Title: A PHASE II STUDY OF PACLITAXEL PROTEIN BOUND + GEMCITABINE + CISPLATIN+ PARICALCITOL AS PREOPERATIVE TREATMENT IN PATIENTS WITH UNTREATED RESECTABLE, BORDERLINE RESECTABLE AND LOCALLY ADVANCED ADENOCARCINOMA OF THE PANCREAS

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A PHASE II STUDY OF PACLITAXEL PROTEIN BOUND + GEMCITABINE + CISPLATIN+ PARICALCITOL AS PREOPERATIVE TREATMENT IN PATIENTS WITH UNTREATED RESECTABLE, BORDERLINE RESECTABLE AND LOCALLY ADVANCED ADENOCARCINOMA OF THE PANCREAS

IND Exempt
SPONSOR HonorHealth Research Institute 10510 N 92nd Street, Suite 200, Scottsdale, AZ, 85258
VERSION DATE Amendment 4, Version 4.0, 17 February 2020 Amendment 3, Version 3.2, 25 October 2018 Amendment 2, Version 3.0, 20 February 2018 Amendment 1, Version 2.0, 24 July 2017 Original Protocol, Version 1.0, 16 February 2017
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INVESTIGATOR'S PROTOCOL AGREEMENT

Protocol No.: NABPLAGEM-NEO 2017-001

Version 4.0, 17 February 2020

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the study specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on Form FDA 1572 and on other document(s) required by local regulatory authority.
- Retain records and documents related to this Trial for at least 7 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 7 years have elapsed since the formal discontinuation of clinical development of the investigational products.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of HonorHealth confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendments to the protocol, and periodic re-approval as required, and to keep the IRB informed of adverse events and periodically report the status of the study to them.
- Not implement any deviations from or changes to the protocol without agreement from the Lead Sponsor-Investigator and HonorHealth and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the Trial has read, understands, and has signed the Informed Consent.
- Ensure that I and all persons assisting me with the study are adequately informed and trained about the investigational drug and of their study-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths (within 1 business day of learning of the death and 2 business days of learning of the SAE) to HonorHealth.
- Assure access by HonorHealth monitors, and/or FDA to original source documents.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to HonorHealth.
- Cooperate fully with any study-related GCP audit as performed by HonorHealth quality assurance group.
- Abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the study.

Investigator's Printed Name: _____

Investigator's Signature: _____ Date: _____

SAE REPORTING

All SAEs must be reported promptly to HonorHealth after the Investigator recognizes/ classifies the event as a SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE **within 1 business day** of becoming aware of the event, preferably by fax or alternatively by phone or email.

HonorHealth Drug Safety Team
24 Hour Phone #: 480-323-1350
Fax #: 480-323-1560
Email: DrugSafety@honorhealth.com

Cohort A

Cohort B

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1. BACKGROUND AND RATIONALE

1.1 Pancreatic Cancer

In 2020, the estimated number of new cases of pancreatic ductal adenocarcinoma (pancreatic cancer) in the US is 57,600 with an estimated 47,050 deaths from the disease [Siegel et al, 2020]. Worldwide about 210,000 cases are diagnosed every year, however only 10-15% are surgical candidates and undergo a potentially curative operation. Generally, most new cases of pancreatic cancer are advanced with extensive tumor growth usually due to the lack of symptoms during the early stages of the disease. Even in the minority of patients who undergo surgical resection with a curative intent, there are few long term survivors. Current guidelines regarding patients with pancreatic cancer whose tumors are deemed resectable are to undergo resection and then to pursue adjuvant therapy. Adjuvant therapy with either gemcitabine or 5-Fluoruracil (5-FU) is well established, and should be considered for patients who have recovered from surgery [Neoptolemos et al, 2004, Regine et al, 2008, Neoptolemos et al, 2004]. Recently, combination chemotherapy has been advised by NCCN guideline for adjuvant therapy for pancreatic cancer. A phase III trial reported that adjuvant gemcitabine plus capecitabine had a statistically significant improvement in survival compared to gemcitabine monotherapy with a median overall survival (mOS) of 28 versus 25.5 months (Neoptolemos et al, 2016). A phase III trial adjuvant combining 5-FU with leucovorin, oxaliplatin, and irinotecan (FOLFIRNOX) a mOS of 54.4 months compared to 35.0 months (p=0.003) with gemcitabine alone in individuals with resected pancreatic cancer [Conroy et al 2018]. The addition of chemotherapy with radiation therapy is becoming less acceptable, as its improvement in overall survival is debatable. A recent meta-analysis of nine trials reported a worse overall survival with chemoradiation

compared to single agent gemcitabine or 5-FU [Liao et al 2013]. Investigators at Memorial Sloan Kettering Institute in NY published an analysis of a prospectively maintained database (1983-2001) of 618 patients who underwent resection for pancreatic adenocarcinoma. There were only 75 patients (12%) who survived > 5 years after resection, and 18 patients (5%) who survived >10 years. Stage and negative margins were associated with 5-year survival, and patients with stage IA disease had the best outcome with 5 year survival of 26% [Ferrone et al, 2008]. Thus, for patients with resectable disease overall survival still remains to be low.

1.2 Preoperative Therapy for Pancreatic Cancer

Neoadjuvant therapy has become the consensus treatment for individuals with locally advanced unresectable disease and borderline resectable disease [Seufferlein et al 2012]. Typical regimens utilize those that are used in the metastatic setting for pancreatic cancer, such as FOLFIRINOX (5-FU, Leucovorin, Irinotecan, and Oxaliplatin) and paclitaxel protein bound plus Gemcitabine. Currently, the recommendation of utilizing neoadjuvant therapy for potentially resectable pancreatic cancer has been met with controversy. However a recent study published an analysis of individuals with potentially resectable pancreatic cancer and showed a median overall survival of 31.5 months with 44.9 months for the 60 individuals who underwent neoadjuvant therapy and resection compared to 8.1 months for the 9 patients who were not resected [Christians et al 2016]. Another study examined the use of nab-paclitaxel, gemcitabine, capecitabine, and cisplatin (PAXG regimen) in individuals with unresectable or borderline resectable pancreatic cancer patients. A partial response was observed in 67% of the patients along with progression-free survival at 6 months being 96% [Reni et al 2016]. Furthermore, a recent study examining stage I or stage II pancreas cancer patients who received either neoadjuvant therapy followed by resection or those who received upfront resection was reported. In those receiving neoadjuvant therapy, overall survival was 26 months compared to 21 months [Mokdad et al 2017]. Neoadjuvant, as opposed to adjuvant therapy potentially increases the amount of exposure of drug to the tumor. It allows for the completion of therapy prior to surgery to prevent patient drop-out due to perioperative complication. Neoadjuvant therapy also acts as a selection tool for optimal surgical candidates by identifying aggressive tumor biology prior to surgery and therefore selecting out those who will not benefit from resection. Radiation therapy may be also employed in the neoadjuvant setting as a means to help with local control and survival in individuals without micrometastatic disease.

1.3 Rationale for the use of paclitaxel protein bound, Gemcitabine, Cisplatin, and Paricalcitol

The combination of nab-paclitaxel (now called paclitaxel protein bound) and gemcitabine demonstrated an improvement in survival and response rate in advanced pancreatic cancer. In the phase III (MPACT study, n=861) patients were randomly assigned to nab-paclitaxel plus gemcitabine (431 patients) or gemcitabine (430). The median overall survival was 8.5 months in the nab-paclitaxel–gemcitabine group as compared with 6.7 months in the gemcitabine group ($P<0.001$). The one year survival rate was 35% in the nab-paclitaxel–gemcitabine group versus 22% in the gemcitabine group, and 9% versus 4% at 2 years. The median PFS was 5.5 months in the nab-paclitaxel–gemcitabine group, as compared with 3.7 months in the gemcitabine group ($P<0.001$); the response rate according to independent review was 23% versus 7% in the two groups ($P<0.001$). Adverse events were tolerable with grade > 3 events of neutropenia (38% in the nab-paclitaxel–gemcitabine group vs. 27% in the gemcitabine group), fatigue (17% vs. 7%), and neuropathy (17% vs. 1%) and febrile neutropenia (3% versus 1%). Based on the results of this study, nab-paclitaxel plus gemcitabine is a FDA approved regimen for pancreatic cancer [Von Hoff et al 2013].

Building on the design and mechanisms of action of the nab-paclitaxel and gemcitabine combination, a prior protocol introduced a third cytotoxic agent cisplatin, was added to this

doublet [Jameson et al 2019]. The rationale for adding cisplatin to nab-paclitaxel and gemcitabine was that in a study of 1,029 patients whose pancreatic cancer tumors were sent for molecular profiling, 57% of these tumors were negative for ERCC1, indicating sensitivity to a platinum anti-tumor agent [Von Hoff 2012]. In addition to the above, in our whole genome/transcriptome sequencing analysis, we found that abnormal repair pathways were a feature of all of the pancreatic cancers that were sequenced [Liang et al 2012]. Cisplatin prevents cellular DNA repair by binding to and causing crosslinking of DNA, triggering apoptosis. Cisplatin has been used in other combination regimens to treat patients with PDA. For example, the cisplatin, epirubicin, 5-fluorouracil and gemcitabine (PEFG) regimen had an acceptable toxicity profile and was associated with a 24% partial response rate, 5 month progression-free survival (PFS) and 8.3 month overall survival as second line therapy [Reni et al 2008].

A team led by Gayle Jameson [Jameson et al, 2019] recently reported on the phase Ib/II trial of the combination of paclitaxel protein-bound plus gemcitabine plus cisplatin in advanced pancreatic cancer. In 24 evaluable patients with stage IV pancreatic cancer they reported a response rate of 71% (Complete Response (CR) + Partial Response (PR)) along with an 88% disease control rate (CR + PR+ Stable Disease (SD) at 9 weeks). Utilizing this highly active therapy in the neoadjuvant setting may lead to further improvement in overall survival and progression free survival in patients with pancreatic cancer.

