TITLE: Randomized Phase II trial of Pre-Operative Gemcitabine, Nab-Paclitaxel, and hydroxychloroquine with or without Avelumab (PGHA vs. PGH)

INSTITUTION STUDY NUMBER:	HCC 17-134
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COMMERCIALLY AVAILABLE AGENTS:	Plaquenil® (Sanofi Aventis) Gemzar® (Lilly) Abraxane® (Celgene) Avelumab® (Pfizer)

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RESEARCH PROTOCOL ABSTRACT

This is a randomized phase II trial that will examine the ability of Avelumab to improve the clinical activity of a pre-operative regimen of gemcitabine, nab-paclitaxel and hydroxychloroquine in subjects with potentially resectable adenocarcinoma of the pancreas. Eligible subjects will receive 2 cycles of gemcitabine and nab-paclitaxel (1000mg/m^2 & 125mg/m^2 – days 1, 8, 15) and hydroxychloroquine (1200mg/day) with or without Avelumab (days 1 and 15 of each 28-day cycle). Subjects will be allocated by means of a response-adaptive randomization based on Grade IIB or greater histologic response followed by surgical resection. The 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 levels of autophagy in tumor, liver and peripheral blood.

1.0 BACKGROUND AND SIGNIFICANCE

Pancreatic cancer is a major unsolved public health problem in the United States, with approximately 42,000 new cases in the year 2016, 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 clear 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 25% at 5 years, and the median disease-free survival is 10-13 months. This uniformly poor prognosis even in the earliest stage of disease utilizing our best treatment modalities underscores the need for newer approaches to pancreatic cancer treatment. 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 the metabolic stress response of autophagy plays a major role in the pathogenesis of this disease. [1-10]

We have spent the last several years investigating the clinical feasibility and activity of adding an autophagy inhibitor to cytotoxic chemotherapy. The finding that autophagy is a critical mediator of damage-associated molecular patterns (DAMP)-induced tumor cell survival led us to investigate this pathway as a therapeutic target. We hypothesized that much of the immunopathology in the pancreatic cancer tumor microenvironment (PDA TME) could be explained by high levels of autophagy induced by release of DAMPs11. Chloroquine (CQ) and its derivatives, such as hydroxychloroquine (HCQ), are synthetic 4-aminoquinolines that have been clinically used for 60 years for malaria prophylaxis, and are central for treating patients with rheumatoid arthritis and human immunodeficiency virus (HIV). They are inexpensive, orally available drugs with a large therapeutic index. CQ blocks acidification of the lysosome, thus inhibiting the last step in autophagy. Evidence in mouse models and human cancer cell lines suggests that CQ has significant anti-tumor activity by inhibiting autophagy induced by cancer therapy12-14. Yang *et al.* demonstrated significant responses in a xenograft model to single-agent CQ. [13,14]

Based on the above findings, we conducted a Phase I/II trial examining preoperative gemcitabine in combination with oral hydroxychloroquine for treatment of high risk PDA (UPCI 09-122/NCT01128296)15. Fixed dose-rate gemcitabine (1500 mg/m^2) was administered every 2 weeks for two cycles. HCQ (200 mg/day-120 0mg/day) was administered 48 hours prior to the

first dose of gemcitabine, and continued for 31 consecutive days until the day of surgery. Toxicity, evaluated based on National Cancer Institute (NCI) criteria, was found to be minimal. Response to treatment was assessed by decrease in CA19-9 levels and PET. Thirty-five patients were enrolled. There were no dose-limiting toxicities, and no Grade 4/5 events related to treatment. Nineteen patients (61%) had a decrease in CA19-9 following treatment. Twenty-nine patients (94%) underwent surgical resection as scheduled with a 77% R0 resection rate. Median overall survival was 34.8 months (95% CI [11.57 months, not reached]). Clinical outcomes were compared to those from the previously established cohort of high-risk patients at our institution, which defined eligibility for this trial. [16]. Demographics and high-risk criteria were not different between patients from the prior series and the UPCI 09-122 trial. The resection rate for patients treated with Gemcitabine/hydroxychloroquine (GH) was 94% compared to 52% in the prior series ($p<0.001$), with R0 resection achieved in 77% versus only 34% ($p<0.01$). Treatment with GH resulted in improved overall median survival compared with the prior cohort (34.8 vs. 12.3 months, $p=0.03$).

Next, we launched an NCI-supported (R01CA181450) randomized phase II trial of neoadjuvant gemcitabine/nab-paclitaxel, with (PGH), and without (PG), hydroxychloroquine (UPCI-13-074/NCT01978184), to better assess the true contribution of autophagy inhibition in the setting of a gemcitabine/nab-paclitaxel regimen proven to be more effective than gemcitabine alone in metastatic disease in patients with PDA. We have completed the planned 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 III/IV histologic response, as defined by Evans *et al.* [17]. Secondary endpoints are response of the tumor marker CA19-9, and the proportion of positive lymph nodes in resected specimens. Analysis of the primary endpoint in subjects enrolled to date, 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 (Wilcoxson test $p=0.014$) (**Fig.1B**). Similarly, the number of involved lymph nodes is statistically different between the arms, enhancing the response to the PGH combination.

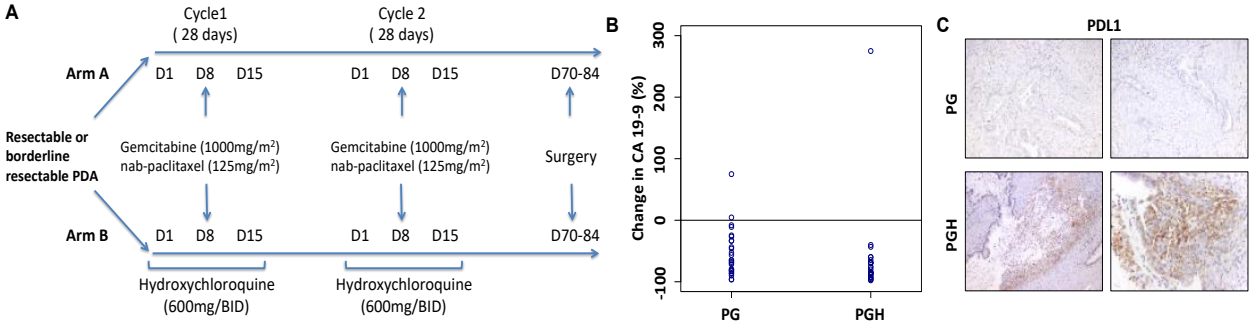


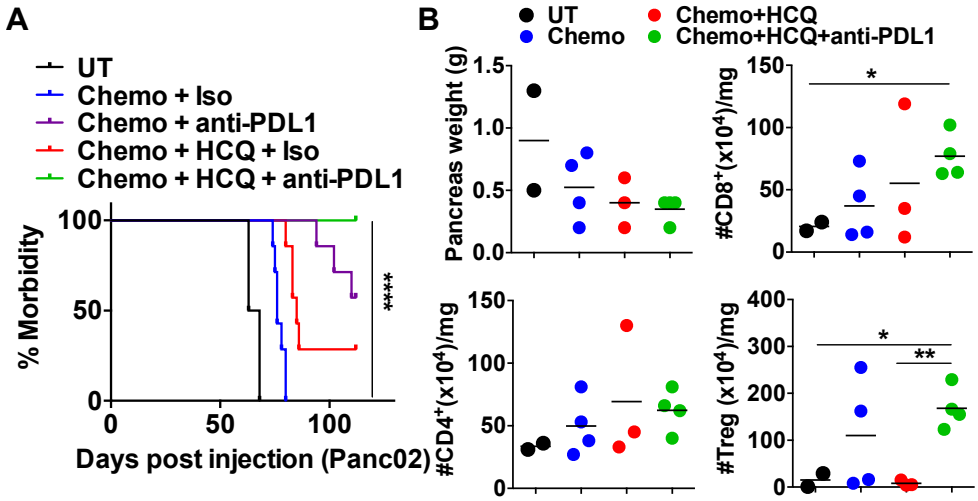
TABLE I: *Histopathologic responses of the first 53 evaluable patients from UPCI-13-074*

