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Protocol Level
May 18, 2019

Phase IB/II Trial of High Dose Ascorbic Acid (AA) + Nanoparticle Paclitaxel Protein Bound + Cisplatin + Gemcitabine (AA NABPLAGEM) in Patients who Have Had No Prior Therapy for Their Metastatic Pancreatic Cancer

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HonorHealth Research Institute

SU2C HRI NPG-002

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INVESTIGATOR PROTOCOL AGREEMENT

Protocol#:	SU2C HRI NPG-002
Protocol Title:	Phase IB/II Trial of High Dose Ascorbic Acid (AA) + Nanoparticle Paclitaxel Protein Bound + Cisplatin + Gemcitabine (AA NABPLAGEM) in Patients who Have Had No Prior Therapy for Their Metastatic Pancreatic Cancer
Protocol Version/Date:	Version 7.0 30 Apr 2019

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 clinical trial specified herein. In particular, I/we have agreed to:

- Abide by all obligations as required by local and federal regulatory authorities.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of Sponsor and SU2C confidential documents
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendment to the protocol, and periodic re-approval as required, and to keep the IRB informed of any adverse events and periodically report the status of the trial to them.
- Not implement any deviations from or changes to the protocol without agreement from the sponsor 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 trial (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 trial are adequately informed and trained about the investigational drug and of their trial-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/or of learning of the SAE) to Sponsor Assure access by Sponsor including assigned CRO 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 the Sponsor.
- Retain records and documents related to this trial for at least 3 years after the completion of the trial as confirmed by the sponsor.
- Cooperate fully with any trial-related GCP audit as performed by the assurance group specified by the Sponsor.
- Abide by the stipulations in the Disclosure of Data section and the manuscript preparation/authorship guidelines established at the outset of the trial.

Investigator's Printed Name: _____

Investigator' Signature: _____ Date: _____

Glossary of Abbreviations	
Term	**Definition**
AA	Ascorbic Acid
ADL	Activity of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMPK	Adenosine monophosphatase activated protein kinase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATM	Ataxia-telangiectasia mutated
ATP	Adenosine triphosphate
BPI	Brief Pain Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA-125	Cancer Antigen 125
CA 19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CEA	Carcinoembryonic Antigen
CMH	Cochran-Mantel-Hanzel
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DHA	Dehydroascorbate
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ERC	Ethics Review Committee
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose -positron emission tomography
G6DP	Glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
GSH	Glutathione
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	Intrauterine Device
IV	Intravenous

Glossary of Abbreviations	
Term	**Definition**
MDASI-GI	MD Anderson Symptom Inventory - Gastrointestinal
MTD	Maximum Tolerated Dose
MRI	Magnetic Resonance Imaging
Nab	Nanoparticle paclitaxel protein bound
NABPLAGEM	Nanoparticle paclitaxel protein bound + cisplatin + gemcitabine
NADPH	Nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NIH	National Institutes for Health
NS	Normal saline
OS	Overall Survival
OTC	Over-the-counter
PDA	Pancreatic Ductal Adenocarcinoma
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
ROS	Reactive Oxygen Species
QTA	Quantitative Textural Analysis
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SU2C	Stand Up to Cancer
TGen	Translation Genomic Research Institute
ULN	Upper Limit of Normal

TRIAL SCHEMATIC
The study is divided into two phases:

Phase IB – Dose Escalation Estimate up to 24 pts.
Patients with metastatic pancreatic cancer will be enrolled (3-6 pts each) in 4 dose cohorts of chemotherapy plus increasing doses of ascorbic acid (25, 37.5, 56.25, 75 g/m^2) to determine MTD for Phase II.

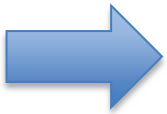
- No prior systemic therapy for advanced pancreatic cancer
- No G6PD deficiency
- No acetaminophen
- No history of oxalate kidney stone

Endpoint for this study is determining the maximum tolerated dose (MTD) for the phase II dose

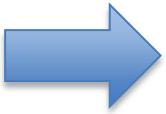
Phase II – Selected Dose Phase I (MTD) selected dose of ascorbic acid in up to 21 patients.

Patient with metastatic pancreatic cancer

- No prior systemic therapy for advanced pancreatic cancer
- No G6PD deficiency
- No acetaminophen
- No history of oxalate kidney stone



Premedication
+
Ascorbic Acid
+
Paclitaxel Protein Bound
+
Cisplatin
+
Gemcitabine



Patient followed for:

- Complete and partial response
- Disease control rate (CR+PR+SD) X 18 weeks
- PFS
- Survival
- Toxicities

A cycle is defined as 3 weeks (21 days) with the following treatment schedule/order of infusions of agents and pre-medications.

Important Note: Prior to receiving any high dose of ascorbic acid all patients in each part of this study will receive a test dose of 15 grams ascorbic acid to preclude hypersensitivity reactions (administered between day -7 and -1). The type of IV access (peripheral versus central line) must be assessed prior to receiving the test dose. For subjects receiving the 15 g test dose of IV Ascorbic Acid (AA) in a peripheral vein, it is recommended that the AA be added to the 500 ml of NS for a final osmolarity <900 mOsm/L. This volume should be infused over at least 30 minutes and up to 60 minutes. If no hypersensitivity is observed then the first high dose of ascorbic acid (25-75 grams/m^2) will be given in accordance with the protocol on Cycle 1/day 1.

Phase 1b – Four dose levels (25, 37.5, 56.25, and 75 grams/m^2 of ascorbic acid) are planned in order to determine the MTD for Phase II. A minimum of 3 patients will be entered at each dose level. Three of 3 patients at a given dose level will be followed for a minimum of one cycle plus 24 hours following their Cycle 2 dose before initiating dosing at the next level. If any patient experiences a DLT, an additional 3 patients will be added at that dose level. All 6 patients will be followed through the first cycle plus 24 hours following their Cycle 2 dose before further dose escalation occurs. If no more than 1 of 6 develops a DLT, dose escalation will continue to the next level for the succeeding patients. However if another patient experiences a treatment related toxicity qualifying as a DLT, that dose will be considered the toxic dose. The MTD will then be defined at the next lower dose level whereby 6 patients were treated and ≤ 1 patient experienced treatment related toxicity qualifying as a DLT.

Patients will be treated with 25, 37.5, 56.25, or 75 grams/m^2 of ascorbic acid via infusion at the rate of 0.5 – 1.0 grams/minute (max). Infusions will occur two times per week administered prior to chemotherapy during weeks 1 & 2 and on intervening weeks of a 21-day cycle. Approximate days for ascorbic acid infusion will be Day 1, 3, 8, 10, 15, and 17 of each 21-day cycle. Chemotherapy and associated premedication and post medication hydration will be dosed on approximate days 1 and 8 as described below.

Phase II- The high dose ascorbic acid selected from the Phase 1b study will be given to up to 21 patients via infusion at the rate of 0.5-1.0 grams/minute. Infusions will occur two times per week prior to chemotherapy (weeks 1 & 2) and on intervening weeks of a 21-day cycle. Approximate days for ascorbic acid infusion will be Day 1, 3, 8, 10, 15, and 17 of each 21-day cycle. Chemotherapy and associated premedication will be dosed on approximate days 1 and 8 as described below.

Chemotherapy infusion (NABPLAGEM) with associated premedication will be as follows:

- Palonosetron (Aloxi®) 0.25mg IV, fosaprepitant (Emend®) 150mg IV and dexamethasone 12mg IV within 30 minutes prior to treatment on days patient is receiving paclitaxel protein bound (Abraxane®) + cisplatin (Platinol®) + gemcitabine (Gemzar®). Patients will continue oral antiemetic prophylaxis at home with ondansetron (Zofran®) 8mg twice daily and dexamethasone 4mg twice daily for 2 days after chemotherapy. Olanzapine (Zyprexa®) 10mg po at bedtime x3 days can be considered if additional antiemetic is needed. The type of antiemetic prophylaxis used can vary based on institutional procedures.
- Paclitaxel protein bound 125mg/m^2 over 30 minute IV infusions on days 1 and 8 repeated every 21 days, followed by:
- Cisplatin 25mg/m^2 in 500*mL of NS over 60minute IV infusion on days 1 and 8 repeated every 21 days followed by:
- Gemcitabine 1000mg/m^2 in 500*mL over 30 minute IV infusion on days 1 and 8 repeated every 21 days
- Post cisplatin hydration: 0.9% Sodium Chloride Injection 1000*mL plus Magnesium Sulfate 2 grams IV infusion over 3 hours on days cisplatin is administered. May start at the same time as the gemcitabine infusion.