Most recently the spectacular work of Mara Sherman [Sherman et al 2014] has awakened the world of pancreatic cancer research to the possibility that Vitamin D could be a substantial player in normalizing the tumor microenvironment from an immunologically friendly (to the tumor) one to an immunologically hostile one (e.g. decreased IL6, decreased CXCL12 etc.). In addition, the vitamin D analog decreased production of collagen, decreased Myeloid Derived Suppressor cells (MDSCs) and decreased regulating T cells. In a completed neoadjuvant trial utilizing gemcitabine and paclitaxel protein bound with paricalcitol compared to gemcitabine and paclitaxel protein bound, a modulation of the tumor microenvironment has been seen including greater infiltration of CD3 positive lymphocytes (unpublished SU2C data courtesy of Drs. O'Dwyer and Drebin of the University of Pennsylvania). Therefore, a trial utilizing gemcitabine, paclitaxel protein bound, cisplatin and paricalcitol may yield promising results in the neoadjuvant setting. We conducted a prospective, phase 2 clinical trial of patients with resectable, borderline resectable, and locally advanced pancreatic cancer utilizing a regimen combining Paclitaxel protein bound (A) plus gemcitabine (G) plus cisplatin (C) plus paricalcitol (P). Preliminary data of this study was presented at the AACR Pancreatic Cancer conference 2019 demonstrating a 50% normalization rate of CA 19-9 out of the first 22 patients on the study ; 10 of the 22 patients proceeded with surgery, with an ORR 33% [Borazanci et al 2019]. As of December 2019, enrollment of the 24 patients planned for the study is complete. Grade 3 adverse events greater than 10% incidence related to therapy include anemia (59.1%), thrombocytopenia (50%). Grade 4 adverse events related to therapy over 10% include thrombocytopenia (31.8%). Publication after final data analysis is pending.

1.4 Rationale for the use of CA19-9 as a primary endpoint.

Cancer Antigen 19-9 (CA 19-9) is the most commonly used serum biomarker for pancreas cancer. Several reports have indicated a sensitivity, specifity values at 80, 85 percent respectively [Steinberg 1990, Goonetilleke and Siriwardena 200]. Despite this, CA 19-9 remains the best tumor marker for pancreas cancer and its utility has been demonstrated in a few studies in the neoadjuvant setting. In a study examining patients with pancreas cancer with borderline resectable and locally advanced disease, those patients whose pre-operative CA 19-9 were normalized (≤ 35 U/ml) had an overall survival of 71.4 months compared to those with an

elevated CA 19-9 (>35 U/ml) having an overall survival of 32.5 months [Williams et al 2016]. Another study in borderline resectable pancreatic cancer also demonstrated an improvement of overall survival in both the non-resected (15 months versus 11 months) and those who underwent resection (38 months versus 26 months) in those who had a normalized CA 19-9 [Tzeng et al 2013]. Thus, the use of normalized CA 19-9 as a primary objective in a neoadjuvant trial may represent a significant insight to the overall clinical benefit of a given regimen.

Based upon the encouraging preliminary results of this regimen, an additional 24 patients will be enrolled to further solidify the findings of the CA 19-9 normalization rate.

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives

- To evaluate:
  - The normalization rate of CA 19-9 of individuals with non-metastatic pancreas cancer following up to 6 months of neoadjuvant chemotherapy.

2.2 Secondary Objectives

- To assess:
  - Resectability (R0) rate following neoadjuvant chemotherapy
  - Pathologic Complete Response Rate (pCR)
  - Safety and tolerability of the neoadjuvant chemotherapy
  - Radiologic response rate
  - The 2 year survival from date of study entry

2.3 Exploratory Objectives

- To evaluate: cell-free DNA as biomarker for pancreatic cancer in relation to CA 19-9 and/or clinical response by RECIST 1.1
- To monitor and compare the gut microbial communities and to determine the differences in gut microbial communities within and between fecal samples using alpha and beta diversity metrics based on 16S rRNA sequencing.
- To evaluate imaging biomarkers and tumor vascularity for response to therapy

3. STUDY POPULATION

3.1 Inclusion Criteria

1. Patient has histologically or cytologically confirmed resectable, borderline resectable, or locally advanced (unresectable) PDAC (based upon Tempero et al 2016)
   - Definition of Resectable Pancreatic Cancer includes all of the following:
     - No evidence of extra pancreatic disease
     - No evidence of tumor-arterial abutment (celiac, SMA [superior mesenteric artery] or HA [hepatic artery])
     - If tumor induced narrowing of the SMV [superior mesenteric vein], PV [portal vein] or SMV-PV [superior mesenteric-portal vein] confluence is present, it must be <50% of the diameter of the vessel
   - Definition of Borderline Resectable Pancreatic Cancer

    - To include at least one of the following:
    - Tumor abutment <180° of the SMA or celiac axis
    - Tumor abutment or encasement of a short segment of the HA
    - Tumor induced narrowing of SMV, PV or SMV-PV of >50% of the diameter of the vessel.
    - Short segment occlusion of the SMV, PV or SMV-PV with a suitable PV above and SMV below, for reconstruction
    - Biopsy proven N1 disease (regional lymph nodes involved) from pre-referral biopsy or EUS-guided FNA
  - Definition of Locally Advanced (Unresectable)
    - Artery: Tumor encasement (> 180°) of SMA or celiac artery
    - Vein Occlusion of SMV, PV or SMV-PV without suitable vessels above and below the tumor to allow for reconstruction (no distal or proximal target for vascular reconstruction)
    - No extra pancreatic disease: No evidence of peritoneal, hepatic, or extra-abdominal metastases
2. Age ≥ 18 years.
3. If a female patient is of child-bearing potential, she must have a negative serum pregnancy test (≥β-hCG) documented within 72 hours of the first administration of study drug
4. If sexually active, the patient and partner must agree to use contraception considered adequate and appropriate by the Investigator
5. Patient must have received no prior chemotherapy or radiation therapy for PDAC
6. Patients must have normal organ and marrow function as defined below:
   - absolute neutrophil count ≥ 1,500/mm^3
   - platelets ≥ 100,000/mm^3
   - Hematocrit level > 27%
   - total bilirubin within 1.25 times institutional upper limit of normal (ULN)
   - AST/ALT ≤ 10 × institutional ULN
   - Creatinine < 1.5 mg/dl
7. Patient has acceptable coagulation status as indicated by an INR ≤ 1.5 x ULN. Patients on anticoagulation can be included at the discretion of the investigator.
8. Karnofsky Performance Status (KPS) of ≥70%.
9. Have an elevated CA 19-9

3.2 **Exclusion Criteria**

1. Patient will be excluded from this study if any of the following criteria apply: Evidence of metastatic disease. No metastatic disease defined as any one or more of the following:
   - Suspicious lymphadenopathy outside of the standard surgical field (i.e. aortocaval nodes, distant abdominal nodes)
   - Radiographic evidence for metastatic disease in distant organs, peritoneum, or ascites
2. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.
3. Known infection with HIV, hepatitis B, or hepatitis C.
4. Has undergone major surgery, other than diagnostic surgery (i.e.--surgery done to obtain a biopsy for diagnosis without removal of an organ), within 4 weeks prior to Day 1 of treatment in this study.
5. History of allergy or hypersensitivity to the study drugs.
6. Serious medical risk factors involving any of the major organ systems such that the Investigator considers it unsafe for the patient to receive an experimental research drug.

7. Current, serious, clinically significant cardiac arrhythmias as determined by the investigator.
8. Patient is unwilling or unable to comply with study procedures.
9. Patient is enrolled in an industry sponsored clinical trial involving treatment with investigational therapy. Patients enrolled in HonorHealth sponsored research studies may be eligible to participate as long as their participation in the other research studies does not confound the data collected for this study.
10. Patient with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.
11. Use of non-FDA approved cannabinoids are prohibited. Total daily usage of up to 40 mg per day of marinol is acceptable.

3.3 Patient Enrollment

This is an open-label study. A patient ID number will be assigned by the site when the patient signs the Informed Consent Form. A copy of the signed informed consent will be required for study entry.

The exact date and time of each administration of medications will be recorded in the case report form (CRF). Paricalcitol, cisplatin, paclitaxel protein bound and gemcitabine will be administered according to the clinical study protocol only to patients who have given written informed consent. Patients withdrawn from the study will retain their patient ID number. New patients must always be allotted a new patient ID number.

3.4 Patient Discontinuation

Patients will be discontinued from the treatment under the following circumstances:

1. Disease progression.
2. Patient's physician considers a change of therapy would be in the best interest of the patient.
3. Patient requests discontinuation.
4. Continued unacceptable toxicities despite optimal treatment or dose reduction.
5. Patient becomes pregnant or fails to use adequate birth control (for those patients who are fertile).
6. Need for any treatment not allowed by the protocol.
7. Non-compliance.

3.5 Study Discontinuation

HonorHealth has the right to terminate the participation of either an individual site or the study at any time. Reasons for terminating the study include, but are not limited to, the following:

1. Incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
2. Patient enrollment is unsatisfactory.
3. Investigator does not adhere to the protocol or applicable regulatory guidelines in conducting the study.

4. STUDY TREATMENT

4.1 Treatment Pathways

All patients will be offered up to 6 months neoadjuvant therapy. For those who during therapy normalize their CA19-9 will be re-evaluated for surgery and will come off study. The patient will then proceed with standard of care therapy for their pancreatic cancer. Those completing 6 months of neoadjuvant therapy will come off study and proceed with standard of care therapy for their pancreatic cancer.

The recommended treatment will take into account input from the medical oncology investigators, patient performance status, co-morbidities, and contraindications. When necessary, other relevant factors concerning the patient's clinical history and current medical literature will also be taken into consideration. The individual will be assessed through appropriate imaging, endoscopic evaluation, and surgical staging to determine resectability status and will undergo treatment based upon the following pathways.

4.2 Neoadjuvant Treatment

Each cycle of paricalcitol, paclitaxel protein bound, cisplatin and gemcitabine will last for 21 days (see section 4.8 Administration and Dosing).

Restaging will be done after 3 cycles. If progressive disease is noted the individual will be taken off study and undergo therapy at the discretion of the investigator.

The patient may receive up to 6 months of study treatment.

If the patient has a normal CA19-9 (i.e. ≤ 35 U/ml) the individual will be evaluated for surgery. If the patient's tumor is deemed resectable then they will come off study for standard of care treatment.

4.3 Administration and Dosing

Treatment must be administered in a hospital, clinic or other out-patient setting appropriate for chemotherapeutic infusions. No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the patient's malignancy.

