules in AM and 3 capsules in PM). Patients should be told to swallow the whole capsule in rapid succession without chewing. Hydroxychloroquine will not be held when chemotherapy is held for toxicity unless in the opinion of the treating physician it is believed to be contributing to ongoing toxicity
- There will be no dose modifications of hydroxychloroquine

6.3 Management of Toxicities

- **Non-Neutropenic Fever.**

- Due to the instances of non-neutropenic sepsis in early trials of this regimen, at the first occurrence of fever > 38.5 degrees Celsius (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally 2 times daily) or amoxicillin/ clavulanate (Augmentin, 500 mg orally 2 to 3 times daily, in patients with allergy to fluoroquinolones) should be initiated.
- On their first visit, patients are to be provided with enough supplies of ciprofloxacin (or the alternative antibiotic) for use at home, and instructed to initiate its intake at the first recorded temperature of >38.5 degrees Celsius (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation.
- 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.
- Patients with persisting fever after 3 weeks despite uninterrupted antibiotic treatment will discontinue study treatment.

- **Febrile Neutropenia**

- Patients can receive white cell growth factors in addition to antibiotic treatment per standard of care of the treating physician.
- Upon resolution of febrile neutropenia, nab-Paclitaxel and gemcitabine treatment can be resumed at the current dose.
- Should a second instance of Grade 4 Febrile Neutropenia occur, dosage of nab-Paclitaxel and gemcitabine will be resumed at the next lower dose
- Administration of long-term prophylactic ciprofloxacin (or the alternate antibiotic) to prevent recurrences in patients already having experienced a first febrile episode (and managed as above) will be at the discretion of the treating physician.
- Administration of prophylactic antibiotics to otherwise uncomplicated patients with biliary stents will be at the discretion of the treating physicians. Biliary stents should be monitored closely to determine need for replacement.

- **Interstitial Pneumonitis**

In a recently completed Phase III trial utilizing the ABI-007 and gemcitabine combination in patients with metastatic adenocarcinoma, 10 patients have developed interstitial pneumonitis, 9 in the ABI-007 + gemcitabine arm (3.0%) of which 3 were fatal, and 1 in the gemcitabine arm (0.3%). The median time to onset of interstitial pneumonitis after initiation of study medication was 86 days (range = 50-166 days). In the combination arm, 6 of the 9 patients showed ground glass opacities on CT scans and 4 patients had lung metastases. None of the patients had any clear evidence of infection. Six of these 9 patients received steroids. The outcome was fatal in 3 patients (all in the combination arm). The remaining 7 cases (including the 1 case in the gemcitabine monotherapy arm) resolved. Analysis of these cases for common trends revealed history of multiple drug or contrast media allergy (4 out of 9 patients or 44% in the combination arm) and a higher patient weight (mean of 81.4 kg), with the caveat of the small overall numbers precluding generalizations. Pulmonary toxicity has been reported for both gemcitabine and paclitaxel. Epidemiology reports show that gemcitabine monotherapy is weakly associated with lung toxicity. A retrospective review (Meadors, 2006) of pooled clinical trial data of 4,448 patients with mixed cancer indications reported an incidence of dyspnea of 0.2% and serious pulmonary toxicity of 0.06%. Paclitaxel monotherapy is weakly associated with lung toxicity (Rowinsky, 1995). Dyspnea with bronchospasm has been reported in 0.3 to 0.9%, with 30% of type 1 hypersensitivity reactions. Combination chemotherapy of gemcitabine/paclitaxel shows a higher incidence of this complication compared to either drug alone.

- **Prevention, Surveillance and Management of Interstitial Pneumonitis**

- Before enrollment, evaluate candidate patients for familial, environmental or occupational exposure to opportunistic pathogens, and do not enroll those with a history of slowly progressive dyspnea and unproductive cough, or of conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.
- During study treatment, episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and 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.
- Infections should be ruled out with routine immunological/ microbiological 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.
- Study drug administration should be interrupted upon diagnosis of interstitial pneumonitis and patients permanently discontinued from further study drug treatment. 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.