*The investigator may reduce the volume of NS to 250mL of NS for cisplatin and gemcitabine and/or post hydration volume to 500ml NS as clinically indicated.

TRIAL SYNOPSIS

Protocol#:	SU2C HRI NPG-002
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Sponsor:	HonorHealth Research Institute
Lead Principal Investigator:	Gayle Jameson, RN, MSN, ACNP-BC, AOCN
Consulting Investigator	Daniel D. Von Hoff, MD, FACP
Trial Sites:	Honor Health Research Institute, Scottsdale, AZ
Clinical Phase:	Phase IB/II
Trial Design:	Phase IB/II Pilot Trial
Objectives:	
Primary:	• Phase IB: To determine the maximum tolerated dose (MTD) of high dose ascorbic acid (AA) with triple therapy of nanoparticle paclitaxel protein bound+ cisplatin + gemcitabine (NABPLAGEM) in patients with advanced stage IV metastatic pancreatic cancer. • Phase II: To determine the preliminary efficacy (Disease control rate of CR+ PR+SD X 18 weeks) of the combination of high dose ascorbic acid (AA) at MTD with triple therapy of nanoparticle albumin- bound paclitaxel + cisplatin + gemcitabine (NABPLAGEM) in patients with advanced stage IV metastatic pancreatic cancer.
Secondary:	• Define the toxicity of the combination of AA + NABPLAGEM • Define the percent of patients who normalize their CA19-9 (or CA125, or CEA if not expressers of CA 19-9). • Determine progression free survival and overall survival • Determine if there is improvement in patient's self-reported quality of life and pain levels during this study and if this correlates with response to treatment
Exploratory:	• Assess tumor texture radiologic scans as an imaging biomarker of response drug concentration within tumors and reference tissue • Assess if plasma concentration of ascorbic acid corresponds with response to treatment • Assess tumor and peripheral blood pharmacodynamics of the combination cytotoxic and ascorbic acid treatment
Endpoints:	
Primary:	• Phase IB: Recommended Phase II dose (to give ≥ 20 mM) of ascorbic acid for Phase II • Phase II: Disease control rate (CR+PR+SD x18 weeks).
Secondary:	• Incidence of toxicities

	• Percent of patients who normalize their CA19-9(or CA 125, or CEA if not expressers of CA 19-9). • Progression free and overall survival • Changes in patient's self-reported quality of life and pain levels using MD Anderson Symptom Inventory (MDASI-GI) and Brief Pain Inventory (BPI)
Exploratory:	• Tumor texture on radiologic scans as a non-invasive imaging biomarker for response, biologic, pathologic and outcome measures • Correlation between peak plasma concentration of ascorbic acid and response to treatment • Potential biomarkers in the tumor including tumor immune cell infiltration, stromal activation, stem cell enumeration • Changes in numbers of circulating tumor stem cells and macrophage lineage changes
Statistical Methods:	The sample size of this pilot study will be up to 24 patients in Phase IB and up to 21 patients in Phase II. The entry sample size is based on a test of a null hypothesis of a 5% complete response or less, versus an alternative hypothesis of a 30% complete response rate or greater. In phase II, we will treat an initial cohort of 10 patients, and if there are no complete responders the trial will be closed. If there are 1 or more complete responders, the trial will be expanded to 21 patients. Four or more complete responders out of 21 patients will be sufficient evidence for rejection of the null hypothesis of insufficient activity of the regimen. This design has a power of 90% at a one-sided Type I error rate of 2.5%.
For Efficacy:	The efficacy analysis will include summaries for the following parameters: complete response rate (CR), objective response rate (CR + PR), disease control rate (CR + PR + SD at 18 weeks), percent of patients who normalize their CA 19-9 (or CA 125 or CEA if these are used to follow the patient disease), progression-free survival (PFS), and overall survival (OS). The efficacy analysis will only be conducted on patients who have received at least one dose of ascorbic acid, albumin-bound paclitaxel, cisplatin, gemcitabine and have at least one post baseline tumor assessment. Objective responses will be evaluated using the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1). Changes (i.e. improvements) in tumor measurements from baseline values will be assigned a status of CR or PR or SD. Objective response measurements will comprise the sum of CR plus PR. The overall response rate, as well as the rates for the individual categories of response (i.e. CR, PR, SD, and PD) will be estimated by the percentage of patients achieving these criteria. The disease control rate will consist of the sum of CR + PR + SD for 18 weeks. All proportions will be estimated using an exact 95% binomial confidence interval. For the estimation of

	progression-free and overall survival, a Kaplan-Meier analysis will be performed. Progression-free survival is defined as the interval from the date of registration (i.e. assignment of patient number) to the earliest date of documented evidence of recurrent or progressive disease, or the date of death due to any cause, whichever occurs first. Patients who do not progress and remain alive will be censored at their last radiographic assessment date. Overall survival will be measure from the date of registration (i.e. assignment of patient number) to the date of death due to any cause, or the date of last contact (censored observations).
For Safety:	All patients who receive any amount of ascorbic acid, paclitaxel protein bound, cisplatin, or gemcitabine will be included in the following safety analyses: • The incidence, severity, duration, causality, seriousness, and type of AEs • Changes in the patient's physical examination, vital signs, and clinical laboratory results • Grading of clinical laboratory results per CTCAE criteria for selected laboratory parameters • Deaths • Concomitant medications
Name, dose of drugs:	Prior to receiving any high dose of ascorbic acid, all patients in each part of the pilot study will receive a test dose of 15 grams ascorbic acid to preclude hypersensitivity reactions (administered between day -7 and -1). The type of IV access (peripheral versus central line) must be assessed prior to receiving the test dose. For subjects receiving the 15 g test dose of IV Ascorbic Acid (AA) in a peripheral vein, it is recommended that the AA be added to the 500 ml of NS for a final osmolarity <900 mOsm/L. This volume should be infused over at least 30 minutes and up to 60 minutes. If no hypersensitivity is observed then the first high dose of ascorbic acid (25-75 grams/m2) will be given in accordance with the protocol on Cycle1/Day1. Chemotherapy associated premedication will be administered prior to AA infusion as follows on Days 1 and 8 of each treatment cycle: • palonosetron 0.25mg IV, fosaprepitant 150mg IV and dexamethasone 12mg IV within 30 minutes prior to treatment on days patient is receiving paclitaxel protein bound + cisplatin + gemcitabine. Patients will continue oral antiemetic prophylaxis at home with ondansetron 8mg twice daily and dexamethasone 4mg twice daily for 2 days after chemotherapy. Olanzapine 10mg po at bedtime for 3 days can be considered if additional antiemetic is needed. The type of antiemetic prophylaxis used can vary based on institutional procedures. • Four escalating dose levels (25, 37.5, 56.25 or 75 grams/m^2 of ascorbic acid) are planned in order to

	determine the MTD for Phase II. A minimum of 3 patients will be entered at each dose level. Patients will receive 25, 37.5, 56.25 or 75 grams/m^2 of ascorbic acid via an infusion at the rate of 0.5 - 1 gram/minute.. **NOTE: Rate must not exceed 1 gram/minute for central line (for total doses > 120 g). If using a peripheral line, rate must not exceed 0.5 gram/minute. A central line is required for infusion rates above 0.5 gram/minute. Rate may be slowed for incidence of infusion intolerance (e.g., nausea, shakes, chills).** • AA Infusions will occur two times per week prior to chemotherapy (weeks 1 & 2) and on intervening weeks of a 21-day cycle. Approximate days for ascorbic acid infusion will be Day 1, 3, 8, 10, 15, and 17 of each 21-day cycle. The dose level for Phase II patients will be determined following completion of the Phase 1b study based on response from 3-6 patients receiving either the 25, 37.5, 56.25 or 75 grams/m^2 dose level of ascorbic acid. • Paclitaxel protein bound 125mg/m^2 over 30 minute IV infusions on days 1 and 8 repeated every 21 days, followed by: • Cisplatin 25mg/m^2 in 500*mL of NS over 60minute IV infusion on days 1 and 8 repeated every 21 days followed by: • Gemcitabine 1000mg/m^2 in 500*mL over 30 minute IV infusion on days 1 and 8 repeated every 21 days • Post cisplatin hydration: 0.9% Sodium Chloride Injection 1000*mL plus Magnesium Sulfate 2 grams IV infusion over 3 hours on days cisplatin is administered. May start at the same time as the gemcitabine infusion. *The investigator may reduce the volume of NS to 250mL of NS for cisplatin and gemcitabine and/or post hydration volume to 500ml NS as clinically indicated.
Total # of Patients:	Total of up to 24 in the Phase IB portion and up to 21 in the Phase II portion
Patient Population:	Patients with stage IV pancreatic cancer who have had no prior therapy for their metastatic pancreatic cancer.
Trial Duration	Anticipated duration of the trial is projected for 3 years, with the first 24 months anticipated to complete enrollment.
Inclusion criteria:	• Be willing and able to provide written informed consent/assent for the trial. • Be ≥ 18 years of age on day of signing informed consent. • Histologically or cytologically confirmed metastatic pancreatic adenocarcinoma (with measurable disease according to RECIST 1.1) • Have a performance status of 0 or 1 on the ECOG performance scale.