The solution for infusion will be prepared at each investigational site. Detailed guidelines for the preparation and administration of paricalcitol, paclitaxel protein bound, cisplatin and gemcitabine are provided in Appendix D. An administration window of -5/+15 minutes is permitted. The order of infusion with premedication is as follows:

Pre cisplatin hydration: up to 1000 mL with additional electrolytes as clinically indicated (i.e. Mannitol 12.5 grams and Magnesium Sulfate 2 grams) IV infusion over 2 hours on days 1 and 8 repeated every 21 days.
Palonosetron (Aloxi®) 0.25 mg IV, fosaprepitant (Emend®) 150 mg IV and dexamethasone 12 mg IV, or equivalent antiemetic regimen, within 30 minutes prior to treatment on days patient is receiving paclitaxel protein bound + cisplatin + gemcitabine. (see Appendix H for details of

reduced dosing of dexamethasone with concomitant administration of fosaprepitant). Patients will continue oral antiemetic prophylaxis at home with ondansetron 8 mg bid and dexamethasone 4 mg twice daily for 2 days after chemotherapy. Olanzapine 10 mg po at bedtime x 4 days after chemotherapy can be considered if additional antiemetic is needed. (Navari RM, et al, 2016.) The type of antiemetic prophylaxis used can vary based on institutional procedures.

Paclitaxel protein bound 125 mg/m^2 over 30 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:

Cisplatin 25 mg/m^2 in 500* mL of 0.9% Sodium Chloride Injection over 60 minute IV infusion on days 1 and 8, repeated every 21 days, followed by:

Gemcitabine 1000 mg/m2 in 250* mL 0.9% Sodium Chloride Injection over 30 minute IV infusion on days 1 and 8 repeated every 21 days

Post cisplatin hydration: IV fluids up to 1000 mL (with additives as clinically indicated) IV given as infusion on days cisplatin is administered. This may start at the same time as the gemcitabine infusion.

Paricalcitol will be given at a dose of 25 micrograms days 1 and 8 and repeated every 21 days

* The investigator may reduce the volume of 0.9% Sodium Chloride Injection to 250 mL.

In the event of extravasation during the infusion of paclitaxel protein bound, paricalcitol, cisplatin or gemcitabine, the infusion should be immediately terminated and patients treated according to local site protocols. The infusion should then be restarted in another vein.

Doses may be rounded per institutional guidelines.

4.3.1 Body Surface Area Calculation

The calculation of the dose of cisplatin, gemcitabine, and paclitaxel protein bound will be based on the patient's body surface area (BSA) using the Mosteller formula (Verbraeken 2006). The BSA will be calculated at baseline and before each new cycle, based on the actual height and weight of the patient. The calculated dose will be rounded to the nearest whole milligram. If there has been a ≥ 10% weight change from baseline, the drug doses will be recalculated based on the new BSA value. If the change in weight is less than 10%, drug doses will not be recalculated. The dose of paricalcitol will be a flat 25 micrograms.

4.3.2 Dose Modification for Toxicity

Toxicities will be graded using the NCI CTCAE v4.0 (see Appendix F). If toxicity occurs during or after any treatment cycle, the toxicity will be graded and appropriate supportive care treatment may be administered to decrease the signs and symptoms (e.g. antiemetics, antidiarrheals, antipyretics, antihistamines).

For paclitaxel protein bound or gemcitabine or cisplatin or paricalcitol

Doses of paclitaxel protein bound and gemcitabine may be reduced in individual patients in accordance with the schedule in Tables 2, 3, 4, 5 and 6. In general, doses that have been reduced for toxicity will not be escalated back to the starting level. Growth factors may be used to treat hematologic toxicity and will not constitute a dose reduction.

Table 1: Dose Reductions Schema

Dose Level	paclitaxel protein bound (mg/m2)	Cisplatin Dose** (mg/m2)	Gemcitabine (mg/m2)	Paricalcitol* (micrograms)
Level - 0 (baseline)	125mg/m^2	25	1000mg/m^2	25 micrograms
Level -1	100mg/m^2	25	800mg/m^2	25 micrograms
Level -2	75mg/m^2	25**	600mg/m^2	25 micrograms

*Note if any toxicity is deemed certainly relatable to the paricalcitol (e.g. renal stone, etc.) the paricalcitol will be discontinued
**Note cisplatin should not be given unless creatinine is ≤ 1.5 X ULN

4.3.2.1 Hematological Toxicity

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of paclitaxel protein bound, cisplatin, and gemcitabine may be adjusted as detailed in Table 1. Please note that all four drugs will be held at the start of a new cycle if Table 2 criteria are not met. Dosing delays up to 14 days are permitted for each cycle. Further dosing delays must be discussed with the principal investigator.

Dose Modifications at Day 1

Table 2: Dose Modifications for Day 1 of Each Cycle*

*a cycle being defined as 21 days

ANC		Platelets	Timing
≥ 1.5 x 10^9/L	And	≥ 100 x 10^9/L	Treat on time
< 1.5 x 10^9/L	Or	< 100 x 10^9/L	No treatment

Dose Adjustments within a Treatment Cycle

In the event that patients have missed doses within a treatment cycle due to hematologic toxicities, those doses not given during a cycle will not be made up. Dose modifications due to

hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Table 3.

Table 3: Modification for Days 8 of Each Cycle

Day 8 Laboratory Results	Day 8 Album-bound paclitaxel	Day 8 Cisplatin	Day 8 Gemcitabine	Days 8 Paricalcitol
ANC > 1000 and Platelets ≥ 75,000	100%	100%	100%	100%
ANC 500-1000[a] or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	100%	Decrease dose by 1 level (treat on time)	100%
ANC < 500 or Platelets < 50,000	Hold	Hold	Hold	100%
Febrile Neutropenia (Grade 3 or 4)[b]	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Hold	Hold. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment	100%
Recurrent Febrile Neutropenia (Grade 3 or 4)	Decrease 2 dose levels (to 75 mg/m2) and do not re-escalate throughout the rest of treatment	Hold	Decrease 2 dose levels (to 600 mg/m2) and do not re-escalate throughout the rest of treatment.	100%

4.3.2.2 Non-hematological Toxicity

Dose reductions for non-hematologic toxicity that occur despite adequate background medical therapy should be undertaken in accordance with Table 5.

Table 4: Paclitaxel protein bound and gemcitabine and cisplatin - Dose Modifications for Day 1 of Each Cycle (Non hematologic Toxicity)*

Non Hematologic Toxicity and/or Dose Hold with Previous Cycle	
Toxicity/dose held	**Paclitaxel protein bound + gemcitabine + cisplatin dose this cycle**

Grade 0, 1 or 2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of paclitaxel protein bound and gemcitabine should be reduced to next lower dose level: please refer to Section 4.3.2.5**).** Note cisplatin should not be given unless creatinine is ≤ 1.5 mg/dl
Grade 3 toxicity[a,c]	Decrease paclitaxel protein bound and gemcitabine to next lower dose level[a] (see table 1)
Grade 4 toxicity	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease paclitaxel protein bound and gemcitabine to next lower dose level and continue throughout the rest of treatment

* Excluding peripheral neuropathy (section 4.3.2.3) and nephrotoxicity (section 4.3.2.4).

[a] If the toxicity only affects neuropathy, then only paclitaxel protein bound should be reduced (please see Section 4.3.2.3).

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.2.7).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

Table 5: Paclitaxel protein bound and gemcitabine and cisplatin Dose Modifications Day 8 of Each Cycle (Non hematological Toxicity)

CTC Grade	**Percent of Day 1 *paclitaxel protein bound* + gemcitabine + cisplatin Dose**
0-2	100%[a]
3+	Hold treatment until resolution to ≤ Grade 1 [b,c].

[a] Except for cutaneous toxicity: please refer to Section 4.3.2.5.

[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.3.3).

[c] Excluding electrolyte abnormalities per judgment of the physician/investigator.

Please note when one drug is discontinued then it will be a matter of patient situation and clinical judgement as to whether some or all of the other agents are discontinued.

4.3.2.3 Peripheral Neuropathy

Cisplatin and paclitaxel protein bound treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine and paricalcitol administration can continue during this period. Cisplatin may be resumed at the same dose and paclitaxel protein bound treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. The time to resolution to Grade ≤ 1 should be the adverse event duration used for adverse event reporting.

4.3.2.4 Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics (see Appendix D). The serum creatinine, BUN, creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy, and prior to each subsequent course. Cisplatin should not be given unless serum creatinine is ≤ 1.5.

4.3.2.5 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level as per Table 4. 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.

4.3.2.6 Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, all 4 study drugs should be withheld until resolution to ≤ Grade 1, then reinstituted at the next lower dose level as per Table 1.

4.3.3 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.
Interstitial Pneumonitis

Pulmonary toxicity has been reported for gemcitabine and paclitaxel. Epidemiology reports show that gemcitabine monotherapy is weakly associated with lung toxicity. A retrospective review [Meadors et al, 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 and Donnehouer 1995)]. Dyspnea with bronchospasm has been reported in 0.3 to 0.9%, with 30% of type 1 hypersensitivity reactions. Combination chemotherapy of gemcitabine and paclitaxel protein bound shows a higher incidence of this complication compared to either drug alone but the two are no more than additive [Von Hoff et al, 2013].

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. 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). Administration of study drugs will be permanently discontinued upon making a diagnosis of interstitial pneumonitis. (See Section below)

4.3.3.1 Prevention, Surveillance and Management of Interstitial Pneumonitis

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 and secondary pathogen coverage should be instituted without delay. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

4.3.4 Hypersensitivity Reactions

Hypersensitivity reactions are not usually expected with cisplatin, paclitaxel protein bound 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 the offending agent and aggressive symptomatic therapy. Patients who develop a severe hypersensitivity reaction should not be re-challenged.

4.3.5 Colony Stimulating Factors

Based on the ASCO guidelines [Smith 2015] for use of granulocyte colony stimulating factors, (G-CSF) for regimens with at least a 20% risk of febrile neutropenia, pegfilgrastim will be administered subcutaneously on day 9 of each treatment cycle. G-CSF may also 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. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

4.3.6 Prophylaxis against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5°C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily) or amoxicillin/clavulanate (Augmentin®, 500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts and to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. If hospitalization is required, please refer to Section 8.3 of this protocol to report the event as a Serious Adverse Event (SAE).

4.3.7 Intended Dose Delays

Intended cycles may be delayed for non-toxicity reasons for up to 14 days (for reasons such as scheduling conflicts), but only with documentation and explanation in the CRF after discussion with the study Principal Investigator.

