RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	Phase IB/II Trial of High Dose Ascorbic Acid (AA) + Nanoparticle Paclitaxel Protein Bound + Cisplatin + Gemcitabine (AA NABPLAGEM) in Patients who Have No Prior Therapy for Their Metastatic Pancreatic Cancer
PROTOCOL NO.:	SU2C HRI NPG-002 WIRB® Protocol #20172882
SPONSOR:	HonorHealth Research Institute
INVESTIGATOR:	Gayle S. Jameson, RN, MSN, ACNP-BC, AOCN HonorHealth Research Institute 10510 N 92nd Street Scottsdale, AZ 85258 United States
STUDY-RELATED PHONE NUMBER(S):	Gayle S. Jameson, RN, MSN, ACNP-BC, AOCN 480-323-1350 (24 hours)

INTRODUCTION

You are being asked to take part in a clinical trial, a type of research study. Your participation is entirely voluntary. To allow you to make an informed decision as to whether you want to take part in this research study, this document describes the purpose of the study, your rights and obligations, the procedures needed by the study, and the possible benefits and risks of participating. You should read all of this information carefully and discuss your questions and concerns with your study doctor or healthcare team. You may take home an unsigned copy of this consent form to think about or discuss your decision with your family, friends and anyone you choose. You should not join this research study until all of your questions are answered. A person who takes part in a research study is called a research or study subject. In this consent form, "you" always refers to the research subject.

Clinical trials include only people who choose to take part. Please take your time to make your decision. If you have any questions, you can ask your study doctor for more explanation about the clinical trial, this form, or your disease. This consent form may contain words that you do not understand. Please ask the study doctor or study staff to explain any words or information that you do not understand.

You are being asked to participate in a research study of an investigational treatment regimen with a combination of paclitaxel protein bound, gemcitabine, cisplatin, and Ascorbic Acid (Vitamin C) for the treatment of pancreatic cancer. This treatment regimen has not been approved for the use described in this study by the Food and Drug Administration (FDA) but each medication has been individually approved for patient use by the FDA. Ascorbic Acid is considered a safe dietary supplement by the FDA but treatment with high doses of Ascorbic Acid

administered intravenously has not been recognized as an effective treatment for pancreatic cancer by the FDA.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study.

PURPOSE OF THE STUDY

The purpose of this study is to see if a treatment regimen with a combination of paclitaxel protein bound (also known as nab-paclitaxel), gemcitabine, and cisplatin when given with high dose Ascorbic Acid will be safe and effective in individuals with untreated metastatic pancreatic cancer.

The combination of paclitaxel protein bound and gemcitabine has been studied in treating patients with pancreatic cancer, and as of September 2013, was approved by the FDA for the treatment of patients with advanced pancreatic cancer.

Vitamin C is a nutrient found in food and dietary supplements. It is an antioxidant and also plays a key role in making collagen. High-dose vitamin C may be given by intravenous (IV) infusion (through a vein into the bloodstream) or orally (taken by mouth). When taken by intravenous infusion, vitamin C can reach much higher levels in the blood than when the same amount is taken by mouth. Some human studies of high-dose IV vitamin C in patients with cancer have shown improved quality of life, as well as improvements in physical, mental, and emotional functions, symptoms of fatigue, nausea and vomiting, pain, and appetite loss. Intravenous high-dose ascorbic acid has caused very few side effects in clinical trials. While generally approved as a dietary supplement, the U.S. Food and Drug Administration (FDA) has not approved the use of IV high-dose vitamin C as a treatment for cancer or any other medical condition.

For more information on High-Dose Vitamin C, you can go to the National Cancer Institute's webpage at https://www.cancer.gov/about-cancer/treatment/cam/patient/vitamin-c-pdq.

Cisplatin is approved by the FDA for the treatment of advanced bladder cancer, advanced ovarian cancer, and advanced testicular cancer and other childhood cancers. However, cisplatin is not approved by the FDA for the treatment of advanced pancreatic cancer.