6.4 Guidelines for Toxicity Management

- Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 3 weeks.
- **If toxicity during study is predominantly attributed to nab-Paclitaxel or gemcitabine, and if dose reduction is poorly tolerated, and if it is determined that it is not in the best interest of the patient to continue combination therapy, then the therapy may continue with either drug alone with the approval of the principal investigator only. If one drug needs to be held due to specific toxicity, the other drug may be given.**
- **Examples for discontinuation of nab-Paclitaxel: Persistent grade 2 or Grade 3 neuropathy**
- **Examples for discontinuation of gemcitabine: Persistent drug-related fevers, refractory edema, neutropenia or thrombocytopenia**
- **Missed doses are not to be made up**
- **In the event of dose or drug modification of gemcitabine and nab-Paclitaxel, the use of hydroxychloroquine will not be discontinued.**
- **Toxicity will be graded according to the NCI Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. A copy of this document can be found at the following internet site: <http://ctepinfo.nih.gov/reporting/ctc.html>.**
- **Patients experiencing serious adverse events will be followed as described in section 11.**
- **For patients who have had dosing delays, all evaluations will be correspondingly delayed.**
- **Reasons for dose modifications, dosing delays, the supportive measures taken, and the outcome will be documented in progress notes**

6.5 Dose Modifications

Refer to Appendix D for dose modification details.

- Up to 2 dose level reductions of nab-Paclitaxel and 2 dose level reductions of gemcitabine are permitted. Patients should be taken off study if further dose reduction is required
- No dose modification of hydroxychloroquine is allowed

6.6 Concomitant Medications

- Concomitant medications should be avoided with the exception of analgesics (only acetaminophen or narcotics may be given for pain), chronic treatments for concomitant medical conditions, or anti-nausea medications and agents required for life threatening medical problems.

- The subject must refrain from taking the following medications beginning 7 days prior to taking study drugs and lasting until after the last study drug is taken and a decision about surgical resection has been reached:
 - **Nonsteroidal anti-inflammatory medications (NSAIDs)**
 - **Clopidogrel (Plavix)**
 - **Aspirin >325 mg/day**
 - **If possible, the use of drugs with laxative properties should generally be avoided because of the potential for the exacerbation of diarrhea associated with gemcitabine. Subjects should be advised to contact their physician to discuss any laxative use.**

7.0 SUBJECT DISCONTINUATION

Subjects will be removed from the study for the following reasons:

- Progression of disease (i.e. development of metastasis) during protocol treatment. Subjects who develop metastases will be removed from the study and evaluated by an oncologist as part of routine cancer care. Depending on the subject's performance status, the subject may be treated with another chemotherapy regimen (such as 5-FU) at the discretion of the treating oncologist.
- Intercurrent illness that prevents further administration of treatment,
- Treatment-related toxicities,
- Subject decides to withdraw from the study, or is non-adherent,
- General or specific changes in the subject's condition rendering the subject unacceptable for further treatment in the judgment of the investigator.

8.0 SAFETY PLAN

8.1 General Plan to Manage Safety

- Subjects will be monitored for treatment-related toxicity from the time of enrollment until the first outpatient evaluation after surgery and ongoing for any grade 4 or 5 event felt to be directly related to treatment regimen.
- Safety will be monitored throughout the study at Pre-Study, Cycle 1, Day 1, 3, 10, 1; Cycle 2, Day 1 8 and 15; Pre-Op Evaluation visit and 4 Weeks Post-Discharge (+/- 2 weeks), for subjects who have received one or more doses of study drugs during trial intervention. Subjects will be reevaluated more frequently for clinical indications.
- The initial toxicity assessment is dependent on monitoring for toxicity, the criteria for which are defined by the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0, Appendix B). The NCI CTC V 4.0 can be downloaded at <http://ctep.info.nih.gov/reporting/ctc.html>. Toxicities are defined as adverse events that are possibly, probably, or definitely related to treatment.
- The Principal Investigator will continuously monitor study progress for safety. The PI, GI Oncology Program Manager, Clinical Research Coordinators and other relevant study personnel will meet on a bi-weekly basis at the GI Oncology data safety monitoring meetings or as needed to review overall conduct and progress of the study. During these meetings, study data from the site, subject safety issues and subject recruitment, accrual and retention will be reviewed and discussed. Data records will be reviewed periodically and safety reports monitored as they are received. An unusual frequency of treatment-related adverse events will be reviewed by the GI Oncology Safety Monitoring Board.