5. CONCOMITANT THERAPY

5.1 Permitted Concomitant Therapy

Necessary supportive measures for optimal medical care may be given throughout the study, including IV antibiotics to treat infections, blood components, and antiemetics. Additional care will be administered as indicated by the treating physician and the patient's medical need. No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study. All concomitant medications and supportive therapy must be recorded on the appropriate CRF.

Routine prophylactic use of a granulocyte colony-stimulating factor (G-CSF) will be used according to the American Society of Clinical Oncology guidelines (Appendix E), on Day 9 of the 21 days cycle.

The use of erythropoietin stimulating agents (ESA) is permitted if clinically indicated.

5.2 Concomitant Therapies Requiring Caution

Cisplatin nephrotoxicity may be exacerbated by treatment with other nephrotoxic drugs (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs). Caution with use of other nephrotoxic drugs.

If anticoagulation with warfarin is necessary, frequent monitoring of prothrombin time and the International Normalized Ratio (INR) is recommended. Please see Appendix J for special precautions on the use of dexamethasone with concomitant fosaprepitant.

5.3 Prohibited Concomitant Therapy

No concomitant cytotoxic therapy, whether conventional or investigational, will be allowed during this study.

Immunosuppressive corticosteroid use is not permitted while enrolled in the study. Corticosteroids for treatment or prevention of nausea and vomiting, or to modulate symptoms from an event of suspected immunologic etiology are permitted. Inhaled (nasal or pulmonary), ophthalmic, topical steroids and local steroid injections are permitted.

The use of vitamins or supplements that have reported use for the treatment or prevention of cancer, or that may interact with any of the study medications is not permitted.

The use of medical marijuana (except FDA-approved therapy) in any formulation should be avoided while enrolled in this study.

The use of additional vitamin D supplements while receiving study-administered paricalcitol should be avoided unless the patient is vitamin D deficient.

6. STUDY ASSESSMENTS

6.1 Screening

1. Written informed consent
2. Complete medical history including concurrent baseline conditions (using NCI CTCAE version 4.0; Appendix F), prior cancer therapy (including documentation of prior surgery, adjuvant or neoadjuvant chemotherapy and radiotherapy).
3. Complete physical examination including height (cm) and weight (kg).
4. Karnofsky Performance Status (KPS) (see Appendix G).
5. Vital signs (blood pressure, pulse, respiratory rate, and temperature).
6. Computed tomography (CT) / magnetic resonance imaging (MRI) scan to document disease status (including chest, abdomen, pelvis, and other regions as clinically indicated. In addition, brain scan is required to exclude brain metastases if clinically indicated only). If a CT scan was taken within 28 days prior to first dose, a new scan is not necessary.
7. Electrocardiogram (ECG).
8. Hematology - Complete blood count (CBC) with differential and platelet count.
9. Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
10. PT/INR
11. CA19-9
12. Provide fecal sample collection kit and review instructions with patient for return of sample within 48 hours of the next scheduled visit
13. Urinalysis (lab); protein, specific gravity, glucose, and blood.
14. Serum pregnancy test (if applicable).
15. Concomitant medication notation (to include all medications taken within 30 days prior to enrollment).
16. Archived tumor tissue, if available, will be obtained for further profiling work.
17. Patient to complete MDASI-GI and BPI questionnaires

Once eligibility is confirmed, a patient ID will be assigned and will be used throughout the trial.

6.2 On Study Assessments

Patients must begin Cycle 1 within 21 days of signing the IRB approved informed consent document and after the screening assessments. Treatment will be administered by qualified and trained site personnel in a hospital, clinic, or other outpatient setting appropriate for chemotherapeutic infusions. All assessments should be performed within 72-hours of each specified time parameter, with the exception of Cycle 1 in which assessments must be conducted within 24 hours (except those noted), or if medical or scheduling conditions require a delay.

Day 1 of each cycle (except where noted)

1. Inclusion/exclusion review (Cycle 1 only)
2. Directed physical exam

3. Vital signs (blood pressure, pulse, respiratory rate, and temperature).
4. Measurement of weight (kg)
5. BSA calculation prior to dosing (After Cycle 1, the BSA only needs to be changed if there has been a change > 10% in body weight from Cycle 1 – Day 1
6. Karnofsky Performance Status (KPS) (see Appendix G)
7. Hematology: CBC with differential and platelet count
8. Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), parathyroid hormone (PTH) and electrolytes (chloride, sodium, potassium, and bicarbonate).
9. CA19-9
10. Blood sample for research for exploratory biomarkers
11. Urinalysis (lab); protein, specific gravity, glucose, and blood
12. Provide fecal sample collection kit and review instructions with patient for return of sample within 48 hours of the next scheduled visit.
13. Serum Pregnancy (if applicable)
14. AEs using the NCI CTCAE V4.0 (see Appendix F)
15. Concomitant medication notation
16. Patient to complete MDASI-GI and BPI questionnaires

Day 8 and 15 of each cycle

1. Directed physical exam
2. Vital signs (blood pressure, pulse, respiratory rate, and temperature).
3. Measurement of weight (kg)
4. Karnofsky Performance Status (KPS) (see Appendix G)
5. Hematology: CBC with differential and platelet count
6. Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
7. AEs using the NCI CTCAE Version 4.0 (see Appendix F)
8. Concomitant medication notation
9. Patient to complete MDASI-GI and BPI questionnaires

After Cycle 3, 6, 9 a CT/MRI scan to evaluate disease status using same imaging method as Baseline will be completed at the end of the cycle prior to starting the next cycle.

Note: In order to more precisely determine time to progression, the investigator is encouraged to obtain radiological assessments and CA19-9 values earlier if there is a strong clinical suspicion of disease progression. In order to either confirm or refute the clinical impression.

6.3 **End of Study**

The patient will continue on study until there is normalization of CA 19-9, evidence of clear cut tumor progression, has treatment ending toxicities, completion of 6 months of therapy, or withdraws from treatment. The following assessments will be performed 14-28 (+/- 2) days after completing the last dose of trial therapy:

1. Directed physical exam
2. Karnofsky Performance Status (KPS) (see Appendix G)
3. Vital signs
4. ECG
5. Hematology: CBC with differential and platelet count
6. Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
7. CA19-9
8. Blood sample for research for exploratory biomarkers
9. Urinalysis (lab); protein, specific gravity, glucose, and blood
10. Concomitant medication
11. AEs using the NCI CTCAE Version 4.0 (see Appendix F)
12. Patient to complete MDASI-GI and BPI questionnaires

If the patient goes to surgery, additional tissue will be obtained for further molecular analysis.

6.4 **Follow-Up Assessments**

Follow up assessments by telephone will be conducted for all patients or their families every 12 weeks to determine the date of death.

7. **EVALUATION OF RESPONSE**

7.1 **CT Imaging**

Tumors will be assessed at the established staging intervals by CT scan of the abdomen/pelvis and CT of chest or Chest X-ray (if clinically indicated). Magnetic Resonance Imaging (MRI) or Magnetic Resonance cholangiopancreatography (MRCP) will be performed as clinically indicated. Treatment response will be classified by the RECIST version 1.1 criteria (see Appendix C). In addition, tumors will be assessed for conversion of tumor from borderline resectable to resectable based on clinical judgement.

7.2 **3D Volumetric Measurement and Histogram Analysis**

Post contrast CT images of the abdomen will be transferred into 3DQI imaging software (MGH in-house 3D software). All thin reconstructed images will be uploaded into 3DQI workstation. Region of interest (ROI) will be drawn around tumor by using manual tool. Editing of ROI will be performed if needed. The pancreatic tumor based imaging biomarker will be defined by using the 3D QI software.

7.3 **Diffusion Weighted MRI Imaging**

A diffusion-weighted MRI of the abdomen will be performed by a commercially available 3.0 tesla MRI system with a coil combination as appropriate for patient body habitus. The protocol will include standard T1 and T2 weighted sequences, in and out of phase imaging, and pre- and post-contrast imaging with the standard gadolinium-based contrast agents used in abdominal

imaging. A power injector will be used for the intravenous administration of the contrast agent to ensure correct timing of the early arterial, late arterial/parenchymal and venous phase. Diffusion weighted imaging will also be performed. Apparent diffusion coefficient (ADC) maps will be generated by the console from the diffusion weighted imaging data. The ADC map will be used to determine the hyper cellular/malignant portions of the tumor. Tumor response assessments will be made based on the anatomic and functional comparison of the tumors before and after therapy. MRI's per physician discretion.

7.4 **Biochemical Testing**

CA19-9 will be evaluated serially in all patients with documented elevated CA19-9 at initial screening.

7.5 **Exploratory Biomarkers**

At Screening, individuals with core or fine needle aspirate (FNA) biopsies obtained previously will be obtained by the investigator's site for further exploratory analysis if available. Up to a total of 7 micron slice slides will be obtained or a cellular block of tumor tissue. Future analysis will include PD-1, interferon gamma, and other immunological assays along with those that will assess for sensitivity to DNA repair targeted therapy. The sites may send the unstained core samples to HonorHealth to be stored at room temperature and will be analyzed at a later date.

On Day 1 of every cycle, 20 mLs of blood will be collected for exploratory biomarker analyses until the patient stops participating in the study. These research samples will be stored for exploratory biomarker testing to be determined and conducted at a later date. A research sample will also be collected at the End of Study visit. In addition, patients will be asked to consent to long term storage and future exploratory research testing for any left-over biospecimens collected during the study including archived tissue samples, blood samples and/or urine.

7.6 **16S Gut Microbiome rRNA Analysis**

The bacterial communities living in and on our bodies interact with our epithelial cells and can influence adaptive immunity, metabolic functions, and inflammation at a local and systemic level. The gut microbiota has been particularly well-studied and regulates the barrier functions of the gut epithelium, prevents pathogen or pathobiont overgrowth, facilitates metabolism of dietary fibers, and regulates metabolism. The gut microbiota may also influence the initiation, progression, and treatment of cancer including pancreatic [Ertz-Archambault et al 2017]. Monitoring the microbiota in patients may enhance our ability to predict the likelihood of a positive patient response to therapy as well as indicators of adverse treatment effects and sensitive metrics of general patient health [Chaput et al 2017]. Given the possibility of altering the microbiome of a patient, future research is likely to include manipulating microbiotic communities to maximize the effectiveness of other therapies.