You will also receive additional medications as part of your treatment. A list of the medications and any possible side effects is provided in the Risks and Discomforts section.

Who can participate in this study?
A total of 36 patients who meet eligibility criteria will be recruited from up to 4 study centers in the United States. Patients with stage IV metastatic pancreas ductal adenocarcinoma who have not received treatment previously will be enrolled. Up to 15 patients will be enrolled into the phase IB portion of this study and up to 21 patients will be enrolled in the phase II portion of this study. The expected duration of this study is about 36 months. Enrollment into the screening or treatment phase of the study will be stopped when the anticipated patient accrual is complete.

PROCEDURES

Screening Evaluation
In the first part of the study, you will have an extensive evaluation of your medical condition. The purpose of this evaluation is to find out if you qualify for this research study. Screening procedures for this study include:

- Sign the informed consent form
- Complete medical history including pre-existing/current conditions, prior cancer therapy, and prior surgery
- Complete physical examination including height and weight
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Tumor Imaging to include a computed tomography (CT) and/or magnetic resonance imaging (MRI) scan, as well as a FDG-PET scan of your chest, abdomen, pelvis, and any other part of your body will be completed. This would include a brain scan if your study doctor determines that it is necessary. If CT/MRI and FDG-PET scans were taken within 28 days prior to receiving your first dose, new scans are not necessary.
- Electrocardiogram (ECG)
- Collect blood for laboratory tests. About 3 Tbsp will be taken for the following tests:
    - Complete blood count (CBC) with differential and platelet count
    - Serum chemistry panel including liver and kidney function tests
    - Vitamin C levels
    - Iron levels
    - G6PD Enzyme levels
    - Coagulation Panel to include PTT and PT/INR
    - CA 19-9 (or CA 125, or CEA if not expressers of CA 19-9)
    - Serum pregnancy test (if applicable)
- Collect a urine sample for a urinalysis
- Review all medications taken within the last 30 days

- Collect a fresh tumor biopsy. If a tumor biopsy was completed within 4 weeks of C1, D1 then a new biopsy is not necessary.
- Collect blood for research lab tests. This will need to be collected within 14 days of C1, D1. About 2.5 Tbsp will be collected.
- Complete questionnaires regarding quality of life and pain

If you are eligible to participate in this study, you will be assigned a unique ID that will be used to identify you while you are participating in the study. You will receive a test dose of 15 grams of vitamin C by intravenous infusion as a test dose within one week of your Day 1 visit to see if you will tolerate treatment without having an allergic reaction.

Treatments will be administered in cycles. For the purposes of this study, each cycle will be 21 days long. The following assessments will be completed during each cycle on a specific day of the study:

Day 1 of each cycle (except where noted)

- Directed physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight
- Body Surface Area (BSA) calculation prior to dosing
- Collect blood for laboratory tests. About 2 Tbsp. will be taken for the following tests:
    - Hematology: CBC with differential and platelet count
    - Blood chemistries (for liver and kidney function tests)
    - CA19-9 (or CA 125, or CEA if not expressers of CA 19-9)
    - Serum Pregnancy (if applicable)
- Collect a urine sample for a urinalysis
- Collect blood for research lab tests. About 2.5 Tbsp will be collected. (Cycles 1, 2, 4, 6 and then every other cycle after that only)
- Collect blood for Vitamin C levels before start of the infusion, 5-10 minutes before the end of the infusion, and 1 hour after the end of the infusion. (Cycles 1 and 2 only)
- Review any changes to your health since the last visit
- Review any changes to your medications since the last visit
- Complete questionnaires regarding quality of life and pain
- Administer anti-nausea medication before treatment
- Administer Vitamin C
- Administer Paclitaxel Protein Bound
- Administer Cisplatin
- Administer Gemcitabine
- Administer Intravenous Hydration