8.2 Recruitment Procedures

Potential subjects will be identified from the Principal Investigator's and Co-Investigators' current clinic population, or will be referred to the Principal Investigator by their own physician. They will be approached and informed of the study by an individual who is involved in their care. No cold-calling will occur, and no advertising will be used. The consent process will be carried out as a joint effort among the subject's physician, the study coordinator, and/or co-investigators on the study. Informed consent shall be obtained and the certification of informed consent statement signed (at the time of obtaining consent) by the investigator or co-investigators, all of whom are physicians.

8.3 Costs and Payments.

- Research Study Costs: **The study drug hydroxychloroquine will be provided at no cost to subjects or their insurance companies. Gemcitabine and nab-Paclitaxel are a standard of care treatment. As a result, subjects and/or their insurance will be billed in the standard fashion. Subjects will be billed in the standard fashion for the routine clinical care that they receive, and either the subject or their insurance provider will be responsible for this payment.**
- Research Study Payments: **Subjects will not be paid for participating in this study.**

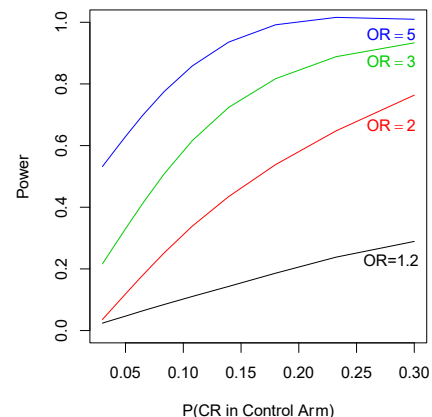
9.0 CORRELATIVE STUDIES/SECONDARY ENDPOINTS

- 9.1 CA19-9: **The tumor marker Carbohydrate antigen 199 (CA19-9) has well-established prognostic value in patients with PDA. Baseline levels of CA19-9 correlate with overall survival in patients with all stages of disease regardless of the treatment modality (1-6). For patients with resectable PDA baseline CA19-9 is predictive of tumor resectability and early metastases, and postoperative CA19-9 is prognostic for overall survival (OS) [16, 17]. Moreover, increases in CA19-9 levels closely correlate with time to radiographic progression, (10-12). Data that changes in CA19-9 are a reliable marker of response to treatment are more controversial. A number of reports have suggested that changes in CA19-9 reliably predict clinical response while others suggest that only baseline levels are prognostic [13, 18-19].**
- 9.2 Basic Science Studies of Autophagy and Apoptosis in the Tumor, Peripheral Blood: We will compare autophagy, apoptosis and IL-6/STAT3 signaling between tumors treated with chemotherapy alone versus tumors treated with chemotherapy plus hydroxychloroquine. We will correlate levels of apoptosis, autophagy and IL-6/STAT3 with histologic and biomarker response. We will utilize samples from pre-operative cell blocks as well as final resected specimen cell blocks as well as final resected specimens. We will examine the liver and peripheral blood for markers of autophagy and DAMPs. Each patient will serve as their own control pre and post neoadjuvant chemotherapy, pre- and post-operative. We will correlate changes in systemic autophagy/inflammation with metrics of clinical efficacy, levels of autophagy, apoptosis and pSTAT3 in the tumor. We will perform this analysis first on the remaining specimens in our ongoing clinical trial of Gem/HCQ. These studies will be performed in the DAMP Lab and in collaboration with Liotta lab at George Mason University.
- 9.3 Coagulation Studies: **Preliminary data from murine models in our lab (DAMP Lab) suggest that hydroxychloroquine can reverse hypercoagulability associated with malignancy, through inhibition of autophagy and decreases neutrophil NETs. Therefore we will be assessing TEG coagulation profile on all subjects at three time points: 1) pre-treatment 2) post-chemotherapy 3) post-operative (4-6 weeks)**
- 9.4 Future Studies: **All unused portions of the specimens collected will be stored in the DAMP lab for future investigation. Samples collected for research purposes will be stored indefinitely. These samples may be shared with scientific collaborators. If this occurs the samples will not contain personal identifiers (for example, name, social security number) and will include assigned code numbers. The information linking these code numbers to subjects' identity will be kept on a secure UPMC hard drive.**