	Evans Grade				
Tx	I	IIA	IIB	III	Total
PG	10	14	3	0	27
PGH	3	9	9	5	26

We are in the process of examining the resected tissues for evidence of autophagy inhibition and apoptosis. However, a pilot correlative study performed on the first 18 subjects accrued to this trial yielded provocative data suggesting that addition of the autophagy inhibitor to the chemotherapy led to marked upregulation of PDL-1 expression in subjects treated on the HCQ arm (**Fig.1C**). Interestingly, most of the PDL-1 expression appeared to be in infiltrating myeloid cells rather than in tumor cells. This finding led us back to the bench to examine the potential of adding anti-PDL-1 to the backbone of PGH. There was strong

rationale for this, not just from our own bedside studies, but from two recent reports demonstrating that targeted ablation of the stromal activation marker, fibroblast activation protein-α (FAP), or inhibition of its expression by blockade of C-X-C chemokine receptor type 4 (CXCR4)/C-X-C motif signaling increased T cell infiltration, increased PD-1 and PDL-1 expression, and unmasked the response to immune checkpoint inhibitors in murine models of PDA18,19. We hypothesized that HCQ might be working in a similar fashion on the stroma, based on animal studies demonstrating that HCQ can block autophagy and decrease FAP expression in stroma. In addition, HCQ has also been reported to be a direct antagonist of CXCR4, which could directly inhibit stromal activation in the murine studies cited above. We tested the combination of chemotherapy, autophagy inhibition and immune check point blockade (anti-PDL1) in our orthotropic murine model of PDA. We observed that addition of checkpoint pathway blockade yielded statistically improved survival in this model (**Fig.2A**). We also observed reduced pancreas weight, due to reduced tumor burden, and that these tumors had the highest level of $CD8^+$ and $CD4^+$ T cell infiltration (**Fig.2B**). Thus, it appears that the addition of the autophagy inhibitor HCQ to PG behaves similarly to agents that target stroma, and results in accumulation of T cells in the PDA TME that can then be targeted with immunotherapy.

FIG.2: *Enhanced efficacy against Panc02 with cytotoxic chemotherapy in combination with HCQ and anti-PDL1.*



LEGEND: *Mice were injected with 106 Panc02 orthotopically on day 0. Gemcitabine (25mg/mL) and Taxol (10mg/mL) were injected every 7 days starting on day 15. Anti-PDL1 (250ug) was injected every 3 days starting after first chemo treatment. (A) Morbidity over time assessed. (B; top left) Pancreas was weighed 21 days post-inoculation. (B; other panels) Lymphocytes were isolated and stained for analysis on post-inoculation day 28. n=2-3. [Kaplan Meier (A) and Unpaired Student's t-test (B)].*

Rationale for this protocol

As noted above, our preliminary observations at the bedside and bench provide strong rationale for adding immune checkpoint blockade to our backbone of chemotherapy and autophagy inhibition (PGH).

Gemcitabine

Gemcitabine chemotherapy is the standard of care for inoperable pancreatic cancer, although its clinical activity is modest. In the initial phase 2 trial of single-agent gemcitabine, an 11% partial response rate was observed (Casper, Green et al. 1994). A phase 3 randomized study of gemcitabine versus 5-flourouracil in 126 patients reported a 5% objective response rate in the

gemcitabine arm, with a median survival of 5.65 months and a 1-year survival rate of 18% (Burris, Moore et al. 1997). Twenty-four percent of patients in the gemcitabine arm experienced a clinical benefit, consisting of improved pain control, performance status, or weight stabilization. In 1996, the US Food and Drug Administration (FDA) approved gemcitabine for the treatment of locally advanced and metastatic pancreatic cancer.

Paclitaxel Albumin-bound Particles (Nab-Paclitaxel)

Nab-paclitaxel is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. Nab-paclitaxel has been developed to reduce the toxicities associated with Taxol (paclitaxel) Injection (in which paclitaxel - from the native crystalline form - is formulated with Cremophor EL/ethanol as the solvent) while maintaining or improving its chemotherapeutic effect. Nab-paclitaxel has been approved for commercialization in 38 countries, including the United States (US), Canada, the EU, Australia, China, India and Korea for the treatment of women with metastatic breast cancer. Nab-paclitaxel alone and in combination chemotherapy is being evaluated in several cancers, including metastatic melanoma, non-small cell lung cancer, pancreatic cancer, and other solid tumors.

A recent phase 3 clinical trial of nab-paclitaxel in combination with gemcitabine in treatment- naïve patients with metastatic pancreatic cancer demonstrated a statistically significant improvement in overall survival compared to patients receiving gemcitabine alone [(median of 8.5 vs. 6.7 months) (HR 0.72, P=0.000015)]. In the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) study, nab-paclitaxel plus gemcitabine demonstrated a 59% increase in one-year survival (35% vs. 22%, p=0.0002), double the rate of survival at two years (9% vs. 4%, p=0.02), and an improvement in 3-year survival (4% vs. 0%) as compared to gemcitabine alone. Nab-paclitaxel plus gemcitabine also demonstrated a statistically significant improvement in key secondary endpoints compared to gemcitabine alone, including a 31% reduction in the risk of progression or death with a median progression-free survival (PFS) of 5.5 vs. 3.7 months (HR 0.69, P=0.000024) and an overall response rate (ORR) of 23% compared to 7% (response rate ratio of 3.19, p=1.1 x 10-10).

The most common grade ≥ 3 treatment-related adverse events in the study for nab-paclitaxel plus gemcitabine vs. gemcitabine alone were neutropenia (38% vs. 27%), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%). In the nab-paclitaxel plus gemcitabine arm, the median time to neuropathy improvement was 29 days. There was no difference in serious life-threatening toxicity (4% in each arm).

Avelumab (also referred to as MSB0010718C)

Avelumab is a fully human IgG1 antibody directed against PD-L1. Avelumab binds PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7-H1. This removes the suppressive effects of PD-L1 on anti-tumor CD8+ T cells, resulting in the restoration of cytotoxic T cell response.

The PD-1 receptor is expressed on activated CD4+ and CD8+ T cells. By interaction with its ligands, PD-L1 and PD-L2, PD-1 delivers a series of strong inhibitory signals through its cytoplasmic tail to inhibit T cell functions (Chemnitz et al 2004, Keir et al 2008, Riley 2009). PD-L1 (also called B7-H1 and CD274) can be detected on resting and activated T cells, B cells, macrophages, dendritic cells, and mast cells; PD-L1 expression is greatly up-regulated after activation or interferon treatment (Keir et al 2008). Numerous results from in vitro cellular assays have demonstrated that blockade of the PD-1/PD-L1 interaction enhances T cell responses, such as increases in proliferation and cytokine production (Bennett et al 2003, Blank et al 2004, Blank et al 2006, Brown et al 2003, Dong et al 1999, Freeman et al 2000, Waeckerle- Men et al 2007).

In PD-1–/– mice both T and/or B cells responses are unregulated resulting in an array of autoimmune pathologies (Okazaki and Honjo 2006, Okazaki and Honjo 2007). Breaking tolerance through blocking PD-1 interaction with its ligands, and thus PD-1 signaling, can be applied to enhance T cell activity towards chronic pathologies such as cancer (Blank et al 2005).

External (Okazaki and Honjo 2007) and internal immunohistochemistry studies have demonstrated that PD-L1 is also expressed by a variety of human tumors, both by the tumor cells, as well as by the immune cells that are present in the tumor microenvironment. In contrast to very strong expression on syncytiotrophoblasts in the placenta and in cancer cells, low levels of PD-L1 expression were detected in some normal tissues including fetal cardiac tissue (Brown et al 2003). High levels of PD-L1 expression have been found to be associated with disease progression, increased metastasis, poor response to treatment, and decreased survival in a number of human cancers (Okazaki and Honjo 2007). Importantly anti-PD-L1 blockade has demonstrated therapeutic efficacy in a variety of murine tumor models as monotherapy and has shown synergistic effect in combination therapy setting (Blank et al 2004, Hirano et al 2005, Iwai et al 2002, Iwai et al 2004, Nomi et al 2007, Strome et al 2003, Zhang et al 2009).

The antitumor activity of Avelumab has been investigated in various murine tumor models. Inhibition of the PD-1/PD-L1 interaction is proposed to exert a therapeutic effect by restoring anti-tumor CD8+ T cell responses. To circumvent the need for a surrogate antibody, the lead candidate antibody was specifically selected for cross-reactivity to murine PD-L1, and, as consequence all nonclinical studies were conducted in syngeneic murine tumor models in which the immune system of the host is fully intact. It was demonstrated that the inhibition of the PD-1/PD-L1 interaction restores anti- tumor CD8+ T cell responses, which results in an anti-tumor activity.