	• Demonstrate adequate organ function as defined below in Table 4, all screening labs should be performed within 21 days of treatment initiation. • Female participants of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving first dose of study medication. • Female participants of childbearing potential must be willing to use adequate method of contraception (as outlined in section 4.4.2) for the duration of the trial through one month after the last dose of trial treatment. • Male participants must agree to use adequate contraception (as outlined in section 4.4.2) for the duration of the trial through one month after the last dose of trial treatment. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.
Exclusion criteria:	• Patients must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatments in the adjuvant setting with gemcitabine and/or 5-FU or gemcitabine administered as a radiation sensitizer are allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present. • Palliative surgery and/or radiation treatment less than 4 weeks prior to initiation of study treatment. • Exposure to any investigational agent within 4 weeks prior to initiation of study treatment. • Patients who need constant use of finger stick blood glucose monitoring for tight control of their diabetes being that the ascorbic acid causes false low readings of glucose via that technology (Vasudevan and Hirsch 2014) [39] • Any person with a G6PD deficiency • History of renal oxalate stones (if type of stone is unknown, need to assess urine oxalates level if >60mg/dL, then patient is not eligible for the study) • Patient is taking acetaminophen at any dose or any medication that contains acetaminophen within 72 hours of first dose of ascorbic acid • Hypersensitivity to any of the agents proposed for treatment. • Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. • Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate

	provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. • Has an active infection requiring systemic therapy. • Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator. • Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. • **For female participants:** Is pregnant or breastfeeding, or expecting to conceive within the projected duration of the trial, starting with the pre-screening or screening visit through one month after the last dose of trial treatment. • **For male participants:** Is expecting to impregnate a sexual partner within the projected duration of the trial, starting with the pre-screening or screening visit through one month after the last dose of trial treatment. • Patients with evidence of iron overload, defined as a transferrin saturation > 45 percent AND serum ferritin > 200 ng/mL (males) or >150 ng/mL (females). • Current, serious, clinically significant cardiac arrhythmias as determined by the investigator, or patient receiving a digitalis derivative.
Replacement of Patients:	Patients who are enrolled into the study, but fail to receive ascorbic acid, paclitaxel protein bound, cisplatin, and gemcitabine may be replaced.

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1.0 BACKGROUND AND RATIONALE

1.1 Overview

Pancreatic cancer continues to be a very lethal disease. It was estimated that in 2016, 53,070 Americans would be diagnosed with pancreatic ductal adenocarcinoma (PDA), and 41,780 would die from the disease. This makes pancreatic cancer the third leading cause of death from cancer in the US.[1]

PDA is the twelfth most common cancer in the world with 338,000 new cases diagnosed in 2012. It is estimated that worldwide there will be > 300,000 deaths from pancreatic cancer. Furthermore unfortunately PDA is projected to be the second leading cause of death from cancer in the US by 2030.[2]

Detection of pancreatic cancer has notoriously been very late in the disease and therefore the 5-year survival rate is only 8%, which is actually a slight improvement over the last few years. Right now the only potential cure for pancreatic cancer is surgical resection (if the disease is caught early). However only about 20% of PDA patients are eligible for potentially curable resection and unfortunately most (> 80%) have recurrence of their cancer within 2 years of resection, and those recurrences are almost universally fatal. [3,4]

Recently it has been shown that there are regimens that actually improve survival for patients with advanced stage IV PDA. Conroy and colleagues have developed the Folfirinox regimen, which in a large randomized trial improved survival over gemcitabine as a single agent.[5] Von Hoff and colleagues developed the nanoparticle albumin (nab) associated paclitaxel plus gemcitabine regimen which improved survival over single agent gemcitabine.[6] Even more recently Jameson and colleagues have presented a combined regimen of nab-paclitaxel + gemcitabine + cisplatin in a small 24 patient phase Ib/II trial which showed a response rate of 71% with 2 patients having complete response, a 1-year survival of 65% and a median survival of 16+ months.[7]

1.2 Rationale for the use of high doses of ascorbic acid

1.2.1 Overview

While there have been multiple investigators and investigations into the use of ascorbic acid for patients with cancer (see ClinTrials.gov), its use has generally not been found to be of help for patients particularly when given orally – e.g. 10 grams daily. [8]

1.2.2 New data that led to the need for this clinical trial

Recently due to a publication by Yun and colleagues (2015) there has been a very substantial increase in interest in the use of very high dose of vitamin C to selectively kill cancer cells with KRAS and BRAF mutations. [9] In their work they found that colorectal cancer cells harboring KRAS or BRAF mutation are selectively killed when

exposed to high level vitamin C. This finding is attractive to all of us who are interested in a new approach against pancreatic cancer (where 100% of the cancer have mutated KRAS).

In the Yun study they noted the selective killing of the KRAS mutated colon cancer was due to an increased uptake of the oxidized form of vitamin C (dehydroascorbate) via the GLUT1 glucose transporter. This increased uptake of dehydroascorbate (DHA) causes oxidative stress as the intracellular DHA is reduced to vitamin C, which depletes glutathione (GSH). This depletion of GSH causes reactive oxygen species (ROS) to accumulate and inactivate glyceraldehyde 3-phosphate dehydrogenase. The authors then note the inhibition of GAPDH in highly glycolytic KRAS (or BRAF) mutant cell "leads to an energetic crisis and cell death not seen in KRAS or BRAF wild type cells".

It is well documented by our team that pancreatic cancers are very frequently "hot" on [18F] fluorodeoxyglucose positron emission tomography (FDG PET). This is because the tumor (KRAS mutant cell) has over expression of GLUT 1. [10, 11]
Of importance was that effective treatment for patients with advanced pancreatic cancer caused significant metabolic (PET scan) responses with decrease in SUVs.[12]
Therefore one might target KRAS (or BRAF) mutant cancers by exploiting the selective expression of GLUT 1 (and the metabolic liability that come s from increased reliance on glycolysis).

Prior work of the Yun team pointed out that normal dietary vitamin C is transported across cellular membranes by both the sodium vitamin co-transporters (SVCTs) and the facilitate glucose transporters (GLUTs). [13, 14] The SVCTs transport vitamin C directly into the cell but the GLUTs (mainly GLUT 1 and GLUT 3) transport the oxidized form of vitamin C called dehydroascorbate (DHA). After the DHA is imported it is reduced back to vitamin C by glutathione (GSH), thioredoxin and nicotinamide adenine dinucleotide phosphate (NADPH). [15]

The basis for the current protocol is that because GLUT 1 levels in pancreatic cancer are high, this increase in DHA uptake could "disrupt redox homeostasis" and cause a specific decrease in pancreatic cancer cell viability. It is notable that within one hour of vitamin C treatment, the metabolic profile of the KRAS mutant cells changed markedly (suggested inhibition of GAPDH, depletion of cellular GSH and NADPH). If one cannot restore GSH level the cellular ROS increases. Vitamin C inhibits glycolysis (by inhibiting GADPH) depletes ATP and kills the KRAS (or BRAF) mutant cells.

In addition to the above, Aguilera and colleagues (2016) noted that vitamin C reduces RAS detachment from the cell membrane inhibiting ERK1/2 and PKM2 phosphorylation. [16] As a consequence of that activity there is down regulation of GLUT 1 and pyruvate kinase M2 (PKM2) - PTB dependent protein expression with major blockage of the Warburg effect and therefore energetic stress. They proposed using vitamin C with chemotherapy induced changes to improve the anti Warburg effect.

1.2.3 Other interesting preclinical and clinical data possibly relevant to this study

Table 1 details some of the other important preclinical data on ascorbic acid with or without agents against cancer. As can be seen in the table there is a great deal of evidence that very high doses of ascorbic acid can generate H_2O_2 at the tumor site (and not in normal tissue in the mouse systems).