10.0 STATISTICAL METHODS

10.1 Justification of Design

Adaptive randomization allocates more patients to the better treatment as significant evidence that one treatment is indeed better accrues during the trial. This makes the randomized trial more palatable to patients while retaining the advantages of randomization. To characterize the operating characteristics of the design, we simulated 4,000 trials assuming different Grade IV histologic response probabilities (between 0.0 and 0.3) in the control arm and odds ratios for the experimental versus the control arm (1.2, 2, 3 and 5). We calculated the proportion of trials in which it was concluded that $P(\tau_c > \tau_k) < 0.05$ which we term the 'power' of the design. It was determined that, if nab-Paclitaxel alone is sufficiently effective to induce a probability of Grade IV response of at least 0.15, adequate statistical power will be available for odds ratios of 3.5 or better.



Following Figure 9 in (34), we anticipate that the standard deviation of $\log_0(\text{CA19-9})$ will be approximately 0.5 in responders, and 0.3 in non-responders. Based on these values, we expect the width of 95% confidence intervals for $\log_0(\text{CA19-9})$ to be between 0.3 and 1.15 for responders, and 0.40 and 0.52 for non-responders.

10.2 Monitoring for Futility

$P(\tau_c > \tau_k)$ will be calculated at the enrollment of every patient, beginning with the 21st, using the $\text{Beta}(4,16)$ and $\text{Beta}(8,12)$ priors for τ_c and τ_k , respectively (see 10.3.1). If at any time $P(\tau_c > \tau_k) > 0.80$ the trial will be halted for futility.

10.3 Data Analysis

10.3.1 Assessment of Primary Endpoint

The primary endpoint for this trial will be the Evans Grade histologic response, as defined in Appendix D. Evans Grade will be tabulated by treatment with 94% confidence intervals. The effect of treatment on Evans Grade will be assessed by a cumulative logit model, an extension of logistic regression appropriate for ordinal multinomial endpoints. A likelihood ratio chi-squared test will determine the statistical significance of the effect of treatment on Evans Grade. In secondary analyses, the effect of baseline clinical, demographic and biomarker variables on the relationship between treatment and Evans Grade will be explored by adding those variables to the primary endpoint model.

10.3.2 Assessment of secondary endpoint

10.3.2.1 CA19-9

95% credible intervals for the log-transformed preoperative and postoperative values of CA19-9 will be calculated, along with $P(\mu_c < \mu_k)$. The change in CA19-9 will be compared between arms using ANCOVA, where postoperative CA19-9 will be the dependent variable and preoperative CA19-9 the covariate. If the interaction term between study arm and preoperative CA19-9 is significant, the change in postoperative CA19-9 must be interpreted conditioned on the baseline value. CA19-9 will be treated as a continuous variable; cutoffs for response will not be used.

11.0 ADVERSE EVENT

Clinical study subjects will be routinely questioned about adverse events at study visits.

11.1 Adverse Event Definitions

Adverse event means any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related.

Adverse reaction means any adverse event caused by a drug.