Day 8 and 15 of each cycle

- Directed physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight
- Collect blood for laboratory tests. About 1 Tbsp. will be taken for the following tests:
    - Hematology: CBC with differential and platelet count

  - Blood chemistries (for liver and kidney function tests)
- Review any changes to your health since the last visit
- Review any changes to your medications since the last visit
- Complete questionnaires regarding quality of life and pain
- Administer Vitamin C
- Administer anti-nausea medication before treatment (Day 8 only)
- Administer Paclitaxel Protein Bound (Day 8 only)
- Administer Cisplatin (Day 8 only)
- Administer Gemcitabine (Day 8 only)
- Administer Intravenous Hydration (Day 8 only)
- Repeat tumor biopsy (Day 15 only, Cycle 2 only). This procedure is optional.

Day 3, 10, 17 of each cycle

- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Review any changes to your health since the last visit
- Review any changes to your medications since the last visit
- Administer Vitamin C
- Collect blood for Vitamin C levels before start of the infusion, 5-10 minutes before the end of the infusion, and 1 hour after the end of the infusion (Days 3 and 17; Cycles 1 and 2 only)

Day 9

- Administer pegfilgrastim (Neulasta®)

After Cycle 3, 6, and 9 a CT/MRI scan to evaluate disease status (using same imaging method used during your screening visit) will be completed at the end of the cycle prior to starting the next cycle. If disease progression is suspected, additional imaging and lab tests may be ordered.

An End of Study Treatment office visit will be performed when your study drug treatment ends for any reason. The End of Study Treatment evaluations include the following:

- Direct physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight
- Electrocardiogram (ECG)
- Collect blood for laboratory tests. About 1 Tbsp. will be taken for the following tests:
  - Hematology: CBC with differential and platelet count
  - Blood chemistries (for liver and kidney function tests)
  - CA19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Collect a urine sample for a urinalysis
- Review any changes to your health since the last visit
- Review any changes to your medications since the last visit
- Complete questionnaires regarding quality of life and pain
- Computed tomography (CT) and/or magnetic resonance imaging (MRI) scan of your chest, abdomen, pelvis, and other regions as necessary. A brain scan may be done if

necessary. If a CT scan was taken within 28 days prior to EOT, a new scan is not necessary.

Note that there may be additional blood draws throughout this study required for safety purposes; these will be considered "standard of care", for medical care and evaluation, and not for research purposes.

Post-Study Follow-up
All subjects will continue to be evaluated by telephone after study completion or withdrawal. The study staff will contact you or your regular doctor by telephone every 12 weeks (or 3 months).

If after your last dose of study drugs you have ongoing side effects or other medical problems that started during the study, the study personnel might need to follow those conditions for a certain amount of time or until they reach an acceptable level.

Follow-up evaluations for side effects or other medical problems that started during the study may include the following:

- Physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight
- Collect blood for laboratory tests. About 1 Tbsp. will be taken for the following tests:
    - Hematology: CBC with differential and platelet count
    - Blood chemistries (for liver and kidney function tests)
    - CA19-9 (or CA 125, or CEA if not expressers of CA 19-9)
- Collect a urine sample for a urinalysis
- Review any changes to your health since the last visit
- Review any changes to your medications since the last visit

RISKS AND DISCOMFORTS

<u>Paclitaxel Protein Bound</u>

Common side effects of Paclitaxel Protein Bound:

- Anemia
- Fatigue
- Hair loss (reversible)
- Joint and muscle pain
- Low white blood cell count (which may temporarily place you at risk for infection)
- Nausea
- Numbness, tingling or burning of hands and feet
- Tiredness and weakness

Less common side effects related to Paclitaxel Protein Bound:

- Low platelet count (which can lead to bruising or bleeding)
- Appetite loss

- Constipation
- Diarrhea
- Edema (fluid retention)
- Fever
- Irregular heartbeat
- Irritation or bruising at the site of the infusion
- Itching
- Mouth or lip sores
- Nail changes
- Vomiting