Table 2 outlines all of the clinical trials that have been conducted with both oral and with IV doses of ascorbic acid. It is clear that the oral dosing never achieves plasma concentration of ≥20 mM. The doses necessary to achieve high enough levels of ascorbic acid in blood are between 75-125 grams per infusion 2-3 times weekly. Additionally, these doses have been administered in combination with gemcitabine, with erlotinib, or with carboplatin/paclitaxel therapy. In the recent trial by Ma and colleagues in Science Translational Medicine [6: (222) 222ra18. Feb 5 2014] the therapeutic range of ascorbic acid was 75-100 grams per infusion twice per week for up to 6 months with chemotherapy and continued alone for another 6 months after completion of chemotherapy (safe for at least a year). In fact, Ma et al found that patients with advanced ovarian cancer treated with ascorbate had reduced toxicities associated with chemotherapy and, while not powered for detection of efficacy, it was observed that the PFS was 8.75 months longer for the carboplatin + paclitaxel + AA arm than in the carboplatin + paclitaxel alone arm.

Based on this information we have selected to investigate the regimen of protein-bound paclitaxel, cisplatin and gemcitabine in combination with high-dose ascorbic acid starting at 25 grams/m^2. Since doses of ascorbic acid of at least 100-125 grams are needed to reach the target plasma level of >20 mM (350-400 mg/dl), we feel the 25grams/m^2 is a safe starting dose with the proposed chemotherapy.

For Phase 1B, the ascorbic acid dose will be escalated as follows:

Dose Level	**Dose (g/m^2)**
Level 0 – Starting Dose	25
Level 1	37.5 (50% increase)
Level 2	56.25 (50% increase)
Level 3	75mg (33% increase)

There will be no intrapatient dose escalation.

Table 1. Other Preclinical Data

System	Finding	Reference
Colon cancer in vitro	• L-ascorbic acid can reverse SVCT*-2 dependent cetuximab resistance	Jung et al. 2016 [17]
Triple neg breast in vitro	• Low dose vitamin C and MTX (increases H_2O_2 levels and activated caspase-3 and p38 cell death pathways)	Wu et al. 2017 [18]
MCF7 Breast	• Vitamin C target stem cells inhibit cancer stem-like cells	Bonuccelli et al. 2017 [19]
Invitro/ in vivo	• Thymidine FLT/PET can monitor responses • Ascorbate is a radiosensitizer in pancreatic cancer	Cieslak et al. 2016 [20]
Overview	• IV administration of ascorbate yield very high plasma concentrations while oral treatment does not	Wittmer 2016 [21]
GBM Pancreas and Ovarian tumor grafts	• Single pharmacologic dose of ascorbate produced sustained ascorbate radical and H_2O_2 formation within interstitial fluids of tumors but not in blood	Chen et al 2008 [22]
Ovarian cancer cell Line OVCAR5	Millimolar ascorbate activity as a pro-oxidant induced DNA damage and depleted ATP, activated the ataxia-telangiectasia mutated (ATM) adenosine monophosphatase activated protein kinase pathways (AMPK) resulted in mTOR inhibition and death in ovarian cancer cells. The combination of parental ascorbate and carboplatin and paclitaxel acted synergistically	MA et. al. 2014 [23]
Pancreatic cancer cell lines in vitro and in vivo	This was a time and dose dependent increase in measured H_2O_2 production with increased concentrations of ascorbate (but no effect on immortalized pancreatic ductal epithelial cells)	Du et. al 2010 [24]

*SVCT- Sodium Vitamin C Co-transporters

Table 2. Clinical Trials with Ascorbic Acid (and in combination)

Trial Design	Dose/Route/ Schedule	Tumor /Stage/Prior Rx	n	Findings	Reference
Double blind placebo control	10 g/po/daily	Colorectal/ Stage IV /No	51/49	No response, no change in symptoms, no difference noted in survival 2.9 vs. 4.1 mo, 1-year survival 49% vs. 47%	Moertel et al. 1985 [8]
Uncontrolled	10 g /po/daily 5 - 45 g/IV/daily as a lead in for 0-11 days	Multiple/ Advanced/ No	50	5 tumor regression (10%) and subjective benefit (decrease in bone pain)	Cameron and Campbell 1974 [25]
Historical Control	10 g/po/daily	Multiple/ Advanced/ Yes and No	100	Median survival for ascorbic acid more than 210 days vs. 50 days for control	Cameron and Pauling 1976 [26]
Historical Control	10 g/po/daily	Multiple/ Advanced/ No	100	Median survival for ascorbic acid 293 days vs. 38 days for control	Cameron and Pauling 1978 [27]
Prospective Randomized Double Blind	10 g/po/daily in four divided doses	Multiple/ Advanced/ Yes	150 60 Vit C 63 Placebo	No difference in survival approx. 7 weeks.	Creagan et al. 1979 [28]
Phase I	Gemcitabine 1000 mg/m^2 weekly x 3 + Ascorbic acid 15- 125g (0.75-1.75 g/kg) IV twice weekly to achieve a targeted post-infusion plasma level of ≥350 mg/dL Note: test dose of 15 g ascorbate in 250 ml 5% dextrose water over 30 min. Repeat next week then increase weekly. Need 19-23 mM ascorbate for ascorbate radical (≥20 mM).	Pancreatic/ Stage IV/ No	9	• No dose limiting toxicities • Diarrhea in 4 pts • Dry mouth in 6 pts • PFS 26 weeks, median OS 12 months • Need ≥20 mM ascorbate	Welsh et al. 2013 [29]
Series of clinical cases	Various doses ranging from: 30 g twice weekly IV to 100g per day IV	Renal 2, Colon 1,Pancreas 1, NHL 2, Breast 1 All pts we pre-screened for	7	Toxic reactions were not observed	Riordan et al. 2004 [30]

		G6PD to prevent hemolysis			
Selected Anecdotal	65 g twice weekly 30 g twice weekly 15 g twice weekly No renal insufficiency	Renal Bladder-invasive Diffuse large B-cell lymphoma	3	• Renal- CR • Bladder- CR • Diffuse large B-cell lymphoma- PR	Padayatty et al. 2006 [31]
Phase I Dose escalating	0.4, 0.6, 0.9, 1.5 g /kg IV weekly x 3 Note: 0.1 g/kg first infusion then 0.2 g/kg Doses <15 g were diluted in Ringer's lactate to achieve physiological osmolarity. Doses >15 g were diluted in sterile water to achieve a theoretical osmolarity between 500 and 900 mOsm/l. Doses up to 90 g were infused at a constant rate >90 min; doses >90 g were infused over 120 min.	Multiple/ Advanced/ Yes	24	• Minimal toxicities • No response • Recommend Phase II dose is 1.5 g/kg • Take water freely as ascorbic acid is like an osmotic diuretic	Hoffer et al. 2008 [32]
Phase I Dose escalation	1g/min X 4 days/week X 4 weeks starting at 30 g/m^2 Central line Test dose of 15 g to rule out hypersensitivity Infusion bag protected from light to prevent photoxidation 3 ml blood samples were assayed using Labcorp assay # 001479 Screen for G6PD Ascorbic acid was purchased from Luitpold Pharma- ceuticals,	Multiple/ Advanced/ Yes	17	• Recommended Phase II dose of 70-80 g/m^2 • Treatment related nausea and headache • Moderate to severe hypernatremia and hypokalemia • No Response	Stephenson et al. 2013 [33]

	Inc/American Regent Laboratories, Inc.				
Phase I 3 dose levels	Combination ascorbic acid (50, 75, 100g) IV 3 times weekly + gemcitabine (1000 mg/m2 IV once weekly) + erlotinob (100mg po qd Ascorbic Acid Injection USP was supplied by Bioniche Pharma (Rosemont IL)	Pancreas /Stage IV/ No No hx oxalate renal calculi No G6PD Deficiency No Hx of iron overload	14	• 7/9 Stable disease • No toxicity due to Vitamin C • Mild lightheadedness and nausea	Monti et al. 2012 [34]
Normal Volunteer IV vs po	0.015 to 1.25 g, oral and IV (IV was 250 mg/m^2)	Normal Volunteers	17	• Oral vitamin C absorption tightly controlled • IV bypass tight control	Padayatty et al. 2004 [35]
Randomized	- Dose escalating portion with final dose of 75 or 100 gram per infusion Target peak plasma level of 350-400 mg/dL (20 -23 mM - Once dose determined gave ascorbate infusions 2 xs/ week X 12 mons	Ovarian Cancer III/IV	27	• Trend toward improvement in overall survival and overall progression • No increase in grade ¾ toxicities • Decreased chemotherapy adverse effects.	Ma et al. 2014 [23]

IV administration is critical. The key points for the present clinical trial include:

1. Patients with G6PD deficiency are excluded to avoid hemolytic anemia
2. No acetaminophen (Ascorbic acid reduces excretion of acetaminophen, increasing risk of acetaminophen toxicity).
3. Patients should always have a first dose of high dose ascorbic acid (15 g over 30 minutes). Only then can the dose be escalated to the delivered dose of 25, 37.5, 56.25, and 75 grams/m^2
4. Patients are encouraged to drink and eat during the infusion.
5. No history of kidney stone (oxalate)
6. All studies indicate incredibly few side effects, which bodes well for the proposed study.