- **Serious Adverse Event** Any unwelcome medical occurrence associated with the use of a drug in humans whether or not considered drug related. Specifically, results in death, is life-threatening requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Any subject death within 30 days of the last dose of study drug regardless of the causality or a secondary malignancy should also be recorded as a serious adverse event
- **Life-threatening suspected adverse reaction.** A suspected adverse reaction is considered 'life-threatening' if, in the view of either the investigator (i.e., the study site principal investigator), its occurrence places the patient or research subject at immediate risk of death. It does not include a suspected adverse reaction that had it occurred in a more severe form, might have caused death.
- **Unexpected, suspected adverse reaction.** A suspected adverse reaction is considered 'unexpected' if it is not listed in the general investigational plan or clinical protocol, or is not listed at the specificity or severity that has been previously observed and/or specified. If an investigator brochure is not required or available, suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. 'Unexpected,' as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure can also be considered unexpected. An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.
- **Suspected adverse reaction.** Any adverse event for which there is a reasonable possibility that the drug caused the adverse event (considered "possibly related"). For the purposes of safety reporting "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug
- **All observed or volunteered adverse events (serious or non-serious and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s))** will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event) and 2) an assessment of the causal relationship between the adverse event and the study drug(s). All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0.

Adverse events or abnormal test findings felt to be associated with the study drug(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Principal Investigator.

In the event of an adverse event the first concern will be for the safety of the subject.

Review of safety information. The principal investigator / sponsor must promptly review all information relevant to the safety of the drug obtained or otherwise received from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States. The study sponsor must notify all participating investigators of potential serious risks, from clinical trials or any other source, as soon as possible.

11.2 Reporting of Suspected Adverse Reactions

In the event of a serious adverse event, the PI and the institutional review board will be notified using the FDA Form 3500 MedWatch report.

All events meeting the definition of a serious adverse event should be recorded on a MedWatch 3500 Form (link below) and submitted to:

(<http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf>)

1. Nathan Bahary, MD
 - a. Phone: (412) 412-864-7764
 - b. Email: baharyn@upmc.edu
2. Local Institutional Review Board per institutional reporting requirements

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Event Description (section 5) of the MedWatch 3500 form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original MedWatch 3500 report and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original MedWatch 3500 form.

11.3 Data Safety Monitoring Plan

- ~~Investigator/Subinvestigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following~~
 - serious adverse events
 - subject safety issues
 - recruitment issues
 - accrual
 - protocol deviations
 - unanticipated problems
 - breaches of confidentiality
- ~~All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious at~~

~~least possibly related and unexpected will be reported to the RB. Any modifications necessary to ensure subject safety and decision to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the RB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.~~

- ~~• All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the RB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC which also meets monthly following a designated format~~

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed twice a year rather than monthly.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

12.0 RETENTION OF RECORDS

- ~~• Records pertaining to this study will be kept in accordance with institutional guidelines for a period of at least two years after final report.~~

13.0 PATIENT INFORMED CONSENT: RISK/BENEFIT INFORMATION

- ~~• As with any medication, there may be risks that are unknown at this time. These risks may be severe or life-threatening. In addition, the possibility exists that this protocol also may not improve the outcome for patients with surgically-treated pancreatic cancer.~~

Hydroxychloroquine

Known Potential Toxicities of Hydroxychloroquine:

- Central nervous system: Irritability, nervousness, emotional changes, nightmares, psychosis, headache, dizziness, vertigo, seizure, ataxia, lassitude.
- Heart arrhythmias (premature or extra heartbeats) may cause death
- Dermatologic: Bleaching of hair, alopecia, pigmentation changes (skin and mucosal; black-blue color), rash (urticarial, morbilliform, lichenoid, maculopapular, purpuric, erythema annulare centrifugum, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, and exfoliative dermatitis).
- Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, abdominal cramping.
- Hematologic: Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia, hemolysis (in patients with glucose-6-phosphate deficiency).
- Hepatic: Abnormal liver function/hepatic failure (isolated cases).
- Neuromuscular & skeletal: Myopathy leading to progressive weakness and atrophy of proximal muscle groups (may be associated with mild sensory changes, loss of deep tendon reflexes, and abnormal nerve conduction).
- Ocular: Disturbance in accommodation, keratopathy, corneal changes/deposits (visual disturbances, blurred vision, photophobia - reversible on discontinuation), macular edema, atrophy, abnormal pigmentation,

retinopathy (early changes reversible - may progress despite discontinuation if advanced), optic disc pallor/atrophy, attenuation of retinal arterioles, pigmentary retinopathy, scotoma, decreased visual acuity, nystagmus.