Avelumab has demonstrated significant clinical activity as a monotherapy and in various combination therapy settings. In general, the anti-tumor immunotherapy via blockade of the PD-1/PD-L1 axis seems not to be limited to any specific tumor types, but there is recent evidence that PD-L1 tumor expression is a prerequisite to achieve an objective response upon blockade of the PD-1/PD-L1 axis (Topalian et al 2012b). The clinical relevance of PD-1/PD-L1 blockade has been demonstrated in Phase I trials performed with antibodies targeting either PD-L1 or PD-1 (Topalian et al 2012b, Brahmer et al 2012). More recently, Avelumab has been approved for the treatment of both Merkel Cell carcinomas and bladder cancer. (REF)

Clinical Safety Data Related to Dose

As of 09 June 2016, 53 subjects in the dose escalation part had received Avelumab (4, 13, 15, and 21 subjects had received 1.0, 3.0, 10.0, and 20.0mg/kg of Avelumab, respectively) and 1738 subjects in the pooled safety dataset part (Study EMR100070-001 and EMR100070- 003 Part A) had received 10 mg/kg Avelumab.

In the dose escalation portion of the Phase I study, there was no evidence of differences in the safety profile across all administered dose levels from 1 mg/kg to 20 mg/kg. The MTD was not reached. Ongoing review of the safety data by the Safety Monitoring Committee (SMC) suggests an acceptable safety profile of Avelumab administered 10 mg/kg every 2 weeks. In the pooled safety dataset (Study EMR100070-001 in solid tumors and EMR100070-003 in MCC) with a data cut-off on 09 June 2016, treatment-related TEAEs were observed in 1164 (67.0%) subjects in the pooled safety dataset. The most frequently observed treatment-related TEAEs (with an incidence of ≥5%) of any grade were fatigue (17.7%), infusion related reaction (17.0%), nausea (8.6%), diarrhea (7.1%), chills (6.7%), pyrexia (6.1%), decreased appetite (5.2%), and hypothyroidism (5.0%). Grade ≥ 3 treatment-related TEAEs were observed in 177 subjects (10.2%) in the pooled

Safety dataset. The most frequently reported Grade ≥ 3 treatment-related TEAEs were fatigue, lipase increased (17 subjects each; 1.0%), GGT increased, infusion related reaction (10 subjects; 0.6%), AST increased (8 subjects; 0.5%), pneumonitis (7 subjects; 0.4%), anemia, blood CPK increased (6 subjects each; 0.3%), diarrhea, asthenia (5 subjects each; 0.3%), autoimmune hepatitis, ALT increased, amylase increased, hyponatraemia, hypophosphataemia (4 subjects each; 0.2%). Infusion-related reactions including drug hypersensitivity reactions and immune-mediated adverse reactions (immune-related pneumonitis, immune-related colitis, immune-related hepatitis, immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, new onset type I diabetes mellitus), other immune-related AEs (myositis and myocarditis) have been identified as important risks of Avelumab. The safety profile of Avelumab is consistent with findings reported for other anti-PD-1 or anti-PD-L1 antibodies.

In summary, available data from the dose escalation part of Study EMR100070-001 showed that Avelumab at doses up to 20mg/kg IV every 2 weeks was well tolerated, and data from the pooled dataset (Study EMR100070-001 and Study EMR100070-003) confirmed the dose of 10 mg/kg intravenously every 2 weeks was considered to have an acceptable safety profile.

Efficacy

Avelumab 10 mg/kg once every 2 weeks has demonstrated meaningful clinical activity across various tumor types and treatment settings. Regardless of the tumor type, responses with Avelumab were observed early during treatment and appear durable in nature, including ongoing responses >1 year in several of the cohorts. Overall, many responders experienced ongoing response at the time of database lock. Based on the above analyses, a dose of 10 mg/kg IV once every 2 weeks was considered to have a favorable risk benefit profile.

Human Toxicology

Merkel cell carcinoma is a rare aggressive skin cancer that has previously portended a poor prognosis linked to Merkel cell polyomavirus integration. In a pivotal phase II trial that led to FDA approval of Avelumab for Merkel cell carcinoma, eighty-eight patients with chemotherapy refractory Stage IV Merkel cell carcinoma were treated with Avelumab 10mg/kg every two weeks. Patients received a median of seven doses (IQR 3–18) of Avelumab, and the median duration of treatment was 17 weeks (IQR 7–37). The objective RR was 28/88 patients (31%) with eight CRs and 20 PR's. Five grade 3 treatment-related adverse events occurred in four (5%) patients

- Lymphopenia in two patients
- Blood creatinine phosphokinase (CPK) increase in one patient
- Aminotransferase increase in one patient
- Blood cholesterol increase in one patient
- There were no treatment-related grade 4 adverse events or treatment-related deaths. Serious treatment-related adverse events were reported in six (n=1 each) patients (6%)
- Enterocolitis
- Infusion-related reaction
- Aminotransferases increased
- Chondrocalcinosis
- Synovitis
- Interstitial nephritis (n=1 each)
- Grade 1-2 AE's:
    - fatigue (24%)
    - infusion related reaction (17%)

    - diarrhea (9%)
    - nausea (9%)
    - asthenia (8%)
    - rash (7%)
    - anorexia (7%)
    - maculopapular rash (6%)
- Potential immune related treatment-related AE's:
    - hypothyroidism (3%)
    - hyperthyroidism (2%)
    - pneumonitis (1%)
    - type 1 diabetes mellitus (1%)

In a separate phase 1a study in previously treated solid tumors (JAVELIN), Avelumab was assessed at four doses (1 mg/kg, 3 mg/kg, 10 mg/kg, and 20 mg/kg), with dose-level cohort expansions to provide additional safety, pharmacokinetics, and target occupancy data. Patients were assigned sequentially at trial entry according to the 3+3 dose-escalation algorithm and depending on the number of dose-limiting toxicities during the first 3-week assessment period (the primary endpoint).

In 53 enrolled patients (the safety analysis set), common treatment-related adverse events: (occurring in > 10% of patients) included

- fatigue (21 patients [40%]),
- influenza-like symptoms (11 [21%]), fever (8 [15%]), and chills (6 [11%]).

Grade 3−4 treatment-related adverse events occurred in nine (17%) of 53 patients:

- autoimmune disorder (n=3)
- increased blood creatine phosphokinase (n=2)
- increased aspartate aminotransferase (n=2) each

Six (11%) of fifty-three patients had a serious treatment-related adverse event:

- autoimmune disorder (two [13%]),
- lower abdominal pain (one [7%]),
- fatigue (one [7%]), and
- influenza-like illness (one [7%]) in three patients treated at 10 mg/kg dose level,

At the 20mg/kg dose level:

- autoimmune disorder (one [5%]),
- increased amylase (one [5%])
- myositis (one [5%]), a
- dysphonia (one [5%])

No substantial differences were found in absolute lymphocyte count or multiple immune cell subsets, including those expressing PD-L1, after treatment with Avelumab. Thirty-one (58%) of fifty-three patients in the overall safety population died; no deaths were related to treatment on study.

Together these studies suggest that Avelumab has an acceptable toxicity profile up to 20 mg/kg every 2 weeks, but given various PK parameters, 10 mg/kg has been chosen for this study.

2.0 OBJECTIVES AND SPECIFIC AIMS

2.1 Primary Objective

To determine if addition of Avelumab to the pre-operative regimen gemcitabine/ nab-paclitaxel and hydroxychloroquine can improve the rate of grade IIB or higher histologic responses.