1.3 Potential Risks of Ascorbic Acid

Side effects of high dose ascorbic acid are rare however there are contraindications and potential effects that should be considered. Many of these effects may be attributed to high osmolality, temperature and infusion rate of the solution.

Transient mild soreness may occur at the site of the injection. Too rapid of intravenous administration of the solution may cause temporary faintness or dizziness; this is likely associated with dehydration so adequate hydration and high protein diet prior to dosing are recommended.

Higher dose toxicities have included thrombosis; cardiac-related (thickening of blood vessels); kidney stones; pro-oxidant effects; problems with GI system including nausea, abdominal cramps or pain, and red blood cell destruction - hemolysis can occur in patients with a red cell glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Ascorbic acid in high doses interferes with the effects of anticoagulants such as warfarin. Acidification of the urine by ascorbic acid may cause precipitation of cysteine, urate or oxalate stones and will alter the excretion of certain other drugs administered concurrently.

Use with caution in patients with compromised renal function or urinary voiding capacity; congestive heart failure, edema or ascites due to risks of fluid overload.
Because ascorbate is a chelating agent, some individuals may experience shaking due to low serum calcium or magnesium. If severe shaking occurs, pause infusion and administer a slow (1 ml per minute) intravenous push of 1 gram (10ml of 10% solution) of Calcium Gluconate. After resolution of shaking, may resume AA infusion. For subsequent AA infusions, add 1 mL of Magnesium Chloride (200 mg) to the intravenous ascorbic acid solution.

Some researchers have noted (Riordan IVC Protocol 2013, Hoffer 2015 [36, 37]) that adverse effects of chills, thirst, urinary diuresis (associated with shakiness, pressure and discomfort) can be mitigated during infusions by:

- Ensuring the infusion solution is close to room temperature

- Adjusting the infusion rate (0.5 to 1.0 gram/minute) and/or dose of the infusion
- Ensuring the patient is well hydrated prior to the infusion and continues to re-hydrate during the infusion (frequent bathroom trips are to be expected)
- Avoid any restriction in venous return to mitigate any sodium overload issues with edema and monitor patients closely
- High dose vitamin C interferes with most skin prick or blood glucose measures so these should be discounted until 12 hours post infusion. If needed serum glucose can be measured by the hexokinase method.

1.4 Potential Risks of nab-Paclitaxel

The most common toxicities reported for nab-paclitaxel include myelosuppression, predominantly neutropenia, infections (24%), dyspnea (12%), peripheral neuropathy and nausea and vomiting, myalgias and arthralgias, mucositis, alopecia, transaminitis, serum creatinine elevation. Other reported infrequent toxicities include: allergic reaction, loss of appetite, diarrhea, constipation, cough, edema, fever, pruritus, hypotension, nail changes, vision changes, rash, pulmonary edema, irregular heartbeat (see Appendix 5).

1.5 Potential Risk of Cisplatin

The most common toxicities of cisplatin include nephrotoxicity (28-36%; acute renal failure and chronic renal insufficiency), peripheral neuropathy (dose and duration dependent), nausea and vomiting (76-100%), myelosuppression (25-30%; nadir: day 18-23; recovery: by day 39; mild with moderate doses, mild-to-moderate with high-dose therapy), liver enzymes increased (especially SGOT and bilirubin), ototoxicity (10-30%; manifested as high frequency hearing loss; ototoxicity is especially pronounced in children), tissue irritation (extravasation).

Other toxicities (<1%) include alopecia (mild), anaphylactic reaction, arrhythmias, arterial vasospasm (acute), blurred vision, bradycardia, diarrhea, heart block, heart failure, hemolytic anemia (acute), hemolytic uremic syndrome, hypercholesterolemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, limb ischemia (acute), mesenteric ischemia (acute), myocardial infarction, myocardial ischemia, mouth sores, neutropenic typhilitis, optic neuritis, orthostatic hypotension, pancreatitis, papilledema, phlebitis, reversible posterior leukoencephalopathy syndrome (RPLS), SIADH, stroke, thrombophlebitis, thrombotic thrombocytopenic purpura (see Appendix 5).

1.6 Potential Risks of Gemcitabine

The most common toxicities reported for gemcitabine include myelosuppression, transient elevations in serum transaminases (approximately 70%), nausea and vomiting (69%), fever (41%), rash (30%), diarrhea (19%), flu syndrome (19%), infection (16%), alopecia (15%), edema (13%), stomatitis (11%), neurotoxicity (mild 10%, severe <1%), mild proteinuria and hematuria; Hemolytic Uremia Syndrome (HUS) reported rarely (0.25%), dyspnea (0.2%) and serious

pulmonary toxicity (0.06%). Also reported include constipation and pruritus (see Appendix 5).

1.6.1 Potential risks of Paclitaxel Protein Bound plus Gemcitabine

The safety of paclitaxel protein bound plus gemcitabine was initially reported by Von Hoff and colleagues.[10] The most common toxicities seen at the recommended phase 2 dose were anemia, leukopenia, neutropenia, thrombocytopenia, fatigue, alopecia, sensory neuropathy and nausea.

1.6.2 Potential risks of Paclitaxel Protein Bound, plus Cisplatin, plus Gemcitabine

The combination of paclitaxel protein bound, cisplatin, and gemcitabine has recently been reported by Jameson and colleagues.[7] As noted earlier the response rate in 24 patients was 71%, with 65% one-year survival. Table 3 below outlines the grade ≥ 3 related toxicities. Most common treatment-related adverse events were anemia, thrombocytopenia, and neutropenia. However, a similar combination of paclitaxel, cisplatin, and gemcitabine given on days 1 and 8 every 21 days studied by Frasci, et al. showed anticipated toxicities to include myelosuppression, neutropenia, neuropathy, nephrotoxicity diarrhea, vomiting, fatigue, musculoskeletal pain and rhinorrhagia. In that study, grade 2 neurotoxicity was seen in 8 patients (10.6%), grade 3 sensory and motor neuropathy was seen in one patient (1.3%). Mild or moderate nephrotoxicity occurred in a total of 7 patients (9.3%). [38]

Table 3. Grade 3-5 Treatment-related Adverse Events

	N = 25 n (%)	N = 25 n (%)	N = 25 n (%)
Adverse Event Description	**Grade 3**	**Grade 4**	**Grade 5**
Total Patients with AEs by Maximum Grade	12 (48%)	9 (36%)	1 (4%)
Blood and lymphatic system disorders	**8 (32%)**	**1 (4%)**	
Anemia	8 (32%)		
Febrile neutropenia		1 (4%)	
Gastrointestinal disorders	2 (8%)		
Diarrhea	2 (8%)		
Nausea	1 (4%)		
Vomiting	1 (4%)		
General disorders and administration site conditions	**2 (8%)**		
Fatigue	1 (4%)		
Fever	1 (4%)		
Infections and infestations	1 (4%)		
Anorectal infection	1 (4%)		
Investigations	10 (40%)	9 (36%)	
Lymphocyte count decreased	1 (4%)		
Lymphocyte count increased	1 (4%)		
Neutrophil count decreased	5 (20%)	1 (4%)	
Platelet count decreased	8 (32%)	9 (36%)	
White blood cell decreased	1 (4%)	1 (4%)	
Metabolism and nutrition disorders	**2 (8%)**		
Dehydration	2 (8%)		
Hypokalemia	1 (4%)		
Nervous system disorders	**2 (8%)**		
Peripheral motor neuropathy	1 (4%)		
Stroke			1 (4%)
Respiratory, thoracic and mediastinal disorders	**1 (4%)**		
Epistaxis	1 (4%)		

Note: Percentages are based on the total number of patients in the analysis population. A patient who experienced multiple events within a system organ class (SOC) or preferred term was counted once for that class and once for the preferred term at the maximum observed grade.