Fecal samples are relatively easy to collect and non-invasive. They provide an indication of the gut microbiome which may be an indicator of general health, impact drug availability, and indicate the presence of communities associated with inflammation, digestive inefficiencies, and pathogens. Monitoring the gut microbiome may allow us to predict the risk of any possible side effects.

7.7 **Survival**

PFS will be calculated only in patients who underwent resection, from the date of cytologic or histologic diagnosis until the date of recurrence or the last date at which the patient was known to be free of disease. OS will be calculated from the date of cytologic or histologic diagnosis until the date of death or last contact.

OS and PFS will be calculated on all treated patients. Patients without disease progression at 5 years will be censored at that time. Patients lost to follow-up without documented disease progression will be censored at the time of last contact. This is also true of patients discontinuing due to toxicity. Patients undergoing post-study therapeutic surgery/resection or radiation prior to progression will be censored at the initiation of that therapy if all macroscopic evidence of the tumor was resected. The date of progression will be the earlier of the dates of progression determined by CT or MRI imaging (increased lesion size, new metastases, new arterial/venous involvement) and rising CA19-9.

7.8 **Non-Evaluable**

A patient who completes at least 1 cycle of therapy will be deemed evaluable. Any patient deemed non-evaluable will be replaced.

8. **SAFETY**

8.1 **Background**

These AE management guidelines are intended to ensure the safety of each patient while attempting to characterize the safety and tolerability of the study drugs and procedures. In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for prompt notification of SAEs to the appropriate regulatory authorities.

Adverse events occurring during the study will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (see http://ctep.info.nih.gov/reporting/ctc.html), where applicable. The Investigator should evaluate all AEs and should make an immediate effort to determine their etiology. Non-serious AEs that are determined not to be possibly, probably, or definitely related to study drug may not require further evaluation but will need to be recorded in the patient's source document (e.g., patient hospital records, patient clinic charts, and laboratory reports). Grade 3 and 4 AEs must be recorded on the CRF. All SAEs without regard to causality must be promptly reported (within 24 hours of knowledge of their occurrence) to HonorHealth Research Institute. Study medications may be interrupted for an AE at the discretion of the Investigator. Patients requiring toxicity management should be assessed and evaluated at least weekly as indicated by the severity of the event. AEs occurring following the signature of the informed consent, but prior to the first dose of study drug, will not be reported as AEs.

8.2 **DEFINITION OF AN ADVERSE EVENT**

An AE is any unfavorable medical occurrence in a patient receiving a marketed pharmaceutical product or in a patient who is participating in a clinical trial who is receiving an investigational or non-investigational pharmaceutical agent. The AE does not necessarily have a causal

relationship with the patient's treatment. Therefore, an AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. In cancer clinical trials, many AEs are in fact related to progression of the patient's underlying malignancy.

An AE includes:

- an exacerbation of a pre-existing illness;
- an increase in frequency or intensity of a pre-existing episodic event or condition;
- a condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;
- continuously persistent disease or symptoms that were present at baseline and worsen following the start of the study.

An AE does not include:

- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); however, the condition that leads to the procedure is an AE. [Procedures that occur during the trial should be recorded on the Concurrent Procedure CRF];
- pre-existing diseases, conditions, or laboratory abnormalities present or detected at the start of the study that do not worsen;
- hospitalizations or procedures that are done for elective purposes not related to an untoward medical occurrence (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
- the disease being studied or signs/symptoms associated with the disease unless more severe than expected for the patient's condition;
- overdose of study drug without any clinical signs or symptoms.

8.3 DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

An SAE is defined as any untoward medical occurrence at any dose that:

- is fatal;
- is life-threatening (defined as an immediate risk of death from the event as it occurred);
- results in persistent or significant disability or incapacity;
- requires in-patient hospitalization or prolongs an existing hospitalization. (Exception: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an SAE. NOTE: Complications that occur during hospitalization are AEs and if a complication prolongs hospitalization, then the event is serious);
- is a congenital anomaly/birth defect in the offspring of a patient who received medication;
- is a condition not included in the above definitions that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above unless clearly related to the patient's underlying disease.

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

8.4 ADVERSE EVENT SEVERITY

Adverse events occurring during the study will be graded according to the NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (see http://ctep.info.nih.gov/reporting/ctc.html), where applicable (see Appendix F).

- Grade 1 – Mild AE
- Grade 2 – Moderate AE
- Grade 3 – Severe AE
- Grade 4 – Life-threatening or disabling AE
- Grade 5 – Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on patient/event outcome at the time of the event. For example, the NCI CTCAE grade 4 (life-threatening or disabling AE) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

8.5 CAUSALITY ASSESSMENT

The relationship of an AE to the study drug must be classified as one of the following:
Unrelated: The AE is clearly not related to the study medication
Possibly Related: The AE may be related to the study medication
Definitely Related: The AE is clearly related to the study medication

8.6 SAFETY AND TOLERANCE ANALYSIS

The incidence of all AEs (regardless of causality) and all treatment-related AEs (those AEs thought to be possibly, probably, or definitely related to study drug) will be summarized by NCI CTCAE Version 4.0 term and maximum grade. The incidence of SAEs and AEs that lead to discontinuation of study drug will also be summarized. Listings of patients who discontinue study drug due to an AE and patients with SAEs and deaths will be presented. Narratives will be provided for patients who experience an SAE.
Lack of Efficacy is Not Considered an AE or SAE
“Lack of efficacy” (progressive disease) is not considered an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy should be reported if they fulfill the AE or SAE definitions.

8.7 PATIENT REPORTING OF AES AND SAES

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

Have you had any (other) medical problems since your last clinic visit?
Have you taken any new prescribed or over-the-counter medicines or herbal/vitamin preparations, other than those given to you in this study, since your last visit/assessment?
Have any new procedures been performed since your last study visit?

8.8 INVESTIGATOR REPORTING OF AES AND SAES

The Investigator is responsible for recording, reporting and following all Grade 3 or 4 AEs, regardless of causality, observed during the study period, starting with initial dose of study drug and ending at the time the patient goes off study or 30 days after patient's last dose of study drug, whichever is later. The Investigator should follow AEs until the event is resolved or stabilized, the patient is lost to follow-up, or the event is otherwise explained. Events occurring within 30 days prior to study drug administration should be recorded as pre-treatment signs and symptoms. The only exception to this is for an AE that occurs prior to the first dose of study drug but is due to a procedure associated with assessments carried out to determine eligibility or to permit participation in this protocol – this should be recorded as an AE (rather than a pre-treatment sign or symptom).

The Investigator or designee must completely and promptly record each AE in the source documentation, regardless of relationship to study drug as determined by the Investigator. Grade 3 and 4 AEs must be recorded in the CRF. The Investigator must assess AE/SAE causality for any patients treated at his/her site and for any patients treated under the direct care of his/her sub-Investigators. The Investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Clinically significant laboratory abnormalities present at the baseline visit will be recorded as pre-treatment signs and symptoms.

Grade 3 and 4 adverse events and SAEs should be reported on the appropriate case report forms. In addition, all SAEs must be reported promptly to HonorHealth Research Institute after the Investigator recognizes/classifies the event as a SAE. The specific reporting time frame depends on the type of SAE. For life-threatening or fatal events, the Investigator must report initial information on the SAE within 1 business day (24 hours) of becoming aware of the event, preferably by fax or alternatively by email on the HonorHealth Research Institute Reporting Form. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report. For an event that is not life-threatening or fatal, the Investigator must fax or email a completed SAE report form within 2 business days after he/she recognizes/classifies the event as an SAE.

The Grade 3 or 4 AE or SAE initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study drugs. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on the Follow-Up AE/SAE HonorHealth Research Institute Reporting Form. A final report to document resolution of the SAE is required. The Study protocol number and the institutional protocol number should be included on SAE reports to HonorHealth Research Institute. A copy of the fax transmission confirmation of the SAE report (or on the fax cover letter) sent to HonorHealth Research Institute should be attached to the SAE and retained with the patient records.

The Investigator should follow all AEs/SAEs observed from initial dosing up to 28 days after the last study drug administration until they resolve or stabilize, the patient is lost to follow-up, or the events are otherwise explained.

8.9 IRB Notification of SAEs

The Investigator is responsible for promptly notifying the IRB of all SAEs, including any follow-up information, occurring at his/her site and any SAE regulatory reports and Investigational New Drug Safety Reports that he/she receives from HonorHealth Drug Safety.

8.10 SAE Follow-Up

For all SAEs occurring after first dose of study medication or within 30 days of the last administration of study medication, the investigator must submit follow-up reports to HonorHealth or its representative regarding the status of the SAE and the patient's subsequent course until the SAE has subsided, or until the condition stabilizes (in the case of persistent impairment), the patient receives alternative therapy, or the patient dies.

8.11 Sponsor Notification of Post-Study SAEs

The Investigator should notify HonorHealth of any death or SAE occurring after a patient has withdrawn from the study, or after 30 days of the last study drug dose, whichever is later, when such death or SAE may reasonably be related to the medication used in the study. However, Investigators are not obligated to actively seek AEs in former study participants.

8.12 Pregnancy

While not considered a SAE unless a serious criterion is met, pregnancies occurring in patients enrolled on the study or in their partners must be reported. The investigator should complete the pregnancy report form and fax it to Honor Health within 24 hours of knowledge of the pregnancy.

9. STATISTICS

9.1 Treatment Assignment

This is a Phase II open-label study with the identity of the treatment known to patients and investigators.

9.2 Patient Disposition

Summaries of patient disposition will include:

- Patient discontinuation from treatment.
- Patient discontinuation from study
- Overall qualification status of all patients.

All patients enrolled in the study will be included in the summation. The safety population will include all patients who have received at least one dose of any study drug. The number of

patients who do not qualify for analysis, who die or discontinue before treatment begins, will be summarized.

9.3 Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics
- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments

Other patient characteristics will be summarized as appropriate.

9.4 Statistical Considerations

The trial is a two-arm phase 2 study to design and assess a new treatment regimen. In total, 24 patients with confirmed resectable will be enrolled in one arm and those with borderline resectable and locally advanced (unresectable) pancreatic ductal adenocarcinoma will be enrolled in the other arm. Patients will be stratified into one of two groups. Initial within-group comparisons will be conducted across patient characteristics. Two-tailed t tests or ANOVA tests will be conducted for parametric continuous variables. Non-parametric continuous variables will be compared using the Mann-Whitney U or Kruskal-Wallis tests. Pearson's chi-squares test will be used to compare categorical data across treatment groups.