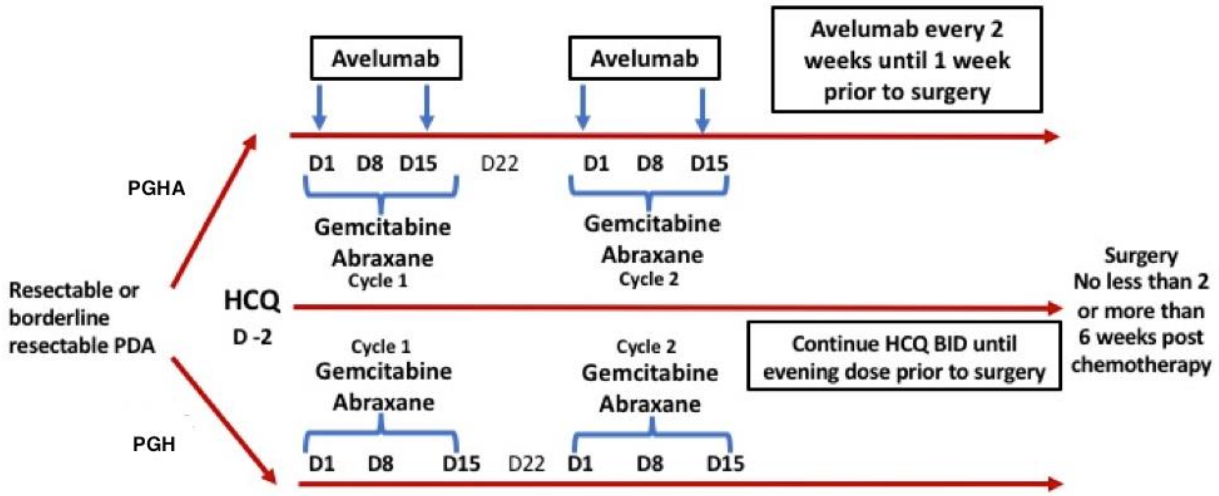
2.2 Secondary Objectives

- To determine if the addition of Avelumab can improve the CA19-9 response to preoperative chemotherapy compared with to the control Gemcitabine/Abraxane and hydroxychloroquine
- To determine if the level of autophagy and inflammation in the tumor and blood of treated patients is correlated with pathological response, and whether that differs between the two experimental arms.

3.0 STUDY DESIGN AND METHOD

This will be phase II, non-blinded, adaptively randomized multicenter trial of 120 participants that will build on the histopathologic responses from the UPCI-13-074 trial (**Fig.1A**). Patients with PDA will be evaluated prior to protocol entry by standard of care testing, including EUS, contrast-enhanced helical abdominal CT scan, or MRI. Patients meeting NCCN criteria for potentially resectable (borderline or resectable) tumors will be eligible. Once they provide consent, subjects will be randomized to receive either 2 cycles of PGH ─ gemcitabine and nab-paclitaxel (1000 mg/m^2 & 125 mg/m^2, respectively: days 1, 8, and 15) plus oral HCQ (1200 mg PO daily) ─ or PGH plus Avelumab (PGHA; days 1 and 15 of each 28-day cycle), by means of response-adaptive randomization based on Grade IIB or greater histologic response, as detailed in Section 9.1. Two-four weeks after the last dose of chemotherapy subjects will undergo a repeat-staging CT scan.

Surgical exploration and pancreatectomy will be performed if technically feasible and all toxicities have resolved. HCQ will be taken until the evening before surgery. Avelumab will be administered every two weeks until up to one week prior to the date of surgery. The Study Coordinator will inform subjects of the date of operation. Specimens will be collected under sterile conditions. Tissue specimens will be stored at -80°C, and as paraffin-embedded blocks for future correlative studies. Following successful surgical removal of tumors, patients will then be free to pursue standard of care adjuvant therapy options, at the discretion of their treating physician.



4.0 HUMAN SUBJECTS

Subject Selection: Up 120 participants will be enrolled in this study. The goal for accrual is 30 participants evaluable for response in each arm. A participant is deemed evaluable for response if he or she has received at least one full cycle of chemotherapy, 80% of the expected HCQ dose, at least 3 doses of Avelumab if the participant is on that arm and undergoes successful surgical extirpation of disease. The racial, gender, and ethnic characteristics of the proposed subject population reflect the demographics of the patients 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.

4.1 Inclusion Criteria

- Participants with biopsy-proven adenocarcinoma of the pancreas that is determined to be potentially or borderline resectable by NCCN criteria
- Karnofsky performance status of 70-100%
- No active second malignancy with the exception of basal or squamous 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) ≥ 1.5×10^9/L,
  - Platelet count ≥100,000/mm^3 (100×10^9/L),
  - Hemoglobin (Hgb) ≥9 g/dL. Patient may receive transfusion as needed.
- Patient has the following blood chemistry levels at Baseline (obtained ≤14 days prior to randomization):
  - AST (SGOT), ALT (SGPT) ≤ 2.5 × upper limit of normal range (ULN).

- Total bilirubin ≤ ULN (Except in patients who have Gilbert's Syndrome or patients with recently placed stents for biliary obstruction when bilirubin should be ≤ 1.5 X ULN).
- Serum Creatinine ≤ 1.5mg/dl OR calculated creatinine clearance ≥ 50 for those patients with creatinine greater than 1.5.
- CPK ≤ ULN.
- Patients who have an elevated lipase or amylase and no history of autoimmune pancreatitis, nor physical exam concerning for, or CT correlates of pancreatitis can be enrolled. The elevated levels will serve as the new baseline. Changes above that will be termed toxicities as per CTCAE guidelines with relation to the new baseline.
- PT WNL+/- 15 % unless on active anticoagulation.
- PTT WNL+/- 15 % unless on active anticoagulation (suggested to be drawn peripherally to prevent port drawn elevation due to routine heparin flush of ports).

- 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
- Prior use of chemotherapy, radiotherapy, and / 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, Avelumab)
- Known or suspected HIV infection
- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sj gren's syndrome, Guillain-Barr syndrome, or multiple sclerosis, with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.
  - Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
  - Rash must cover < 10% of body surface area.
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

    - No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography scan
- Patient with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis or pulmonary hypersensitivity pneumonitis
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening
    - Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody test at screening, are eligible for the study.
    - Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening. The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Known clinically significant liver disease, including alcoholic hepatitis, cirrhosis, fatty liver disease, and inherited liver disease
- Active tuberculosis
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 12 months prior to initiation of study treatment, or unstable arrhythmia or unstable angina within 3 months prior to initiation of study treatment
- Grade ≥ 3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Prior allogeneic stem cell or organ transplantation including corneal transplant
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment.
    - Placement of a stent or central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications as determined by the investigator
- Pregnant or breastfeeding, or intending to become pregnant during the study
- The effects of HCQ, gemcitabine, nab-Paclitaxel and Avelumab 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.

- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with Avelumab or within 5 months after the last dose of Avelumab
    - Attenuated live vaccines include but are not limited to:
        - Tuberculosis (BCG)
        - Oral polio vaccine
        - Measles, Mumps, Rubella, alone or as part of MMR
        - Rotavirus
        - Yellow Fever
        - Typhoid
        - Rabies vaccine should be utilized as recommended by an Infectious Disease specialist
        - Nasal flu vaccine
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti−tumor necrosis factor alpha agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the study, with the following exceptions:
    - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
    - Intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection).
- Patients requiring the use of enzyme-inducing anti-epileptic medication that includes but not limited to: 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 at MD discretion
- Patients on Coumadin must be willing to switch to an alternative subcutaneous LMWH or oral agent (At PI discretion exceptions can be permitted, as determined on a case by case basis and documented)

5.0 CLINICAL AND LABORATORY EVALUATIONS

Arm A (PGH) and Arm B (PGHA)

	Pre-Study ≤ 28 days	Day -2	C1 Day 1	C1 Day 8	C1 Day 15	C2 Day 1	C2 Day 8	C2 Day 15	C3+ Day 1 (Arm B)*	Pre-Op Evaluation (≤ 5 business days prior to surgery +1 day)	Evening before Surgery	Surgery (2-6 wks post-C2D15)	4 weeks Post-Hospital Discharge (± 2 weeks)	Follow up (q 4 months, + 2 weeks)
		(± 3 Days for each visit)												
Informed Consent	X													
Demographics	X													
Medical history	X													
Concomitant meds[1]	X		X	X	X	X	X	X	X	X			X	
Adverse Event Evaluation	X		X	X	X	X	X	X	X	X			X	
Physical exam (includes peripheral neuropathy assessment)	X		X			X			X	X			X	
Vital signs	X		X	X	X	X	X	X	X	X			X	
Height[10]	X													
Weight[10]	X		X			X			X				X	
Performance status (Karnofsky>70)	X[1]		X	X	X	X	X	X	X	X			X	
CBC w/diff, plts[11]	X[1]		X	X	X	X	X	X	X	X			X	
Comprehensive Metabolic Panel[1]	X[1]		X	X	X	X	X	X	X	X			X	
PT/PTT[2]	X[1]									X				
Serum CA19-9	X[13]		X			X			X	X			X	
LDH	X													
Amylase	X		X	X	X	X	X	X	X	X			X	
Lipase	X		X	X	X	X	X	X	X	X			X	
Magnesium	X[1]		X	X	X	X	X	X	X	X			X	
Phosphorous	X[1]		X	X	X	X	X	X	X	X			X	
C-Reactive Protein	X		X			X			X	X			X	
CPK	X		X	X	X	X	X	X	X	X			X	
HBV, & HCV serology	X[12]													
Thyroid Function Tests[4]	X		X	X	X	X	X	X	X	X			X	
Research labs[3]	X[1]									X			X	X
B-HCG[5]	X[1]													
EUS[9]	X													
EKG	X													
Spectral CT or contrast enhanced CT Scan of chest, abdomen and pelvis	X									X				
Gemcitabine (1000 mg/m^2 infusion)			X	X	X	X	X	X						
Nab-Paclitaxel (125 mg/m^2 infusion)			X	X	X	X	X	X						
Avelumab (10mg/kg)*				X[11,4,*]										
Hydroxychloroquine (600 mg PO BID)				X[7]										
Surgical resection and research tissue collection												X[6]		
Survival/Assessment of Progression														X[8]

*C3+D1 for Avelumab only

1. To be completed within 14 days of randomization. Research labs may be drawn within 14 days of dosing of HCQ
2. If patient is given an exception by the PI during screening for con med warfarin derivative PT/INR must be checked weekly prior to treatments.