2.0 HYPOTHESIS

The addition of high dose ascorbic acid to the triple therapy of paclitaxel protein bound + cisplatin + gemcitabine will substantially improve the antitumor activity of the triple therapy (likely through increased formation of ROS).

3.0 OBJECTIVES

3.1 Primary Objective

Phase I

To determine the maximum tolerated dose (MTD) of high dose ascorbic acid (AA) with triple therapy of nanoparticle paclitaxel protein bound + cisplatin + gemcitabine (NABPLAGEM) in patients with advanced stage IV metastatic pancreatic cancer.

Phase II

To determine the preliminary efficacy (Disease control rate of CR+ PR+SD X 18 weeks) of the combination of high dose ascorbic acid (AA) at MTD with triple therapy of nanoparticle paclitaxel protein bound + cisplatin + gemcitabine (NABPLAGEM) in patients with advanced stage IV metastatic pancreatic cancer.

3.2 Secondary Objective

- Define the toxicity of the combination of AA NABPLAGEM
- Define the percent of patients who normalize their CA19-9 (or CA125, or CEA if not expressers of CA 19-9)
- Determine progression free survival and overall survival
- Determine if there is improvement in patient's self-reported quality of life and pain levels during this study and if this correlates with response to treatment

3.3 Exploratory Objectives

- Assess tumor texture radiologic scans as an imaging biomarker of response drug concentration within tumors and reference tissue
- Assess if plasma concentration of ascorbic acid corresponds with response to treatment
- Assess tumor and peripheral blood pharmacodynamics of the combination cytotoxic and ascorbic acid treatment

3.4 Primary Endpoints

- Phase I- Maximum tolerated dose (MTD) for Phase II
- Phase II- The complete response rate, objective response rate (CR+PR), as well as disease control rate (CR+PR+SD x18 weeks).

3.5 Secondary Endpoints

- Incidence of toxicities
- Percent of patients who normalize their CA19-9 (or CA125, or CEA if not expressers of CA 19-9)
- Progression free and overall survival
- Changes in patients' self-reported quality of life and pain levels using MD Anderson Symptom Inventory (MDASI-GI) and Brief Pain Inventory (BPI)

3.6 Exploratory Endpoints

- Tumor texture on radiologic scans as a non-invasive imaging biomarker for response, biologic, pathologic and outcome measures
- Correlation between peak plasma concentration of ascorbic acid and response to treatment
- Potential biomarkers in the tumor including tumor immune cell infiltration, stromal activation, stem cell enumeration
- Changes in numbers of circulating tumor stem cells and macrophage lineage changes

4.0 METHODS

4.1 Eligibility

A total of up to 24 patients in Phase IB and up to 21 in Phase II with advanced metastatic pancreatic cancer who have not previously received treatment for their metastatic disease will be recruited from up to 4 centers.

4.1.1 Inclusion Criteria

Patients must meet the following criteria to be included in the trial:

- Be willing and able to provide written informed consent/assent for the trial.
- Be ≥ 18 years of age on day of signing informed consent.

- Histologically or cytologically confirmed metastatic pancreatic adenocarcinoma (with measurable disease according to RECIST 1.1 criteria).

- Have a performance status of 0 or 1 on the ECOG performance scale.

- Demonstrate adequate organ function as defined below in table 4. All screening labs should be performed within 21 days of treatment initiation.

- Female participants of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving first dose of study medication.

- Female participants of childbearing potential must be willing to use adequate method of contraception (as outlined in section 4.4.2) for the duration of the trial through one month after the last dose of trial treatment.

- Male participants must agree to use adequate contraception (as outlined in section 4.4.2) for the duration of the trial through one month after the last dose of trial treatment.

  Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the participant.

Table 4. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	<1.5 mg/dL OR ≥60 mL/min for patient with creatinine levels > 1.5 mg/dL
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR
	Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for patients with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

4.1.2 Exclusion Criteria

Patients ***must not meet any*** of the following criteria in order to be eligible for the trial:

- Patients must have received no previous radiotherapy, surgery, chemotherapy or investigational therapy for the treatment of metastatic disease. Prior treatments in the adjuvant setting with gemcitabine and/or 5-FU or gemcitabine administered as a radiation sensitizer are allowed, provided at least 6 months have elapsed since completion of the last dose and no lingering toxicities are present.

- Palliative surgery and/or radiation treatment less than 4 weeks prior to initiation of study treatment.

- Exposure to any investigational agent within 4 weeks prior to initiation of study treatment.

- Patients who need constant use of finger stick blood glucose monitoring for tight control of their diabetes being the ascorbic acid causes false low readings of glucose via that technology (Vasudevan and Hirsch 2014) [39]

- Any person with a G6PD deficiency

- History of renal oxalate stones (if type of stone is unknown, need to assess urine oxalates level if >60mg/dL, then patient is not eligible for the study)

- Patient is taking acetaminophen at any dose, or any medication that contains acetaminophen within 72 hours of first dose of ascorbic acid.

- Hypersensitivity to any of the agents proposed for treatment.

- Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

- Has an active infection requiring systemic therapy.

- Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

- Female Participants: Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through one month from the last dose of trial treatment.
- Male participants: Is expecting to impregnate a sexual partner within the projected duration of the trial, starting with the pre-screening or screening visit through one month after the last dose of trial treatment.

- Patients with evidence of iron overload, defined as a transferrin saturation > 45 percent AND serum ferritin > 200 ng/mL (males) or >150 ng/mL (females).

- Current, serious, clinically significant cardiac arrhythmias as determined by the investigator, or patient receiving a digitalis derivative.

4.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 5.

Table 5. Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Palonosetron	0.25 mg	2 x s per 21 day cycle	IV Infusion	30 minutes prior to NABPLAGEM on Days 1 and 8	Pre-medication antiemetic prophylaxis
Fosaprepitant	150 mg	2 x s per 21 day cycle	IV Infusion	30 minutes prior to NABPLAGEM on Days 1 and 8	Pre-medication antiemetic prophylaxis
Dexamethasone	12 mg	2 x s per 21 day cycle	IV infusion	30 minutes prior to NABPLAGEM on Days 1 and 8	Pre-medication antiemetic prophylaxis
High Dose Ascorbic Acid	4 different dose levels (3 patients per dose level in Phase IB to select dose level for Phase II) 25 g/m^2 37.5 g/m^2 56.25 g/m^2 75 g/m^2	2 x s per week	IV infusion (Refer to Table 5a)	Day 1, 3, 8, 10, 15, and 17 of each 21-day cycle	Experimental
Paclitaxel protein bound	125 mg/m^2	2 x s per 21 day cycle	IV Infusion over 30 min	Days 1 and 8	Experimental
Cisplatin	25 mg/m^2	2 x s per 21 day cycle	IV Infusion over 60 min	Days 1 and 8	Experimental
Gemcitabine	1000 mg/m^2	2 x s per 21 day cycle	IV Infusion over 30 min	Days 1 and 8	Experimental
Magnesium Sulfate	2 grams in 0.9% Sodium Chloride Injection 1000mL	2 x s per 21 day cycle	IV Infusion over 180 minutes*	Days 1 and 8	Hydration

* This post-hydration should be infused over 180 minutes and may be started at the same time as gemcitabine, see further details below in Section 4.2.

Treatment must be administered in a hospital, clinic or other out-patient setting appropriate for chemotherapeutic infusions. The solution for infusion will be prepared at each investigative site.

Prior to receiving any high dose of ascorbic acid all patients in each part of the pilot study will receive a test dose of 15 grams ascorbic acid in 250 ml NSS IV over 30 minutes to preclude hypersensitivity reactions (administered between day -7 and -1). The type of IV access (peripheral versus central line) must be assessed prior to receiving the test dose. For subjects receiving the 15 g test dose of IV Ascorbic Acid (AA) in a peripheral vein, it is recommended that the AA be added to the 500 ml of NS for a final osmolarity <900 mOsm/L. This volume should be infused over at least 30 minutes and up to 60 minutes.

If no hypersensitivity then the first high dose of ascorbic acid (25-75 grams/m^2) will be given in accordance with the protocol on Cycle 1/ Day1.