Generic name: Hydroxychloroquine sulfate

Commercial name: Plaquenil

Chemical name: 7-Chloro-4-[4-[ethyl-(2-hydroxyethyl)amino]-1-methylbutylamino] quinoline

Supplied by: Commercially available; Sanofi-Synthelabo

Gemcitabine

Likely- occurs in more than 25% of people (25 out of 100 people)

- Anemia (unusual tiredness or weakness),
- Fever and mild flu-like symptoms
- Hematuria (blood in urine)
- Skin rash, with or without itching,
- Bone marrow suppression (anemia, neutropenia, leukopenia, and thrombocytopenia)
- Abnormal liver function, usually transient
- Constipation; Nausea and vomiting, usually of mild to moderate severity
- Pain

Common - occurs in 10% to 25% of people (10 to 25 out of 100 people):

- Peripheral edema (swelling of fingers, feet, or lower legs)
- Proteinuria (cloudy urine)
- Alopecia (hair loss), usually minimal
- Mouth ulcers (stomatitis)
- Diarrhea
- Constipation
- Bleeding
- Somnolence
- Cutaneous Pruritis

Infrequent - occurs in 1% to 10% of people (1 to 10 out of 100 people):

- Anaphylactoid reaction (change in facial skin color; skin rash, hives, and/or itching; swelling or puffiness of the face, especially the eyelids or area around the eyes) and bronchospasm (shortness of breath, troubled breathing, tightness in chest, and/or wheezing) in less than 2% due to an allergic reaction to gemcitabine
- Hemorrhage: blood in urine or stools; pinpoint red spots on skin
- Cardiovascular toxicity (2%), including myocardial infarction (pain in chest, arm, or back; pressure or squeezing in chest), hypertension (high blood pressure), arrhythmia (fast or irregular heartbeat), cerebrovascular accident (headache, sudden and severe; slurred speech or inability to speak; weakness in arm and/or leg on one side of the body, sudden and severe),
- Febrile neutropenia or other infection (fever or chills; cough or hoarseness; lower back or side pain; painful or difficult urination)
- Abnormal renal function
- Paresthesias (a tingling sensation like “pins-and-needles”), typically mild
- Somnolence (sleepiness)
- Rare- Occurs in less than 1% (less than 1 out of 100 people):
- Congestive Heart Failure (coughing; noisy, rattling, or troubled breathing; generalized weakness, leg swelling)
- Hemolytic-Uremic Syndrome (black, tarry stools; blood in urine or stools; fever; increased or decreased urination; pinpoint red spots on skin; swelling of face, fingers, feet, or lower legs; unusual bleeding or bruising; unusual tiredness or weakness; yellow eyes or skin),
- Lung toxicity, parenchymal, or pneumonitis (coughing; shortness of breath),
- Renal failure requiring dialysis.
- Severe infection
- Serious hepatotoxicity including death

- Severe paresthesias

Blood Samples:

- Obtaining blood can cause pain, bleeding, bruising or swelling at the site of needle insertion. Fainting sometimes occurs and infection rarely occurs.

Breach of Confidentiality:

- Knowledge of the subject's medical and/or research data could potentially impact future insurability, employability, or plans for reproduction; or have a negative impact on family relationships; and/or result in shame or embarrassment.