3. Due to logistical reasons research blood maybe omitted after approval from the investigator
4. Thyroid function testing: thyroid-stimulating hormone(TSH), at screening a free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4) will be performed and then as clinically indicated
5. Serum pregnancy test for women of child bearing potential as defined by ECOG within 14 days of randomization.
6. 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.
7. To be self-administered by subjects: Take three 200mg capsules, AM and PM every day through the evening dose before surgery.
8. 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 (see appendix E for specific tests to be completed).
9. Endoscopic ultrasound for assessing tumor invasion of vascular structures if CT findings of unresectability are equivocal
10. BSA calculation (recalculated per the site's standard of care, or if body weight changes by more than 10%)
11. Patient may receive a transfusion as needed
12. HBV serology: HBsAg, hepatitis B surface antibody, and total HBcAb If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening. HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection
13. CA19-9 must be drawn when bilirubin is within eligibility limits
14. Avelumab to be given every 2 weeks until 1 week prior to surgery for arm B

NOTE: There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the treating investigator, and as discussed with the Sponsor-Investigator if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar [i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject (i.e., non-UPMC insurance coverage) or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.].

5.1 Screening Evaluations

The following are the required ≤ 28 days prior to randomization, unless otherwise specified:

- Review of medical history
- Concomitant medications
- Adverse event evaluation
- 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*
- Magnesium and Phosphorous *within 14 days prior to randomization*
- PT, PTT *within 14 days prior to randomization*
- Amylase and Lipase
- C-Reactive Protein
- CPK
- Serum CA-19-9
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)

- HBV serology: HBsAg, hepatitis B surface antibody, and total HBcAb If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection
- LDH
- 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, and pelvis. Patients with a contrast allergy may use corticosteroid prophylaxis at baseline
- Endoscopic ultrasound for assessing tumor invasion of vascular structures if CT findings of unresectability are equivocal
- Electrocardiogram (EKG)
- Research labs within 14 days of randomization

5.2 Treatment Phase Evaluations

Once deemed eligible, patients will be assigned to Gemcitabine, Nab-Paclitaxel, and **Hydroxychloroquine** with or without Avelumab. 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 a 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

5.3 Prior to Chemotherapy Dosing on all cyles (Day 1) (PGH and PGHA Arms)

- 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
- Magnesium and Phosphorous
- Serum CA19-9

- TSH (free triiodothyronine T3 OR total T3, and free thyroxine T4 should additionally be performed if TSH is abnormal)
- CPK
- Amylase, lipase
- C- Reactive Protein
- CPK

5.4 Prior to Dosing on Cycle 1 and 2 (Day 8 and 15) (PGH and PGHA Arms)

- KPS performance status
- Concomitant medications evaluation
- Vital signs
- Adverse event evaluation
- CBC, differential, and platelet count
- CMP
- TSH (free triiodothyronine T3 OR total T3, and free thyroxine T4 should additionally be performed if TSH is abnormal)
- Magnesium and Phosphorous
- CPK
- Amylase and Lipase

5.5 Surgery Evaluation (PGH and PGHA Arms)

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
- TSH
- CPK
- Amylase, lipase
- C-Reactive protein

5.6 Surgery (to occur no sooner than 2 weeks post last dose of chemotherapy and no longer than 6 weeks post-chemo) (PGH and PGHA Arms)

- 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 patients that did not have a pretreatment liver biopsy*.

5.7 Four (4) Weeks Post Discharge From Hospital Stay (+/- 2 Weeks) (PGH and PGHA Arms)

- Physical examination
- Weight
- Vital signs
- KPS performance status
- Review of concomitant medications
- CMP
- Magnesium and Phosphorous
- CBC, differential, platelets
- Research labs
- Serum CA19-9 level
- TSH
- CPK
- Amylase, lipase
- C reactive protein
- 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 (PGH and PGHA Arms)

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

Gemzar will be prepared and administered per manufactures recommendations. For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of Gemzar 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 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 -2 (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/m^2 as a 30-minute infusion (+/- 10 Minutes) followed by gemcitabine 1000 mg/m^2 as a 30-minute infusion (+/- 10 Minutes) will be administered on days 1, 8, and 15 of cycle 1.

Cycle 2 will start 30 days after the start of Hydroxychloroquine. Cycle 2 (day 1) 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 twice daily starting at cycle 1 day -2 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 Avelumab Administration

- Subjects randomized to Arm B (PGHA) will receive Avelumab 10mg/kg, administered as an intravenous infusion over 60 minutes, every 2 weeks Cycle 1, 2,on Days 1, 15, and every two weeks (C3+) up until one week prior to surgery.
- Subjects will be premedicated with an antihistamine and with acetaminophen prior to the first 4 infusions of Avelumab. Premedication should be administered for subsequent Avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions.

6.4 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), consider institution of antibiotics per SOC.
- Febrile patients (regardless of neutrophil count) should undergo full diagnostic work-up, while continuing antibiotics if appropriate.

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 grade 3 febrile neutropenia, nab-Paclitaxel and gemcitabine treatment can be resumed at the current dose.
- Should a second instance of Grade 3 Febrile Neutropenia occur, dosage of nab-Paclitaxel and gemcitabine will be resumed at the next lower dose upon resolution
- 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. 6 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 gemcitabine, paclitaxel and Avelumab. 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.

6.5 Guidelines for Toxicity Management

- Regardless of the reason for holding study drug treatment, the maximum allowable length of treatment interruption is 3 weeks.
- Examples for discontinuation of nab-Paclitaxel: Persistent 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 noted above the hydroxychloroquine or Avelumab (if applicable) 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://ctep.info.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 or delays, the supportive measures taken, and the outcome will be documented.

6.6 Dose Modifications

Refer to Appendix D for dose modification details of chemotherapy.

- 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 or Avelumab is allowed.

Dose Modifications of Avelumab

There will be no dose modifications for Avelumab. The dose of Avelumab will either be given or delayed/discontinued. Patients may develop study drug-related toxicities that may require skipping doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs. Details of how to dose study medication in the presence of adverse drug reactions that may or may not be IRAEs are addressed below.

Patients will delay or discontinue treatment with Avelumab if they experience at least one adverse event, specified below, considered by the investigator to be definitely, probably, or possibly related to Avelumab treatment. The following criteria will be used to determine dosing delay, restarting doses, or discontinuing Avelumab.

Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease Avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	Temporarily discontinue Avelumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	Stop Avelumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
-If Avelumab infusion rate has been decreased by 50% or interrupted due to an infusion reaction, it must remain decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment. -If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice.	

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 3. Management of Immune-mediated Adverse Reactions

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue Avelumab therapy Symptomatic treatment (e.g. loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold Avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume Avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold Avelumab for Grade 3. Permanently discontinue Avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume Avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Continue Avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Withhold Avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume Avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.

Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold Avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume Avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding Avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold Avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume Avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue Avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Continue Avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold Avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume Avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue Avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue Avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold Avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume Avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue Avelumab therapy	If returns to Grade ≤1: Taper steroids over at least 1 month.

	Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy Nephrology consult	

Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold Avelumab therapy. Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start Avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue Avelumab. Guideline based supportive treatment as appropriate as per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).
*Local guidelines, or e.g. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine irAEs		
Endocrine Disorder	**Initial Management**	**Follow-up Management**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue Avelumab therapy Endocrinology consult if needed	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.

	Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold Avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume Avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue Avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month	Resume Avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume Avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement/suppression therapy as appropriate.

	• Withhold Avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v4)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold Avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting Avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold Avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume Avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue Avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month.
Grade 4	Permanently discontinue Avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue Avelumab therapy Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PRL=prolactin;T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal.

Prohibited and Restricted Therapies during the Study

Patients in this study may not use vaccines for the treatment of cancer or prevention of disease (including those for common medical conditions) for up to one-month pre and post dosing with Avelumab. Concomitant systemic or local anti-cancer medications or treatments are prohibited in this study while receiving Avelumab treatments.

Patients may not use any of the following therapies during the study:

- Any non-study anti-cancer agent (investigational or non-investigational)
- Any other investigational agents
- PD1 or PDL1 antagonists
- Immunosuppressive agents
- Chronic systemic corticosteroids
- Any non-oncology vaccine therapies used for the prevention of infectious diseases (for up to 30 days prior to or after any dose of study drug)

6.7 Concomitant Medications

Pre-medications suggested for this regimen may include Kytril and Emend IV, given as per standard of care institutional guidelines

- Concomitant medications should be avoided except for analgesics (only acetaminophen or narcotics may be given for pain), chronic treatments for concomitant medical conditions, anti-nausea medications, anti-diarrheal, and/ or agents required for life threatening medical problems.
- The subject should try to 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:

    - Non-steroidal anti-inflammatory medications (NSAIDs).
    - Clopidogrel (Plavix).
    - Aspirin > 325 mg/day.
    - Drugs with laxative properties should generally be avoided because of the potential for the exacerbation of diarrhea associated with treatment. Subjects should be advised to contact their physician to discuss any laxative use.
    - Steroids (unless documented consultation with PI providing waiver upon case by case review).

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.
- 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 RECRUITMENT AND COSTS

8.1 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.

8.2 Costs and Payments

Research Study Costs: The study drugs Avelumab and 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 STATISTICAL METHODS

9.1 Method of Randomization

This trial will use the method of Thall and Wathen [Thall P and Wathen J (2005) Covariate-adjusted adaptive randomization in a sarcoma trial with multi-stage treatments. *Statistics in Medicine* 24: 1947-64.] To adaptively randomize participants to PGH versus PGHA based on the probabilities that participants experience histologic response of Evans Grade IIb or better, $P(\pi_{PGHA} > \pi_{PGH})$. Adaptive randomization tends to allocate more patients to the better treatment when significant evidence accrues during the trial suggesting that one treatment is indeed better. This design makes the randomized trial more palatable to patients, while retaining the advantages of randomization. In UPCI-13-074, out of the first 26 patients randomized to the PGH arm, 14 had a histologic response of Evans Grade IIb or better. Throughout the trial, a beta-binomial model will be used to estimate $P(\pi_{PGHA} > \pi_{PGH})$, where the hyperparameters will be $\alpha_{PGH}=14$, $\beta_{PGH}=12$, reflecting the UPCI-13-074 experience, and $\alpha_{PGHA}=3$, $\beta_{PGHA}=2$, representing some confidence that the probability of response will be greater in the PGHA arm. Initially, 30 participants will be randomized to PGH versus PGHA 1:1 (the "burn-in phase"). Beginning with the 31st participant, $P(\pi_{PGHA} > \pi_{PGH})$ will be calculated from the accrued data and the hyperparameters, and participants will be randomized to PGHA with probability p, where $p= P(\pi_{PGHA} > \pi_{PGH})^c$, where $c=i/2N$ for the i^{th} randomized participant. Accrual will continue until a total of 120 (including the "burn-in" participants) participants are accrued, or the trial is interrupted for futility (Section 10.2).

9.2 Monitoring for Futility and Autoimmune Toxicity

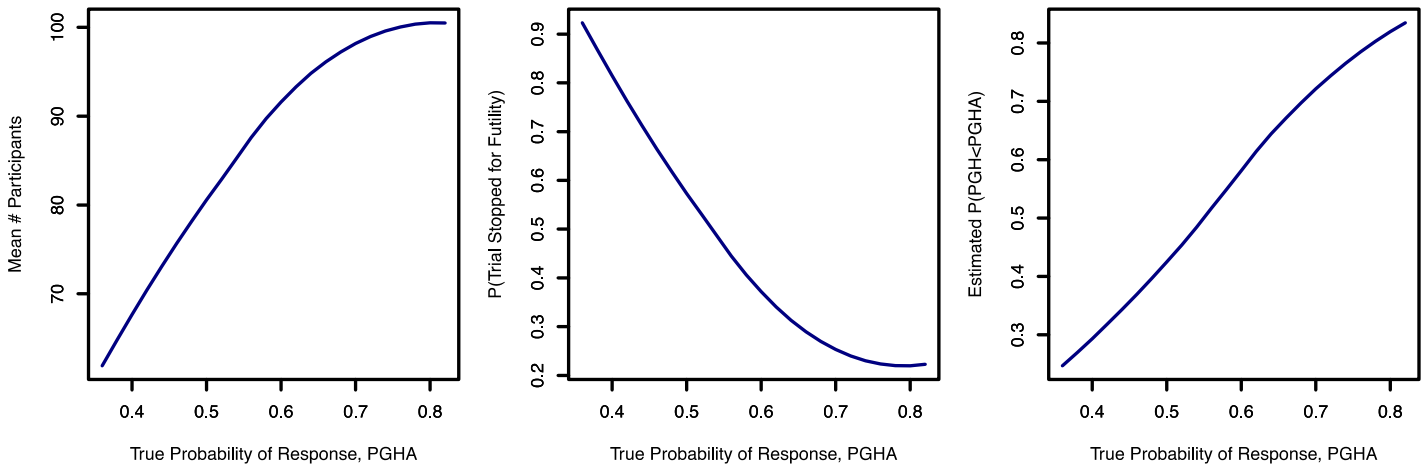
Monitoring for Futility
Using the same beta-binomial as for the randomization, if, at any time after the first 30 response-evaluable participants are treated, $P(\pi_{PGHA} > \pi_{PGH}) < 0.25$, accrual to the trial will be paused and the protocol will be reconsidered for futility.

Monitoring for Autoimmune Toxicity
It is anticipated that the proportion of participants on the PGHA arm experiencing autoimmune toxicities will be less than or equal to 0.1, and a probability of such toxicity greater than 0.2 would be unacceptable. Using a beta-binomial model for toxicity, as above, with $\alpha=1$ and $\beta=9$, the following rule will be used to pause the trial if $P(P(\text{autoimmune toxicity}) \geq 0.2) \geq 0.8$:

# Participants on PGHA Arm	# Autoimmune Toxicities
5	4
10	5
15	6
20	8
25	9
30	10
35	11
40	12
45	13
50	14
55	15
60	17
65	18
70	19

9.3 Justification of Design

Monte Carlo simulation was employed to determine the operating characteristics of the design. It was assumed that the probability of histologic response in the PGH arm was as in UPCI-13-074, 14/26=0.53. The probability of histologic response in the PGHA arm was varied from 0.4 to 0.8 and the randomization and futility rules were applied as above. One hundred trials were simulated for each value of π_{PGHA} between 0.4 and 0.8 (in 0.02 steps). The operating characteristics are displayed in the figure below as a function of the true value of π_{PGHA}. It is seen that, if $\pi_{PGHA} = \pi_{PGH,}$ the expected sample size is 80 (compared to a maximum of 120), but if if $\pi_{PGHA} = 0.8$, the probability the trial is paused for futility equals 0.22. The estimates probability that $\pi_{PGHA} > \pi_{PGH}$ increases linearly with π_{PGHA}.



9.4 Study Timelines and Milestones

Our previous neoadjuvant study (see background) on which this study is based, accrued 60 evaluable patients in a similar two arm fashion over a period of 36 months. We have no knowledge of any change in referral or other patterns at this time to suggest that we cannot reach a similar study milestone. Indeed, accrual picked up as the trial progressed and continued to accrue into an expansion phase. We expect to similarly accrue to this study. However, if after 1 year we have not accrued 10 patients, we would plan remediation efforts amongst ourselves and Pfizer.