The order of infusion with premedication is as follows:

Chemotherapy associated premedication will be administered prior to AA infusion on Days 1 and 8 of each treatment cycle:

- palonosetron 0.25mg IV, fosaprepitant 150mg IV and dexamethasone 12mg IV within 30 minutes prior to treatment on days patient is receiving paclitaxel protein bound + cisplatin + gemcitabine. **Note:** If fosaprepitant is discontinued for a specific patient, the dexamethasone IV premedication dose should be increased to 20 mg. Patients will continue oral antiemetic prophylaxis at home with ondansetron 8mg twice daily and dexamethasone 4mg twice daily for 2 days after chemotherapy. Olanzapine 10mg PO at bedtime x3 days can be considered if additional antiemetic is needed. **The type of antiemetic prophylaxis used can vary based on institutional procedures.**

- Ascorbic Acid - Patients will receive 25, 37.5, 56.25 or 75 grams/m^2 of ascorbic acid, infused over 120 minutes*. For patients in the 75 grams/m^2 dose cohort, with a BSA > 1.9 m^2 , the maximum dose of ascorbic acid to be infused will be 142.5 g. Refer to Table 5a below for complete instructions on compounding and infusion of ascorbic acid.
    - Mixing: See Table 5a. Equivalent volume of ascorbic acid to be added will be removed from NS or Sterile Water bag prior to addition of ascorbic acid volume. (For example 50 g of AA = 100 ml, 100 ml to be removed from NS bag prior to addition of AA volume.)
    - Dose may be rounded down to nearest vial size if the vial size dose is within 10% of calculated dose.
    - Rate of infusion: Infuse over a minimum of 120 minutes.
      NOTE: Rate must not exceed 1 gram/minute for central line (for total doses > 120 g). If using a peripheral line, rate must not exceed 0.5 gram/minute. A central line is required for infusion rates above 0.5 gram/minute. Rate may be slowed for incidence of infusion intolerance (e.g., nausea, shakes, chills).

Table 5a. Compounding and Infusion of IV Ascorbic Acid

Dose Level	Solution	Final Volume Osmolarity ~ 900 mOsm/L*	Rate not to exceed: (central line)	Rate not to exceed: (peripheral line)
25 g/m^2	0.9 % Sodium Chloride (Normal Saline)	1000 ml	1 g/min	0.5 g/min
37.5 g/m^2	Sterile Water	1000 ml	1 g/min	0.5 g/min
56.25 g/m^2	Sterile Water	1500 ml**	1 g/min	0.5 g/min
75 g/m^2	Sterile Water	2000 ml** (May decrease volume to 1500 ml if patient has central line)	1 g/min	0.5 g/min

* For BSA > 1.9 m^2, osmolarity may slightly surpass 900 mOsm/L, however the required rate of 0.5 g/min for peripheral infusion reduces the tonicity of the solution. If necessary for patient comfort, the volume of solution may be increased for peripheral infusion for BSA ≥ 2.0.
**Post-hydration may be decreased to 500 ml to account for extra fluid volume.

Ascorbic Acid infusions will occur two times per week prior to chemotherapy (weeks 1 and 2) and on intervening weeks of a 21-day cycle. Approximate days for ascorbic acid infusion will be Day 1, 3, 8, 10, 15, and 17 of each 21-day cycle. The dose level for Phase II patients will be determined following completion of the Phase 1b study based on response from 3-6 patients receiving either the 25, 37.5, 56.25 or 75 grams/m^2 dose level of ascorbic acid. If the patient experiences severe shaking during the AA infusion, pause infusion and administer a slow (1 ml per minute) intravenous push of 1 gram (10ml of 10% solution) of Calcium Gluconate. After resolution of shaking, may resume AA infusion if the infusion was interrupted. For subsequent AA infusions, add 1 mL of Magnesium Chloride (200 mg) to the intravenous ascorbic acid solution.

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

- Cisplatin 25mg/m^2 in 500*mL of NS over 60 minute IV infusion on days 1 and 8 repeated every 21 days followed by:

- Gemcitabine 1000mg/m^2 in 500*mL of NS over 30 minute IV infusion on days 1 and 8 repeated every 21 days

- Post cisplatin hydration: 0.9% Sodium Chloride Injection 1000*mL, plus Magnesium Sulfate 2 grams IV infusion over 3 hours on days cisplatin is administered. May start at the same time as the gemcitabine infusion.

*The investigator may reduce the volume of NS to 250mL of NS for cisplatin and gemcitabine and/or post hydration volume to 500mL NS is clinically indicated.

In the event of extravasation during the infusion of paclitaxel protein bound, 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.

4.2.1 Body Surface Area Calculation

The calculation of the dose of ascorbic acid, cisplatin, gemcitabine, and albumin bound paclitaxel 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. If there has been a ≥10% weight change from baseline, the drug doses will be recalculated based on the new BSA value. The calculated dose will be rounded to the nearest whole milligram.

4.2.2 Dose Modification for Toxicity

Toxicities will be graded using the NCI-CTCAE V4.0 (appendix 2). If toxicity occurs during or after any treatment cycle, the toxicity will be graded and appropriate supportive care treatment will be administered to decrease the signs and symptoms (e.g. antiemetics, antidiarrheals, antipyretics, antihistamines).

4.2.3 Dose Limiting Toxicity

DLT (dose Limiting toxicity): DLT will be assessed in the first 21 days of dosing.

Definition of DLT for the Phase 1 part of the trial:

- Any grade ≥3 nonhematologic toxicity (NCI-CTCAE v4.03) with the exception of Grade 3 nausea, vomiting, or diarrhea for more than 24 hours despite anti-emetics or anti-diarrheals related to the regimen
- Grade 3 thrombocytopenia with associated bleeding
- Grade 4 anemia or thrombocytopenia related to the regimen
- Grade 4 neutropenia with fever
- Grade 4 hypotension
- Grade 4 electrolyte imbalances

4.2.4 For paclitaxel protein bound, gemcitabine, and cisplatin

Doses of paclitaxel protein bound, gemcitabine, and cisplatin may be reduced in individual patients in accordance with the schedule in Tables 6, 7, 8, 9 and 10. In general, doses of paclitaxel bound protein, gemcitabine, and cisplatin 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.

A maximum of a 3-week treatment delay is permitted to allow recovery of toxicities.

Table 6. Dose Reduction Schema

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

4.2.4.1 Hematology 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 Tables 7 and 8. Please note that all study drugs will be held at the start of a new cycle if Table 7 criteria are not met.

Dose Modifications at Dav 1

Table 7. Dose Modifications for Day 1 of Each Cycle with a cycle being defined as 21 days (Hematologic Toxicity)

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 8.

Table 8. Dose Modification for Days 8 of Each Cycle (Hematologic Toxicity)*

Day 8 Laboratory Results	Day 8 Paclitaxel protein bound	Day 8 Cisplatin	Day 8 Gemcitabine	Day 8 Ascorbic Acid
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%[c]
Recurrent Febrile	Decrease 2 dose levels (to	Hold	Decrease 2 dose levels (to	100%[c]

Neutropenia (Grade 3 or 4)	75mg/m^2) and do not re-escalate throughout the rest of treatment		600mg/m^2) and do not re-escalate throughout the rest of treatment	

*See Tables 6 for dose reduction schedules

a. If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.
b. Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment interrupted. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to baseline levels before resuming chemotherapy treatment.
c. Ascorbic acid will be discontinued if Grade 4 toxicity is determined to be related or probably related to high-dose ascorbic acid.

4.2.4.2 Non-hematological Toxicity

Dose reductions for non-hematologic toxicity that occur despite adequate background medical therapy should be undertaken in accordance with Table 9.

Table 9. Paclitaxel protein bound and gemcitabine and cisplatin and ascorbic acid – 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 Note cisplatin should not be given unless SCr < 1.5mg/dl.
Grade 3 toxicity [a, c]	Decease paclitaxel protein bound and gemcitabine to next lower dose level[a] (see Table 6)
Grade 4 toxicity[b]	Off protocol treatment[b]
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 4.2.3.3) and nephrotoxicity (section 4.2.3.4.)
[a] If the toxicity only affects neuropathy, then only paclitaxel protein bound should be reduced (please see Section 4.2.3.3).
[b] Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (please see Section 4.2.3.7).
[c] Excluding electrolyte abnormalities per judgement of the investigator.

Table 10. 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%
3+	Hold treatment until resolution to ≤ Grade 1
Please note when one drug is discontinued then it will be a matter of patient situation and clinical judgment as to whether some or all of the other agents are discontinued.	

4.2.4.3 Peripheral Neuropathy

Cisplatin and paclitaxel protein bound treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine and ascorbic acid 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 the adverse event reporting.

4.2.4.4 Nephrotoxicity

Cisplatin (cisplatin injection) produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics (see Appendix 5). 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 (SCr) is < 1.5 mg/dl.