Pregnancy and Fertility:

- The effect of the study drugs on fertility is unknown. It is also unknown what effect these drugs will have on pregnancy. The risks involving pregnancy and fertility will be explained to subject during the informed consent process and are stated in the consent form. Female subjects of childbearing potential will have a serum pregnancy test at screening. This test must be negative in order for the subject to be eligible for study participation. In addition, subjects will be instructed that if they choose to be sexually active they must use an appropriate method of birth control until at least six months after receiving the last dose of study drug. Examples of such methods and the length of time that such methods must be used are provided in the consent form. Subjects will also be instructed to immediately inform the principal investigator if they suspect that they or their partners are pregnant.

Nab-Paclitaxel

The most common side effects experienced with nab-Paclitaxel, include

- hair loss,
- infections due to low count of a type of white blood cell (neutropenia),
- numbness,
- tingling, or burning in the hands and/or feet (neuropathy),
- fatigue and weakness,
- low red blood cell count (anemia),
- mouth or lip sores (mucositis),
- joint and muscle pain,
- stomach upset,
- vomiting, and diarrhea,
- decreased heart rate (bradycardia), or
- low blood pressure (hypotension)

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Appendix A: Performance Status Criteria

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Appendix B. CTCAE 4.0

National Cancer Institute Common Toxicity Criteria, Version 4

Obtain from <http://ctep.info.nih.gov/reporting/ctc.html>

Appendix C. Pathologic Response

Grading System for Pathological Response (adopted from Evans [29])

Grade	Histologic Appearance
I	Characteristic cytologic changes of malignancy present, but little (< 10%) or no tumor cell destruction is evident.
II	Characteristic cytologic changes of malignancy; 10% to 90% of tumor cells are destroyed.
IIa	Destruction of 10% to 50% of tumor cells.
IIb	Destruction of 51% to 90% of tumor cells.
III	Few (< 10%) viable-appearing tumor cells are present.
III _m	Sizable pools of mucin present.
IV	No viable tumor cells present.
IV _m	Acellular pools of mucin present.

Appendix D: Dose Modifications for Gemcitabine and/or Nab-paclitaxel

D.1.1

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.

D.1.2

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.

Dose Modifications

Dose Level ^{a)}	Nab-paclitaxel Dose (mg/m ²) ^{b)}	Gemcitabine (mg/m ²) ^{b)}
Study Dose	125	1000
-1	100	800
-2	75	600

Error! Reference source not found. A maximum of 2 dose level reductions are allowed.

^{b)} Dose reductions may or may not be concomitant. Please refer to [Table 1](#) and [Table 2](#) for specific recommendations regarding dose modifications for Day 1 of each cycle for hematologic and non-hematologic toxicity, respectively. Please refer to [Table 3](#) and [Table 4](#) for specific recommendations regarding dose modifications within a cycle for hematologic and non-hematologic toxicities, respectively.

D.1.3

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;). 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 3, 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).

D.1.4 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 1 and Table 2 as presented below:

Table 1: 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 2: 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 + 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; please refer to Section F 1.5)
Grade 3 toxicity ^{a)}	Decrease gemcitabine and nab-paclitaxel to next lower dose level
Grade 4 toxicity ^{b)}	Off protocol treatment
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.

^{b)} Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or a symptomatic, will be exempt from this requirement.

D.1.5 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 3: Dose Modifications for Hematologic Toxicity within a Cycle

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 \geq 75,000	100%	100%	ANC >1000 and Platelets \geq 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 ^b 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 \geq 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 ^a or Platelets <50,000	Hold	Hold	ANC >1000 and Platelets \geq 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		
			ANC <500 or Platelets <50,000	Hold + G-CSF ^a	Hold + G-CSF ^a		

Table 3: Dose Modifications for Hematologic Toxicity within a Cycle

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
Febrile Neutropenia (Grade 3 or 4)c						Hold. Upon resuming dosing, decrease to next lower level and do not reescalate throughout the rest of treatment.	Hold. Upon resuming dosing, decrease to next lower dose level and do not reescalate 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.

- G-CSF is optional if descent only affects platelets.
- If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.
- 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.