9.5 Data Analysis

9.5.1 Primary Efficacy Endpoint

The primary endpoint for this trial will be the Grade IIB or greater histologic response as defined in Appendix C. The beta-binomial model above will be used to estimate 95% credible intervals for π_{PGH}, π_{PGHA}, and $P(\pi_{PGHA} > \pi_{PGH})$. An analysis with uninformative priors will be performed to check the sensitivity of the results to prior specification. A frequentist analysis with 95% exact binomial confidence intervals for π_{PGH} and π_{PGHA} will also be performed. In secondary analyses, the relationship of histologic response to demographic and baseline clinical and biomarker variables will be explored using logistic regression. The relationship between response and the number of cycles of treatment received will be studies in an exploratory fashion. The assumptions required for the validity of all models will be graphically tested.

9.5.2 Secondary Efficacy Endpoint

95% credible intervals for the log-transformed preoperative and postoperative values of CA19-9 will be calculated, along with $P(\mu_{PGHA} < \mu_{PGH})$. 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. As for the primary endpoint, secondary analyses for CA 19-9 will be performed by means of analysis of covariance.

9.5.3 Adverse Events

Adverse events will be tabulated by type, grade, relatedness to treatment and study arm, along with appropriate 95% exact binomial confidence intervals. For each participant, the worst grade event at least possibly related to treatment will be determined, and this metric will be tabulated by arm.

9.5.4 Secondary Biomarker Endpoints

Change in CA19-9 will be related to treatment by repeated measures ANOVA. The relationship between the change in CA19-9 and final histologic response will be explored by cumulative logit models (since clinical response is and ordinal variable). The relationship between various biomarkers measured in tumors (indicators of, for example, autophagy, apoptosis and IL-6/STAT3 signaling) and treatment will be evaluated using two-sample t-tests or Wilcoxon tests, as appropriate. Mixed effects models will be used if multiple samples (e.g., slides or regions) are available per patient. Changes in markers assessed in blood over time will be analyzed using mixed effects models; relationships between continuous markers will be by means of ANCOVA

10.0 ADVERSE EVENT REPORTING

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

10.1 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 untoward 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 casual 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.

10.2 Reporting of Suspected Adverse Reactions

Safety will be monitored throughout the study at Pre-Study, Cycle 1, Cycle 2, 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.

Subjects will be monitored for treatment-related toxicity from the time study drug is initiated until the first outpatient evaluation after surgery, and throughout follow-up for any grade 4 or 5 event felt to be directly related to treatment regimen.

In the event of a serious adverse event, the PI and the institutional review board, per institutional reporting requirements, will be notified using the CRS Departmental SAE form.

All events meeting the definition of a serious adverse event should be recorded on the CRS Departmental SAE Form and submitted to:

1. Nathan Bahary, MD
   Phone: (412) 864-7764
   Email: baharyn@upmc.edu
2. Clinical Research Coordinator
3. CRSSafetySubmissions@upmc.edu
4. Local Institutional Review Board per reporting requirements, as completed by CRS Safety
6. Contact information for submission of reportable events to Pfizer:
   Fax: Pfizer U.S. Clinical Trial Department, Fax 1-866-997-8322 or
   E-mail: **USA.AEReporting@pfizer.com**, specifying: Protocol number, subject, site and PI, SAE and onset.

Note: Participating Sites must also submit events meeting reporting requirements to the contacts listed above, as well as following their internal processes and reporting to their IRB of record according to that IRB's reporting guidelines.

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 Narrative (Section C) on the departmental SAE 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 departmental form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

Pfizer Reporting Requirements

The investigator primary responsibilities in the safety reporting are to identify and follow-up on Serious Adverse Events (SAEs) experienced by participants in the study and to forward the information to the local regulatory authorities and Pfizer, as required by local regulations (for regulatory reporting) and IIR agreement (for reporting to Pfizer.

The following reportable events must be submitted to Pfizer within 24 hours (or immediately for death or life-threatening events) using the provided *Investigator-Initiated Research Serious Adverse Event Form (IIR SAE)* with *the Pfizer Reportable Events Fax Cover Sheet* with each SAE submission.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAE's

10.3 Data Safety Monitoring Plan

Investigator/Sub-investigators, 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 IRB. Any modifications necessary to ensure subject safety and decisions 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 IRB 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 IRB 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. Minutes from the disease center DSMB meetings are provided to those who are unable to attend in person.

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.

11.0 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.

12.0 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

Likely – more than 25 out of 100 people

- Loss of appetite (anorexia)
- Nausea and vomiting
- Abdominal cramping
- Diarrhea
- Fatigue

Infrequent – between 1 and 10 out of 100 people

- Rash
- Discomfort or pain to the eyes due to light exposure (photophobia)
- Irritability, nervousness or emotional changes

Rare – less than 1 out of 100 people

- Abnormal liver function or liver failure (isolated cases)
- Condition when your body's bone marrow stops producing enough new blood cells, causing fatigue and uncontrolled bleeding (Aplastic anemia)
- Condition when your bone marrow does not make enough neutrophils, a type of white blood cell, and leukopenia, a low count of all white blood cells, which increases risk of infection (agranulocytosis)
- Lowered platelet count, which makes it more likely to bruise or bleed
- Decreased blood sugar level (hypoglycemia)
- Hemolysis, a breakdown of red blood cells, in patients with glucose-6-phosphate deficiency
- Dysfunctional muscle fibers leading to progressive muscle weakness and breakdown of muscle tissue (myopathy)
- Bleaching of hair
- Complete or partial loss of hair (alopecia)
- Pigmentation changes
- A rare, serious disorder in which the skin and mucous membranes react severely to a medication or infection (Stevens-Johnson syndrome). It often begins with flu-like symptoms, followerd by a painful red or purplish rash that spreads and blisters, evenutally causing the top layer of skin to die and shed

- A rare form of drug hypersensitivity characterized by the rapid appearance of many sterile pustules ofn the skin, accompanied by fever and sometimes lowered blood counts (Acute generalized exanthematous pustulosis – AGEP)
- Widespread scaling of the skin, often with itching, skin redness, and hair loss (exfoliative dermatitis)
- Partial of complete wasting away of part of the body's muscle groups (atrophy)
- Inflammation or degeneration of the nerves causing tingling, numbness and burning (neuropathy)
- Visual disturbances
- Nightmares, psychosis, headache, dizziness, vertigo, seizure, ataxia and lassitude
- Premature of extra heartbeats which could lead to death (heart arrhythmias)

Gemcitabine

Likely – 25 out of 100 people
- Lack of red blood cells, causing unusual tiredness or weakness (anemia)
- Fever and mild flu-like symptoms
- Blood in urine (hematuria)
- Skin rash, with or without itching
- Bone marrow suppression (low red blood cells, low white blood cells, low concentration of neutrophils, low platelet count)
- Abnormal liver function, usually transient
- Constipation, nausea and vomiting, usually mild to moderate
- Pain

Common – 10 to 25 out of 100 people
- Swelling of fingers, feet or lower legs (peripheral edema)
- Cloudy urine (proteinuria)
- Partial or complete loss of hair (alopecia)
- Mouth ulcers (stomatitis)
- Diarrhea
- Bleeding
- Sleepiness
- Itchiness of the skin (pruritis)

Infrequent – 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, especailly 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
- Blood in urine or stools (hemorrhage)
- Pinpoint red spots on skin
- Cardiovascular toxicity, including myocardial infarction (pain in chest, arm or back, pressure of squeezing in chest), hypertension (high blood pressure), arrhythmia (fast or irregular heartbeat)
- Cerebrovascular accident (sudden or severe headache, slurred speech or inability to speak, weakness in arm and/or leg on one side of the body)
- Febrile neutropenia or other infection (fever or chills, cough or hoarseness, lower back or side pain, painful or difficult urination)

- Abnormal renal function
- A tingling sensation like “pins and needles” (paresthesias)

Rare – 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; pinpoin red spots on skin; swelling face, fingers, feet or lower legs; unusual bleeding or bruising; unusual tiredness or weakness; yellow eyes or skin)
- Lung toxicity, parenchymal or pneumonitis (coughin; shortness of breath)
- Renal failure requiring dialysis
- Severe infection
- Serious liver toxicity including death