As primary objectives, the rates normalization of CA19-9 in patients will be assessed. Secondary objectives include resectability rates (R0) following neoadjuvant chemotherapy and pathologic complete response rates (CR) will be evaluated using the RECIST criteria (Response Evaluation Criteria in Solid Tumors, see appendix C).

Patients will be classified as CA19-9 non-responders if CA19-9 variation is < 50%; minor responders if CA19-9 variation is between 50 and 89%; and major responders if CA19-9 variation is > 89% [Reni et al, 2009]. Overall survival will be calculated from the date of diagnosis until the date of death or last contact. For those who undergo resection, time to progression will be calculated from the date of cytologic or histologic diagnosis until the date of recurrence or the last date the patient was known to be free from disease. The Kaplan-Meier method will be selected to generate survival curves by clinical characteristics. Employing the log-rank test, researchers will assess differences between survival curves. Follow-up time is measured from time of diagnosis and the median will be calculated for all patients who survived since the time of last follow-up. Statistical tests are two-tailed, with a significance level of an alpha of 0.05. SPSS software version 24.0 will be used for all statistical analyses.

10. ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 Ethics

10.1.1 Institutional Review Board/ Ethics Committee Approval

Before study initiation, this protocol and informed consent form will be submitted for review and approval to the IRBs charged with oversight for the clinical sites. In addition, any form of proposed advertising and advertising text for patient recruitment must be reviewed and approved by HonorHealth prior to submission to the IRB. The Investigator will forward to HonorHealth or Sponsor-nominated designee a copy of the IRB's approval of this protocol, any amendments, informed consent form, and any modifications to the informed consent, based on the FDA regulations set forth in 21 CFR 56 of the Code of Federal Regulations, as well as those of the applicable regulatory bodies in all other participating countries outside of the U.S. In addition, the Investigator will be responsible for forwarding to HonorHealth or Sponsor-nominated designee a description of the IRB board members (including profession and affiliation) or a United States (US) Department of Health and Human Services (DHHS) General Assurance number and expiration date. If neither of these is available, the chairperson must submit a statement indicating that the members of the board responsible for the review meet FDA and other appropriate regulatory requirements. In addition, the labeling for all approved study drugs should be submitted to the IRB for informational purposes.

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

10.1.2 Ethical Conduct of the Study

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

10.2 **Informed Consent**

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

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

Changes made by a participating site to the recommended informed consent must be must be forwarded to HonorHealth for approval prior to submission to the corresponding IRB. A copy of the signed informed consent will be given to the patient or their legal representative and a copy must be retained in the Investigator's study records.

10.3 **Data Safety and Monitoring**

This treatment regimen combines 3 chemotherapeutic agents with known toxicity profiles. Because cancer is a life-threatening disease, treatments that result in Grade 3 and 4 toxicities

are considered to have an acceptable risk profile. Data reported to HonorHealth Research Institute will be received by the Lead Principal Investigator on a regular basis and not less than once a month. In addition, SAEs will be reported to HonorHealth immediately and reviewed as they are received. Any unacceptable toxicities or severe toxicities that occur more frequently than expected will be discussed by the study Principal Investigator who will decide jointly whether the study should be modified, interrupted, or stopped. A monthly conference call will be held with investigators participating in the study. The statistical group will provide listings of toxicities on a regular basis.

10.4 **Study Data Monitoring Plan**

HonorHealth ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an investigator meeting, all aspects of the study are reviewed with the Investigator and the staff. Prior to enrolling patients into the study, a HonorHealth representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and study team as well as any appropriate communications by mail, email, fax, or telephone.

Data monitoring procedures will be carried out by HonorHealth for all participating sites, and will be performed on a regular basis to comply with Good Clinical Practice guidelines.
Review of the case report forms, cross-reference with source documentation (including radiology review), review of study related regulatory documents and logs (e.g., enrollment, study site staff, drug accountability), and review of drug accountability will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the site monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The site Clinical Research Coordinator responsible for the study will be provided with a copy of the written monitoring notes for resolution of the findings.

The HonorHealth site monitor will complete a written monitoring report and forward it to the site Principal Investigator and to HonorHealth Administration. The report will include a summary of what the site monitor reviewed and the site monitor’s statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to HonorHealth Administration and the HonorHealth site monitor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site monitor’s study file at HonorHealth for follow-up at the next monitoring session.

10.5 **Data Safety and Monitoring Committee**

This study will not utilize the services of a Data Safety and Monitoring Committee

10.6 **Confidentiality**

The Investigator and any other study personnel involved in this study shall not disclose, or use for any purposes (other than for the performance of this study), any data, records, or other

information (hereinafter collectively “information”) disclosed to the Investigator or other study personnel. Such information shall remain the confidential and proprietary property of HonorHealth, and shall be disclosed only to the Investigator or other designated study personnel.

The obligation of non-disclosure shall not apply to the following:

- relevant disclosure to potential study participants for the purpose of obtaining informed consent;
- information after such time that it is or becomes publicly available through no fault of the Investigator or other study personnel; and
- information after such time that it is disclosed to the Investigator by a third party entitled to disclose such information.
- If the study site is a ‘covered site’ under the definitions of the Health Insurance Portability and Accounting Act (HIPAA), the Investigator will ensure that the patient consents to the use of data by HonorHealth and its designees for the purposes of regulatory submissions, study publications, and drug approval.

10.7 **Publication**

The Investigator(s) shall have the right, consistent with academic standards and with due regard to the protection of HonorHealth confidential information and intellectual property, to publish or present the results of work performed in accordance with the study; provided that any proposed publication or presentation is first reviewed and approved in writing by HonorHealth shall complete its review within 60 days after receipt of the proposed publication or presentation. Upon HonorHealth request, proposed publication or presentation will be delayed up to 60 additional days to enable HonorHealth to secure adequate intellectual property protection of property of HonorHealth that would be affected by such proposed publication or presentation. If HonorHealth believes in good faith that any proposed publication or presentation contains any confidential information and/or intellectual property HonorHealth shall have the right to remove references to any such confidential information and/or intellectual property.

10.8 **Protocol Compliance**

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from HonorHealth, in addition to written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to HonorHealth and the regulatory authority(ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

10.9 **Quality Assurance**

All aspects of the study will be carefully monitored by HonorHealth and/or its authorized representative for compliance with applicable government regulations with respect to current ICH GCP guidelines as well as other applicable regulations and guidelines.

10.10 On-site Audits

Regulatory authorities, the IEC/IRB, and/or HonorHealth may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10.11 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the Lead Principal Investigator or HonorHealth there is sufficient reasonable cause.

HonorHealth has the right to discontinue the study under the conditions specified in the clinical Trials agreement. Written notification documenting the reason for study termination will be provided to the site investigator by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to HonorHealth.

10.12 Investigator Documentation

10.12.1 Form FDA 1572

As this study has been determined to be IND Exempt and this is not a multi-center study, a 1572 will not be completed.

10.12.2 Curriculum Vitae

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

10.12.3 Financial Disclosures

As a 1572 will not be completed for this study, Financial Disclosure forms will not be required or collected.

10.13 Laboratory Certification and Normal Ranges

The Investigator will provide a copy of all clinical laboratory certifications, certification numbers, dates of certifications, and a list of the normal ranges for all laboratory tests for all facilities

listed. Updated versions of these documents must be provided to HonorHealth as appropriate. In the event the clinical laboratory is changed during the study, the study Principal Investigator will be notified. Appropriate documentation will be submitted to HonorHealth to verify the certification of the new laboratory.

All radiology facilities being utilized outside the investigative site must be pre-approved by HonorHealth.

10.14 Records Retention

In accordance with applicable regulatory requirements, following closure of the study, the Investigator will maintain a copy of all site study records in a safe and secure location. HonorHealth will inform the Investigator of the time period for retaining these records in order to comply with applicable regulatory requirements.

HonorHealth reserves the right to terminate the study for refusal of the Investigator and/or investigational site to comply with any requirements stated in this study protocol.

10.15 Protocol Deviations

Deviations from the protocol must be addressed as protocol amendments with IRB approval required prior to implementation. Apart from the regulatory requirements, it is vital to the success of the study that the Investigator adheres to the details of the protocol and thus holds to a minimum the number of cases that may be later classified as “incomplete,” “unusable,” or “not evaluable.”

11. DATA MANAGEMENT

11.1 Patient Enrollment Instructions

Patients must be registered within 5 working days prior to initiation of protocol therapy. This study uses a web based patient enrollment system for data submission through the data management services of HonorHealth Patient enrollment materials.

11.2 Data Submission Instructions

This study uses a electronic data capture system for data submission through the data management services of HonorHealth. The original reports, traces and films must be retained by the Investigators for future reference.

- Screening Form: at time of screening
- Enrollment Form: after eligibility confirmed.
- All screening/baseline/treatment/off-treatment Forms: within 2 weeks of occurrence.
- Adverse Event Form: within 2 weeks of each scheduled adverse events evaluation until adverse events have resolved following permanent discontinuation of treatment, documenting adverse event information, including toxicities indicated by lab testing.

NOTE: all Serious Adverse Events must also be reported on the Adverse Event Form.

Serious Adverse Events (SAE) documentation: submit directly to HonorHealth and the Site Principal Investigator within the time frame and per the guidelines specified in Section 8.8.

NOTE: all SAEs must also be reported on the Adverse Event Form.

Notice of Death Form: within 2 weeks of knowledge of death.

12. **TERMINATION OF STUDY**

HonorHealth reserves the right to discontinue this study at any time.

13. **INVESTIGATOR'S PROTOCOL AGREEMENT**

The Investigator must sign the Investigator's Protocol Agreement (Page 3 of this document). The original must be kept on file at HonorHealth and the Investigator must retain a copy. The completed Investigator's Protocol Agreement signifies agreement to comply with all procedures outlined by this protocol by the Investigator. An Investigator's Protocol Agreement must be signed if and when a protocol amendment is issued by HonorHealth.