4.2.4.5 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 6. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

4.2.4.6 Pulmonary Embolism

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

4.2.4.7 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 for additional management).

Prevention, Surveillance and Management of Interstitial Pneumonitis

- During study treatment, episodes of transient or repeated dyspnea with unproductive 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 functions tests can show respiratory and ventilation compromise.

- Infections should be ruled out with routine immunological/microbiological methods. Trans-bronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for causes 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.

4.2.4.8 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 interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticarial require

immediate discontinuation of the offending agent and aggressive symptomatic therapy. Patient who develop a severe hypersensitivity reaction should not be re-challenged.

Hypersensitivity reactions can be seen with ascorbic acid and infusions. Therefore, prior to receiving any high dose of ascorbic acid all patients in each part of the pilot study will receive a test dose of 15 grams ascorbic acid .If the patient experiences an infusion reaction, treat according to institutional standard procedure. The investigator is to report the infusion reaction of the ascorbic acid test dose as an adverse event and the patient will be excluded from continuing on the study.

4.2.4.9 Colony Stimulating Factors

Based on the ASCO guidelines (Smith 2006) for use of granulocyte colony stimulating factors, (G-CSF) for regiments 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 cell/μL (see Appendix 6). Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, will discontinue study treatment.

Due to 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 (Auqmentin 500 mg orally, 2-3 times daily) in patients with allergy to fluoroquinolones should be initiated. On their 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 6.2.2.1 of this protocol to report the event as a Serious Adverse Event (SAE).

4.2.5 Rules for discontinuation of Ascorbic Acid

Ascorbic acid will be discontinued if Grade 4 toxicity is determined to be related or probably related to high-dose ascorbic acid (e.g., hypotension)

4.2.6 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.

4.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician.

4.3.1 Acceptable Concomitant Medications

All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 6.2.

4.3.2 Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial. Patients who, in the assessment by the investigator, require the use of any of the below mentioned treatments for clinical management should be removed from the trial.

- Acetaminophen and all acetaminophen-containing products (within 72 hours of first dose of ascorbic acid and for the duration of trial treatment).
- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy
- Chemotherapy
- Investigational agents other than ascorbic acid
- Radiation therapy
    - **Note**: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator’s discretion.

Caution with the use of the following medications and Ascorbic Acid:

- Aluminum-containing antacids – Ascorbic Acid may increase the absorption of aluminum hydroxide. Avoid aluminum-containing antacids.

- Amphetamines - Ascorbic Acid may decrease the serum concentration of Amphetamines

- Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) – Ascorbic Acid may decrease the metabolism of NSAIDs, increasing the risk of adverse effects associated with increased concentration of NSAIDs.

- Barbiturates – Barbiturates may decrease the effects of vitamin C. These drugs include phenobarbital (Luminal), pentobarbital (Nembutal), and seconobarbital (Seconal).

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

If anticoagulation with warfarin is necessary, frequent monitoring of prothrombin time and the International Normalized Ratio (INR) is recommended.

Patients may receive other medications (not listed here as prohibited) that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

4.4 Diet/Activity/Other Considerations

4.4.1 Diet

Patients should maintain a high protein diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

4.4.2 Contraception

Paclitaxel protein bound, cisplatin and gemcitabine (US FDA pregnancy category D) can cause fetal harm when administered to pregnant women. Furthermore, it is unknown whether high dose ascorbic acid (US FDA pregnancy category C) can cause fetal harm, or if any of these trial treatments has transient adverse effects on the composition of sperm.

For this trial, male patients will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female patients will be considered of non-reproductive potential if they are either:

1. Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating

hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3. Has a congenital or acquired condition that prevents childbearing.

Female and male patients of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for one month after the last dose of study drug by complying with one of the following:

1. Practice abstinence† from heterosexual activity;

OR

2. Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female patient's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

  †Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

  ‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

Patients should be informed that taking the study medication might involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to one month after the last dose of trial therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

4.4.3 Use in Pregnancy

If a patient becomes pregnant while on trial treatment, the patient will immediately be discontinued from all trial treatment and have end of visit procedures performed and will be followed-up throughout the remainder of the pregnancy. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 2 working days to the Sponsor if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 6.2.2.

4.4.4 Use in Nursing Women

Cisplatin is excreted in breast milk, while it is unknown whether gemcitabine or ascorbic acid is excreted in breast milk, since many drugs are known to be excreted in breast milk and because of the potential for serious adverse reactions in the nursing

infant, patients who are breast-feeding or plan to breast feed during the course of the trial are not eligible for enrollment and breast feeding is not permitted while taking trial treatment.

4.5 Patient Withdrawal/Discontinuation Criteria

Patients may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a patient may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding assessments to be done at an EOT visit at time of discontinuation or withdrawal are provided in Section 6.1.5.3.

A patient must be discontinued from the trial for any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression
- Unacceptable adverse experiences as described in Section 4.2.4
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient
- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 6.1.5 (Visit Requirements). After the end of treatment, each patient will be followed for 30 days for adverse event monitoring after the end of treatment as described in Section 6.2.3.1. Patients who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each patient will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.6 Patient Replacement Strategy

Patients who discontinue from the study will not be replaced. Patients who discontinue treatment without progression will be followed to determine their disease status at 6 months. Patients who are enrolled into the trial, but fail to receive at least one dose of ascorbic acid, nab-paclitaxel, cisplatin, and gemcitabine may be replaced.

4.7 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other clinical trials indicates a potential health hazard to patients

4.8 The anticipated duration of the trial is projected for 3 years, with the first 24 months anticipated to complete enrollment.

5.0 Trial Schedule

Table 11. Screening – Treatment Period

Screen thru Treatment Period	SCN	Cycle 1								Cycle 2								Cycle 3 and Beyond							
Study week		**1**			**2**			**3**		**4**			**5**			**6**		**7**			**8**			**9**	
Cycle day	-21 to -1	1	2	3	8	9	10	15	17	1	2	3	8	9	10	15	17	1	2	3	8	9	10	15	17
Scheduling Window (Days):	-21 to -1	-3[p]		± 1	± 1		± 1	± 1	± 1	± 3		± 1	± 1		± 1	± 1	± 1	± 3		± 1	± 1		± 1	± 1	± 1
Informed Consent	X [a]																								
Inclusion/Exclusion	X	X																							
Demographics and Medical History	X [b]																								
Prior and Concomitant Medication Review	X	X		X	X		X	X	X	X		X	X		X	X	X	X		X	X		X	X	X
Review Adverse Events		X		X	X		X	X	X	X		X	X		X	X	X	X		X	X		X	X	X
Physical Examination [c]	X	X			X			X		X			X			X		X			X			X	
MDASI-GI and BPI	X	X			X			X		X			X			X		X			X			X	
Vital Signs [d]	X	X		X	X		X	X	X	X		X	X		X	X	X	X		X	X		X	X	X
ECG	X																								
ECOG [e](see appendix 3)	X	X			X			X		X			X			X		X			X			X	
CBC with Differential	X	X			X			X		X			X			X		X			X			X	
Comprehensive Serum Chemistry Panel [f]	X	X			X			X		X			X			X		X			X			X	
Plasma AA level	X	X[g]		X[g]					X[g]	X[g]		X[g]					X[g]								
G6PD Enzyme	X																								
Serum ferritin, Transferrin saturation	X																								
Urinalysis	X	X								X								X							
Serum β Hcg Pregnancy Test (if applicable) [h]	X	X								X								X							

Screen thru Treatment Period	SCN	Cycle 1								Cycle 2								Cycle 3 and Beyond							
Study week		**1**			**2**			**3**		**4**			**5**			**6**		**7**			**8**			**9**	
Cycle day	-21 to -1	1	2	3	8	9	10	15	17	1	2	3	8	9	10	15	17	1	2	3	8	9	10	15	17
Scheduling Window (Days):	-21 to -1	-3[p]		± 1	± 1		± 1	± 1	± 1	± 3		± 1	± 1		± 1	± 1	± 1	± 3		± 1	± 1		± 1	± 1	± 1
PT/INR and aPTT	X																								
Tumor Imaging	X[j]																							X[j]	
•CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)[k]	X	X								X								X							
Tumor Biopsy [l]	X															X									
Central Blood Samples 3 X 10 mL[m]	X	X								X															
Optional IV Hydration			X			X					X			X					X			X			
Ascorbic Acid	X[n]	X		X	X		X	X	X	X		X	X		X	X	X	X		X	X		X	X	X
NABPLAGEM		X			X					X			X					X			X				
Neulasta® [o]						X[o]								X[o]								X[o]			