Nab-Paclitaxel

Common – Greater than 10 out of 100 people
- Low red blood cell count (anemia)
- Decrease in platelet count (thrombocytopenia)
- Infections due to low count of a type of white blood cell (neutropenia)
- Decrease in white blood cell count, which can lead to infection (leukopenia)
- Diarrhea, constipation, abdominal pain
- Nausea, vomiting, mouth and lip soreness or swelling
- Fever, fatigue, weakness, chills
- Swelling or fluid retention (edema)
- Hair loss (alopecia)
- Nail changes such as discoloration or pigmentation
- Generalized rash or itchy rash
- Dehydration
- Decreased appetite
- Decreased liver function

Infrequent – Between 1 and 10 out of 100 people
- Fever with low white blood cell count (febrile neutropenia)
- Visual disturbances, including redness and swelling of the cornea and blurred vision
- Low blood pressure (hypotension) or high blood pressure (hypertension)
- Headache
- Tingling, numbness or burning in the hands and /or feet (neuropathy)
- Shortness of breath (dyspnea)
- Decreased heart rate (bradycardia)
- Infection in the lungs (pneumonia)
- Lower of upper respiratory infection

Rare – less than 1 out of 100 people
- Allergic reactions, such as shortness of breath, flushing, low blood pressure, chest pain and irregular heartbeat
- Cardiovascular events such as heart attack, blood clots, stroke or mini-stroke
- Formation of blood clots in small blood vessels around the body that leads to a low platelet count (thrombotic thrombocytopenic purpura)

Avelumab

Common – Greater than 10 out of 100 people

- Tiredness
- Nausea and vomiting
- Diarrhea
- Constipation
- Decreased appetite and weight loss
- Decrease in number of red blood cells (anemia)
- Fever, cough, shortness of breath
- Swelling or retention of fluid in the body (peripheral edema)
- Headache, dizziness
- Muscle or joint pain
- Increased blood pressure (hypertension)
- Itchy skin
- Infection
- Allergic reactions during infusion, including symptoms of chills, shaking, fever, flushing, back or belly pain, shortness of breath or wheezing, decrease in blood pressure and hives.

In addition, Avelumab can cause side effects from the increased activity of the immune system. These side effects listed below may be temporary, long-term, and permanent or result in death. Most of these side effects are reversible and will stop once drug is discontinued. The reactions that are more severe require treatment with drugs that decrease the immune system function, like corticosteroids. The immune related side effects have been observed in fewer than 10% of patients.

Immune-related side effects observed in 5 to less than 10% of patients:

- Abnormal function of the thyroid gland (low or high function, or inflammation) – symptoms may include rapid heartbeat, increased sweating, extreme tiredness, weight gain or weight loss, hair loss, changes in mood or behavior such as irritability or forgetfulness, feeling cold, constipation, change in voice.
- Inflammation of the skin (rash) – symptoms may include skin rash, itchy skin, skin redness, skin blisters or peeling.

Immune-related side effects observed in 1 to less than 5% of patients:

- Inflammation or the large intestine (colitis) – Symptoms may include diarrhea or more frequent bowel movements than usual, blood in stools or dark, tarry, sticky stools, severe stomach are pain or tenderness.
- Inflammation of the lungs (pneumonitis) – Symptoms may include new or worsening cough, shortness of breath, chest pain.

Immune-related side effects observed in less than 1% of patients:

- Inflammation of the liver (hepatitis) – Symptoms may include yellowing of skin or of the whites of eyes; severe nausea or vomiting; pain on the right side of stomach area (abdomen); drowsiness; dark urine (tea colored); bleeding or bruising more easily than normal; feeling less hungry than usual.
- Inflammation of the kidneys (nephritis) – Symptoms may include urinating less than usual; blood in urine; swelling in ankles; loss of appetite.

- Low function of the adrenal glands (glands on top of the kidneys), which may be due to the reduced function of the pituitary gland (a gland in the head): may include very low blood pressure; extreme tiredness.
- Increase in blood sugar (diabetes) – Symptoms may include urinating more often than usual; feeling more hungry or thirsty than usual, nausea or vomiting, stomach area (abdomen) pain.
- Inflammation of the eyes (uveitis) – Symptoms may include changes in eyesight.
- Inflammation of the muscles (myositis) – Symptoms may include severe or persistent muscle or joint pain; severe muscle weakness.
- Inflammation of the heart (myocarditis) – Symptoms may include chest pain or tightness; tiredness; changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation; swelling of feet and legs; trouble breathing.
- Inflammation of the nerves (Guillain-Barre syndrome) – Symptoms may include "pins and needles" sensations in arms and legs; weakness in legs that spreads to the upper body and may lead to temporary paralysis.

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.

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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

Obtained from **https://evs.nci.nih.gov/ftp1/CTCAE/About.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.
IIIm	Sizable pools of mucin present.
IV	No viable tumor cells present.
IVm	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/m²)[b]	Gemcitabine (mg/m²)[b]
Study Dose	125	1000
-1	100	800
-2	75	600

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 D.1.4 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 2 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;).

Key: ANC = Absolute neutrophil count.

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

Gemcitabine and nab-paclitaxel related 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 asymptomatic, will be exempt from this requirement.

D.1.4 Dose Adjustments for Day 1 and within a Treatment Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	nab-Paclitaxel Dose	Gemcitabine Dose
Day 1	≥ 1500	AND	≥ 100,000	Treat on time at current dose levels	
	≥ 500 between < 1000	OR	≥ 75,000 but < 100,000	Consider GCSF support	
	< 500	OR	< 75,000	Hold until recovery and consider GCSF support	
Day 8	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were given without modification:					
Day 15	≥ 1000	AND	≥ 75,000	Treat on time at current dose levels	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level from Day 8; consider following with WBC growth factors for support*	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were reduced:					
Day 15	≥ 1000	AND	≥ 75,000	Treat with same doses as Day 8; consider following with WBC growth factors for support*	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level from Day 8; consider following with WBC growth factors for support*	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1000	AND	≥ 75,000	Option A: Maintain dose level from Day 1 and follow with WBC growth factors for support* OR Option B: Reduce doses 1 dose levels from Day 1	
	≥ 500 but < 1000	OR	≥ 50,000 but < 75,000	Option A: Reduce 1 dose level from Day 1 and follow with WBC growth factors for support* OR Option B: Reduce doses 2 dose levels from Day 1	
	< 500	OR	< 50,000	Withhold doses	

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

- [a] G-CSF as per SOC
- 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.
- When a dose reduction is required at cycle 1, dose re-escalation at cycle 2 will be permitted at the treating MD discretion

D.1.5 Dose Modifications for Non-Hematological Toxicity within a Cycle

Dose modifications may also be made for non-hematological toxicity within a cycle as specified in Table 2

Table 2: 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 ≤Grade 1. Then resume treatment at the next lower dose level.
4	Hold

D.1.6 Peripheral Neuropathy

Nab-paclitaxel treatment should be withheld in patients who experience ≥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 ≤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.1.7 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.1.8 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.1.9 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.1.10 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 X)
Patients who do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

D.1.11 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: Bio-specimen Research Samples

15mL of Research blood will be collected at various study visits (refer to study calendar in section 5.0).

The following tests will be performed on tissue samples:

- Cl Casp 3
- Ki-67
- PCNA
- Atg7
- Beclin-1
- LC3B
- p62
- HMGB1
- IL-6
- STAT 3 Ser727

The following tests will be completed on blood samples:

1. A soluble checkpoint/costimulation panel.

BTLA; GITR; HVEM; IDO; LAG-3; PD-1; PD-L1; PD-L2; TIM-3; CD28; CD80; CD137; CD27; CD152

2. Cytokine/chemokine/growth factors: 65-plex. Target List

APRIL; BAFF; BLC; CD30; CD40L; ENA-78; Eotaxin; Eotaxin-2; Eotaxin-3; FGF-2; Fractalkine; G-CSF; GM-CSF; Gro a; HGF; IFN-a; IFN-g; IL-10; IL-12p70; IL-13; IL-15; IL-16; IL-17A; IL-18; IL-1a; IL-1b; IL-2; IL-20; IL-21; IL-22; IL-23; IL-27; IL-2R; IL-3; IL-31; IL-4; IL-5; IL-6; IL-7; IL-8; IL-9; IP-10; I-TAC; LIF; MCP-1; MCP-2; MCP-3; M-CSF; MDC; MIF; MIG; MIP1a; MIP-1b; MIP-3a; MMP-1; NGF beta; SCF; SDF-1a; TNF b; TNF-a; TNF-R2; TRAIL; TSLP; TWEAK; VEGF-A

This is a preliminary list of tests to be completed on bio-specimen research samples that can change as the study progresses and the study teams understanding develops.