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15. SCHEDULE OF EVENTS

Assessments	Screening	Cycle 21 days				End of Cycle (EOC)/ End of Treatment (EOT)[11]	Survival FU
		Day 1	Day 8	Day 9	Day 15		
	Day-21	± 3 days	± 3 days	± 3 days	± 3 days	± 2 days	± 7 days
Signed Informed Consent	X						
Review Inclusion/Exclusion Criteria	X	X[10]					
Medical History	X	X					
Directed Physical Exam[1]	X	X	X		X	X	
Height (cm)	X						
Weight (kg)	X	X	X		X	X	
BSA Calculation		X					
Vital Signs[2]	X	X	X	X	X	X	
Karnofsky PS	X	X	X		X	X	
CT/MRI/Tumor Measurements	X[12]					X[9]	
ECG	X					X	
Hematology[3]	X	X	X		X	X	
Serum Chemistries[4]	X	X	X		X	X	
CA19-9	X	X				X	
Biomarker Blood Sample		X				X	
Fecal Sample Collection	X[13]	X[13]					
PT/INR	X						
Urinalysis[5]	X	X				X	
Serum Pregnancy[6]	X	X					
Con Meds	X	X	X	X	X	X	
Adverse Events		X	X	X	X	X	
Subject Questionnaires[7]	X	X	X		X	X	
Paclitaxel protein bound		X	X				
Cisplatin		X	X				
Gemcitabine		X	X				
Paricalcitol		X	X				
Pre-cisplatin hydration		X	X				
Post-cisplatin hydration		X	X				
Neulasta				X			
Telephone Call							X[8]

1. Complete Physical Exam completed on Day 1
2. Blood pressure, pulse, respiratory rate and temperature
3. Includes CBC with differential and platelet count
4. Includes blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate. Parathyroid hormone (PTH) levels will be checked on D1 of every cycle.
5. Includes protein, specific gravity, glucose, and blood
6. For women of child bearing potential
7. Includes MDASI-GI and BPI questionnaires
8. every 12 weeks until confirmation of death
9. Only at the end of Cycles 3, 6 and 9
10. Cycle 1 only
11. EOT assessments to be completed within 14-28 days from the last dose of medication
12. If a CT scan was completed within 28 days of the first dose, does not need to be repeated.
13. To be returned to site within 48 hours of collection.

16. **APPENDICES**

APPENDIX A: ABBREVIATIONS

ADR	**Adverse Drug Reaction**
AE	**Adverse Event**
ALT (SGPT)	**Alanine Aminotransferase (SGPT)**
ANC	**Absolute Neutrophil Count**
AST (SGOT)	**Aspartate Aminotransferase (SGOT)**
AUC	**Area Under the Curve**
β-hCG	**Beta subunit of human chorionic gonadotrophin (hCG)**
BMS	**Bristol-Myers Squibb**
BSA	**Body Surface Area**
BUN	**Blood Urea Nitrogen**
CA19-9	**Carbohydrate Antigen 19-9**
CBC	**Complete Blood Count**
CFR	**Code of Federal Regulations**
CI	**Confidence Interval**
CIB	**Clinical Investigator's Brochure**
CMH	**Cochran-Mantel-Haenszel**
CrEL	**Cremophor-EL**
CRF	**Case Report Form**
CR	**Complete Response**
CRO	**Contract Research Organization**
CT	**Computed Tomography**
CTCAE	**Common Terminology Criteria for Adverse Events**
DHHS	**Department of Health and Human Services**
DLT	**Dose Limiting Toxicity**
DVT	**Deep Vein Thrombosis**
ECG	**Electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
EPR	**Enhanced Permeability and Retention**
EORTC	**European Organization for Research and Treatment of Cancer**
EOS	**End of Study**
FDA	**Food and Drug Administration**
GCP	**Good Clinical Practice(s)**
G-CSF	**Granulocyte Colony-Stimulating Factor**
GFR	**Glomerular Filtration Rate**
GTX	**Gemzar® plus Taxotere® plus Xeloda®**
HA	**Human Albumin**
Hgb	**Hemoglobin**
ICH	**International Conference on Harmonisation**
IND	**Investigational New Drug**
IRB	**Institutional Review Board**
IV	**Intravenous(ly)**
KPS	**Karnofsky Performance Status**
LDH	**Lactate Dehydrogenase**
MR	**Minor Response**
MRI	**Magnetic Resonance Imaging**

MTD	**Maximum Tolerated Dose**
NCI	**National Cancer Institute**
ND	**Not Done**
NIH	**National Institutes of Health**
non-DEHP	**Non-(di(2-ethylhexyl) phthalate)**
PD	**Progressive Disease**
PET	**Positron-Emission Tomography**
PK	**Pharmacokinetics**
PR	**Partial Response**
PT	**Prothrombin Time**
PTT	**Partial Thromboplastin Time**
RECIST	**Response Evaluation Criteria in Solid Tumors**
SAE	**Serious Adverse Event**
SD	**Stable Disease**
S.D.	**Standard Deviation**
SGOT	**Serum Glutamate Oxaloacetic Transaminase**
SGPT	**Serum Glutamate Pyruvic Transaminase**
SOP	**Standard Operating Procedure**
SPARC	**Secreted Protein Acidic and Rich in Cysteine (a glycoprotein)**
SUV	**Standard Uptake Value**
ULN	**Upper Limit of Normal**
US	**United States**
WBC	**White Blood Cell**
WHO	**World Health Organization**

APPENDIX B: PATHOLOGY REPORT

Provide a copy of the pathology report, surgical operative note with the following form completed. Please follow the AJCC staging system, 7th edition1.

1. Margin status Per Frozen Section Diagnosis
    a. R0 resection (margin negative)
    b. R1 resection (margin positive)
    c. R2 grossly positive

2. The tumor sample has (Ref: Evans DB et al2)
    a. No tumor destruction
    b. Grade I: 1-9 % of tumor destruction
    c. Grade II: 10-90% of tumor destruction
    d. Grade III: > 90% of tumor destruction.
    e. Grade IV: absence of viable tumor cells.

3. TNM staging - Primary Tumor (T)
    a. TX Primary tumor cannot be assessed
    b. T0 No evidence of primary tumor
    c. Tis Carcinoma in situ
    d. T1 Tumor limited to the pancreas, 2 cm or less in greater dimension
    e. T2 Tumor limited to the pancreas, more than 2 cm in greatest dimension
    f. T3 Tumor extends beyond the pancreas but without involvement of the celiac axis or superior mesenteric arterya
    g. T4 Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor

    *For T3, extension beyond the pancreas may include invasion of soft tissues adjacent to the pancreas, the extrapancreatic biliary system, and/or duodenum (including the ampulla of Vater). Specifically, peripancreatic tissues include the surrounding retroperitoneal fat (retoperitoneal soft tissue), including mesentery (mesenteric fat), mesocolon, greater and lesser omentum, and peritoneum.

4. Regional Lymph Nodes (N)
    a. NX Regional lymph nodes cannot be assessed
    b. N0 No regional lymph node metastasis Total number of lymph nodes harvested _____
    c. N1 Regional lymph node metastasis

5. Distant Metastasis (M)
    a. M0 No distant metastasis
    b. M1 Distant metastasis

APPENDIX C: RECIST TARGET LESION RESPONSE CRITERIA [EISENHAUR ET AL, 2009].

RECIST Target Lesion Response Criteria v1.1	
Target Response Criteria	Definition
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

APPENDIX D: STUDY DRUG PREPARATION, DOSING, ADMINISTRATION AND STORAGE

See links below to website access

Paclitaxel protein bound (Abraxane™) Prescribing Information (Updated 7/2015) – Accessed via Abraxane Website: http://www.abraxane.com/wp-content/uploads/Abraxane_Prescribing_Information.pdf

Gemcitabine (Gemzar™) Prescribing Information (Updated 6/2014) – Accessed via Gemzar Website: http://pi.lilly.com/us/gemzar.pdf

Cisplatin (Platinol®) Prescribing Information (updated 9/2010) – Accessed Cisplatin FDA website http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018057s080lbl.pdf

Paricalcitol (Zemplar®) Prescribing Information (10/2016) – Accessed via Zemplar Website http://www.zemplar.com/

APPENDIX E: 2006 UPDATE OF ASCO PRACTICE GUIDELINE RECOMMENDATIONS FOR THE USE OF WHITE BLOOD CELL GROWTH FACTORS: GUIDELINE SUMMARY

Setting/Indication	Recommendation
Primary prophylaxis	Primary prophylaxis is recommended for the prevention of FN in patients who have a high risk of FN based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. For “dose-dense” regimens, CSF is required and recommended. Clinical Trial data support the use of CSF when the risk of FN is in the range of 20% or higher.
Primary prophylaxis: Special circumstances	Certain clinical factors predispose to increased complications from prolonged neutropenia, including: patient age > 65 years; poor performance status; previous episodes of FN; extensive prior treatment including large radiation ports; administration of combined chemoradiotherapy; bone marrow involvement by tumor-producing cytopenias; poor nutritional status; the presence of open wounds or active infections; more advanced cancer, as well as other serious comorbidities. In such situations, primary prophylaxis with CSF is often appropriate, even with regimens with FN rates of < 20%.
Secondary prophylaxis	Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose may compromise disease-free or overall survival or treatment outcome. In many clinical situations, dose reduction or delay may be a reasonable alternative.
Therapeutic use: Afebrile neutropenia	CSF should not be routinely used for patients with neutropenia who are afebrile.
Therapeutic use: Febrile neutropenia	CSF should not be routinely used as adjunctive treatment with antibiotic therapy for patients with fever and neutropenia. However, CSF should be considered in patients with fever and neutropenia who are at high-risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected prolonged (> 10 days) and profound (< 0.1 × 109/L) neutropenia, age > 65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever.
Dose intensity/density of chemotherapy	Dose-dense regimens should only be used within an appropriately designed clinical Trial or if supported by convincing efficacy data.