D.1.6

Dose modifications may also be made for non-hematological toxicity within a cycle as specified in [Table 4](#)

Table 4: Dose Modifications for Non-Hematological Toxicity within a Cycle

CTCAE Grade	Percent of Day 1 Nab-paclitaxel + 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 until resolution to \leq Grade 1. Then resume treatment at the next lower dose level.
4	Hold

D.1.7 Peripheral Neuropathy

Nab-paclitaxel treatment should be withheld in patients who experience \geq Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Nab-paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to \leq Grade 1. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-paclitaxel dosing for ≥ 21 days will discontinue study treatment. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

D.1.8 Cutaneous Toxicity

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

D.1.9 Gastrointestinal Toxicity

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

D.1.10 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.

D.1.11 Interstitial Pneumonitis

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (ie, episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Study drug administration should be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

D.1.12 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/ μ L (as per Table 3)

Patients who do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

D.1.13 Prophylaxis Against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5 °C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily)—or amoxicillin/clavulanate (Augmentin[®], 500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones—should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation.

D.1.14 Hypersensitivity Reactions

Hypersensitivity reactions are not expected with either nab-paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, 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 develop a severe hypersensitivity reaction should not be re-challenged.

Appendix E. STUDY CALENDAR

Arm A: Gemcitabine + Nab-Paclitaxel + Hydroxychloroquine

	Pre-Study ≤ 28 days	C1 Day 1	C1 Day 3	C1 Day 10	C1 Day 17	C2 Day 1	C2 Day 8	C2 Day 15	Pre-Op Eval. (≤ 5 business days prior to surgery +1 day)	Evening before Surgery	Surgery (no sooner than 2 wks & up to 6 wks post- C2D15)	4 weeks Post- Hospital discharge (± 2 weeks)	Follow Up (q 4 Mo + 2 wks)
		D1	D3	D10	D17	D31	D38	D45			D59	D87	
Informed Consent	X												
Demographics	X												
Medical history	X												
Concomitant meds	X		X	X	X	X	X	X	X			X	
Physical exam (includes peripheral neuropathy assessment)	X		X			X			X			X	
Vital signs	X		X	X	X	X	X	X	X			X	
Height	X												
Weight	X		X			X						X	
Performance status (Karnofsky>70)	X		X	X	X	X	X	X	X			X	
CBC w/diff, plts ¹	X		X	X	X	X	X	X	X			X	
Comprehensive Metabolic Panel	X		X	X	X	X	X	X				X	
PT/PTT ²	X ²								X				
Serum CA19-9	X		X			X			X			X	
Research labs ³	X ²								X			X	X ⁴
Adverse event evaluation			X	X	X	X	X	X	X			X	
B-HCG ⁵	X												
EUS	X												
EKG	X												
Spectral CT or CT Scan of chest, abdomen and liver	X								X				
Gemcitabine infusion (1000mg/m ²)			X	X	X	X	X	X					
Nab-Paclitaxel (125 mg/m ² infusion)			X	X	X	X	X	X					
Hydroxychloroquine ⁶ (600 mg PO BID)		← X ⁸ →											
Surgical resection and research tissue collection											X ⁷		
Survival/Assessment of Progression													X

¹ To be completed within 14 days of randomization

² If patient on warfarin PT/PTT must be checked weekly during treatments. The prothrombin time must be monitored weekly for patients taking warfarin.

³ To include TEG which must be analyzed on same day as draw. Due to logistical reasons research blood maybe omitted after approval from the investigator.

⁴ If a subject is available, study labs for research will be collected every 4 months (+/- 2 weeks) for the first year. These are not mandatory collections.

⁵ Serum pregnancy test for women of child bearing potential as defined by ECOG within 14 days of randomization.

⁶ To be self-administered by subjects; Take three 200 mg capsules, AM and PM every day through the evening dose before surgery.

⁷ If patient underwent liver biopsy in screening, at time of resection an additional random liver biopsy will be performed to monitor autophagy. This will not be done in those patients that did not have a pretreatment liver biopsy.