Setting/Indication	Recommendation
Adjuncts to progenitor-cell transplantation	Administration of CSF to mobilize PBPC often in conjunction with chemotherapy, and their administration after autologous, but not allogeneic, PBPC transplantation is the current standard of care.
AML: Initial or repeat induction chemotherapy	CSF use following initial induction therapy is reasonable, though there has been no favorable impact on remission rate, remission duration, or survival. Patients > 55 years of age may be most likely to benefit from CSF use.
AML: CSF for priming effects	Use of CSF for priming effects is not recommended.
AML: Consolidation chemotherapy	CSF use can be recommended after the completion of consolidation chemotherapy because of the potential to decrease the incidence of infection and eliminate the likelihood of hospitalization in some patients receiving intensive postremission chemotherapy. There seems to be more profound shortening of the duration of neutropenia after consolidation chemotherapy for patients with AML in remission than for patients receiving initial induction therapy. As yet there is no information about the effect of longer-acting pegylated CSFs in patients with myeloid leukemias, and they should not be used in such patients outside of clinical Trials.
MDS	Intermittent administration of CSF may be considered in a subset of patients with severe neutropenia and recurrent infection.
ALL	CSF administration is recommended after the completion of the initial first few days of chemotherapy of the initial induction or first postremission course, thus shortening the duration of neutropenia of < 1,000/mm^3 by approximately 1 week.
Acute leukemia in relapse	CSF should be used judiciously, or not at all, in patients with refractory or relapsed myeloid leukemia since the expected benefit is only a few days of shortened neutropenia.
Radiotherapy ± chemotherapy	CSF should be avoided in patients receiving concomitant chemotherapy and radiation therapy, particularly involving the mediastinum. In the absence of chemotherapy, therapeutic use of CSF may be considered in patients receiving radiation therapy alone if prolonged delays secondary to neutropenia are expected.
Older patients	Prophylactic CSF for patients aged ≥ 65 years with lymphoma treated with curative chemotherapy (CHOP or more aggressive regimens) should be given to reduce the incidence of FN and infections.
Pediatric patients	As in adults, the use of G-CSF is reasonable for the primary prophylaxis of pediatric patients with a likelihood of FN. Similarly,

Setting/Indication	Recommendation
	the use of G-CSF for secondary prophylaxis or for therapy should be limited to high-risk patients. However, the potential risk for secondary myeloid leukemia or myelodysplastic syndrome associated with G-CSF represents a concern in children with ALL whose prognosis is otherwise excellent. For these reasons, the specific use of G-CSF in children with ALL should be considered carefully.
Comparative clinical activity of G-CSF and GM-CSF	No guideline recommendation can be made regarding the equivalency of the two colony-stimulating agents. Further Trials are recommended to study the comparative clinical activity, toxicity, and cost-effectiveness of GCSF and GM-CSF.
Treatment for radiation injury	Current recommendations for the management of patients exposed to lethal doses of total-body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs, includes the prompt administration of CSF or pegylated G-CSF.

Abbreviations: CSF, colony-stimulating factors; FN, febrile neutropenia; PBPC, peripheral-blood progenitor cell; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphocytic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, filgrastim; GM-CSF, sargramostim; pegylated G-CSF, pegfilgrastim.

APPENDIX F: REVISED NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE), VERSION 4.0 (PUBLISHED 28 MAY 2009)

Revised National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0 (published 28 May 2009)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 can be viewed on-line at the following NCI web site:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX G: KARNOFSKY PERFORMANCE STATUS

Karnofsky Performance Status		
	Score	**Descriptions**
Able to carry on normal activity and to work; no special care needed.	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
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activities or to do active work
	60	Requires occasional assistance, but is able to care for most of personal needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled: requires special care and assistance
	30	Severely disabled: hospital admission is indicated although death not imminent
	20	Very sick: hospital admission necessary; active supportive treatment needed
	10	Moribund: fatal processes are progressing rapidly
	0	Dead

APPENDIX H: MEMO FOR DEXAMETHASONE DOSE REDUCTION WITH CONCOMITANT ADMINISTRATION OF FOSAPREPITANT

The current protocol recommends the following prophylactic medication regimen:

> *Aloxi (palonosetron) 0.25mg IV,* ***Emend (fosaprepitant) 150 mg IV and dexamethasone 20mg IV*** *within 30 minutes prior to treatment on days 1 and 8, repeated every 21 days. Patients will continue oral antiemetic prophylaxis at home with ondansetron 8mg bid and dexamethasone 4mg bid for 2 days after chemotherapy.*

Fosaprepitant is a moderate inhibitor of CYP3A4, resulting in an increased serum concentration of dexamethasone. The dose of dexamethasone, especially on day 1 and day 8, must be decreased to account for the drug-drug interaction.

Per EMEND® Prescribing Information for the 150mg (Single Dose Regimen of EMEND):

EMEND for Injection 150 mg is administered intravenously on Day 1 only as an infusion ***over 20-30 minutes*** *initiated approximately 30 minutes prior to chemotherapy. No capsules of EMEND are administered on Days 2 and 3. EMEND for Injection should be administered in conjunction with a corticosteroid and a 5-HT3 antagonist as specified in Table 1.*

Table 1
Recommended dosing (Single Dose Regimen of EMEND) for the prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy

	Day of Infusion	Post Infusion Day 1	Post Infusion Day 3	Post Infusion Day 4
EMEND	150 mg intravenous	none	none	none
Dexamethasone*	12 mg orally	8 mg orally	**8 mg orally twice daily**	**8 mg orally twice daily**
5-HT3 antagonist	See the package insert for the selected 5-HT3 antagonist for appropriate Dosing information.	none	none	none

* Dexamethasone should be administered 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. **The dose of dexamethasone accounts for drug interactions.**

Due to similar bioavailability of oral and IV dexamethasone, the IV dexamethasone dose should be decreased to 12mg as recommended. The protocol has already conservatively adjusted the dose of oral dexamethasone on days 2 and 3 of treatment to 4mg BID.

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Virginia G. Piper Cancer Center Clinical Trials
HonorHealth

APPENDIX I: THE MD ANDERSON SYMPTOM INVENTORY GASTROINTESTINAL CANCER MODULE (MDASI-GI) (TO BE SUBMITTED SEPARATELY FROM PROTOCOL FOR IRB APPROVAL)

MD Anderson Symptom Inventory (MDASI) modules augment the 19 core MDASI symptom and interference items with additional items identified as unique to a particular patient population. MDASI modules may be disease-specific, disease-site-specific, or treatment-specific.
The MDASI gastrointestinal cancer module (MDASI-GI) is a site-specific module. Along with the core MDASI's 13 symptom items and 6 interference items, the MDASI-GI also assesses 5 symptoms specific to gastrointestinal cancer:

- Constipation
- diarrhea or watery stools
- difficulty swallowing
- change in taste
- feeling bloated

MDASI-GI Features

- Purpose: To assess the severity of multiple gastrointestinal cancer-related symptoms and the impact of these symptoms on daily functioning
- Population: Patients with symptoms caused by gastrointestinal cancer and its treatment
- Assessment areas: Severity of multiple symptoms and the impact of symptoms on daily functioning during the last 24 hours
- Method: Self-report; paper-and-pencil form or tablet PC (self-administered or via interview), or telephone-based interactive voice response (IVR) system
- Time required: Five minutes
- Scoring: Please see the MDASI User's Guide
- Reliability: Cronbach alpha reliability ranges from 0.80 to 0.87

APPENDIX J: THE BRIEF PAIN INVENTORY (BPI) – SHORT FORM (TO BE SUBMITTED SEPARATELY FROM PROTOCOL FOR IRB APPROVAL)

The Brief Pain Inventory (BPI) is available in two formats: the BPI short form, which is used for clinical trials and is the version used for the foreign-language translations; and the BPI long form, which contains additional descriptive items that may be clinically useful (for example, items that expand the possible descriptors of pain, such as burning, tingling, etc.). For brevity's sake and for the patient's ease of use, however, we recommend the short form of the BPI.

In response to the US Food and Drug Administration (FDA) guidance for the pharmaceutical industry on the use of patient-reported outcome measures in medical product development to support labeling claims, we have prepared a BPI User's Guide to provide documentation of the BPI's development and psychometric properties. The information offered therein addresses the recommendations in the FDA guidance and establishes the BPI's adequacy as a measure to support medical product claims.

BPI Features

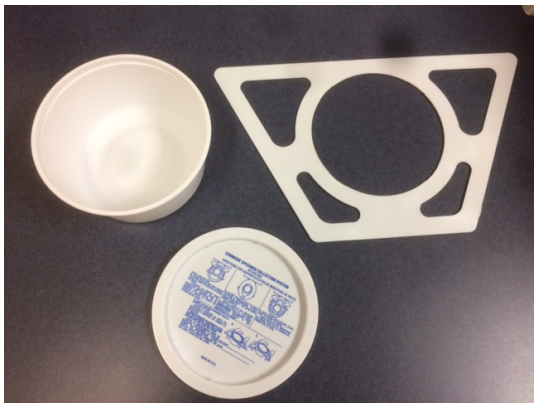
- Purpose: To assess the severity of pain and the impact of pain on daily functions
- Population: Patients with pain from chronic diseases or conditions such as cancer, osteoarthritis and low back pain, or with pain from acute conditions such as postoperative pain
- Assessment areas: Severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or the past week
- Responsiveness: Responds to both behavioral and pharmacological pain interventions
- Method: Self-report or interview
- Time required: Five minutes (short form), 10 minutes (long form)
- Scoring: No scoring algorithm, but "worst pain" or the arithmetic mean of the four severity items can be used as measures of pain severity; the arithmetic mean of the seven interference items can be used as a measure of pain interference
- Reliability: Cronbach alpha reliability ranges from 0.77 to 0.91

APPENDIX K: Fecal Samples for 16S Gut Microbiome rRNA Analysis [Chaput et al 2017]

The instructions below will be provided to each subject and will be submitted separately for review.

Fecal Sample Collection Instructions (to be included in collection kit)

You have been provided with a Commode Specimen Collection System. The collection system includes three items: a specimen container, container lid, and container frame pictured below. Please follow the instructions below.



1. Assemble the container and frame, as pictured below.

2. Place the frame and container under the toilet seat and pushed the container all the way to the rear of the commode.
3. Defecate into the container without allowing any urine into the container.
4. Carefully retrieve the container from the commode and remove the frame.
5. Place the lid on the container as pictured.

6. Write the date and time of collection under your assigned subject ID on the label affixed to the lid. Please do NOT write anything else on the lid or container.
7. Place the specimen container inside the provided specimen bag.
8. Store the specimen container in the provided specimen bag in a cool place, such as a refrigerator (at approximately 4 °C). Sample can be transported in the car without need for ice packs as long as the car is air-conditioned. If the car is not air-conditioned, please transport specimen on ice to keep cool.
9. Return the sample to the clinic within 48-hours of collection. This should correspond with your next scheduled study visit. IMPORTANT: If you cannot return the collected sample within 48 hours of collection, please contact the study team to make arrangements for return of the sample.