Rare side effects related to Paclitaxel Protein Bound:

- Allergic reaction
- Cough
- Difficulty breathing
- Congestive heart failure (the heart does not pump blood effectively)
- Left ventricular dysfunction (when a part of the heart, the left ventricle muscle, does not contract as well as it should which may lead to heart failure)
- Kidney (abnormal function or failure)
- Liver function tests abnormal
- Low blood pressure
- Pulmonary edema (fluid in lungs)
- Rash
- Visual disturbances (temporary), (Flashing lights or blurry vision)

Cisplatin

Common side Effect related to Cisplatin:

- Kidney (abnormal function or failure)
- Nausea
- Numbness, tingling or burning of hands and feet
- Vomiting

Less common side effects related to Cisplatin:

- Anemia (low red blood cell count – which may cause you to feel tired, look pale, and have shortness of breath)
- Fatigue
- Hearing loss
- Irritation or bruising at the site of the infusion
- Liver function test abnormal
- Low platelet count (which can lead to bruising or bleeding)
- Low white blood cell count (which may temporarily place you at risk for infection)

Rare toxicities related to Cisplatin:

- Allergic reaction
- Diarrhea
- Electrolyte imbalance
- Myocardial infarction (heart attack)
- Heart block
- Heart failure
- Irregular heartbeat
- Arterial vasospasm (constriction of the blood vessels)
- Low blood pressure
- Stroke
- Hemolytic anemia (destruction of red blood cells)
- Thrombotic thrombocytopenic purpura (syndrome of abnormal clotting and bleeding)
- Hemolytic uremic syndrome (abnormal clotting and kidney failure)
- Limb and mesenteric ischemia (decreased blood flow to limbs and gut)
- Pancreatitis (inflammation of the pancreas)
- Papilledema (swelling of blood vessels in the eyes)
- Neutropenic typhlitis (infection in the gut due to low white blood cells)
- Reversible posterior leukoencephalopathy syndrome (a syndrome characterized by headache, confusion, seizures and visual loss)
- Visual disturbances (temporary), (Flashing light or blurry vision)
- Mouth or lip sores
- Hair loss (reversible)

Gemcitabine

Common side effects related to Gemcitabine:

- Anemia (low red blood cell count – which may cause you to feel tired, look pale, and have shortness of breath)
- Constipation
- Diarrhea
- Fever
- Flu-like symptoms (fever, feeling tired, loss of appetite, chills and cough)
- Hair loss (reversible)
- Liver function tests abnormal
- Low platelet count (which can lead to bruising or bleeding)
- Low white blood cell count (which may temporarily place you at risk for infection)
- Nausea
- Rash
- Vomiting

Less common side effects related to Gemcitabine:

- Edema (fluid retention)
- Fatigue
- Irritation or bruising at the site of the infusion

- Itching
- Mouth or lip sores
- Tingling, prickling of the skin

Rare toxicities related to Gemcitabine:

- Allergic reaction
- Blood and protein in the urine
- Difficulty breathing
- Abnormal kidney function or failure
- Hemolytic uremic syndrome (abnormal clotting and kidney failure)
- Serious lung toxicity

Vitamin C (Ascorbic Acid)

Side effects related to Vitamin C:

- Vomiting
- Nausea
- Heartburn
- Stomach cramps
- Headache
- Dizziness
- Feeling faint
- Shakiness

Rare toxicities related to Vitamin C:

- Kidney stones

Before each dose of study drug(s), your study doctor will administer certain medications to help control side effects. The lowered blood counts may temporarily place you at risk for infection or bleeding, although this is uncommon. If necessary, these events may require a reduction in the dose of the study drug(s) and/or you will be given medication to help relieve any pain or discomfort.

Information regarding possible side effects for medications given to help manage the side effects from the study drugs is listed below. These medications will be given before, during or after your infusion as part of your treatment. Please discuss any possible changes to your medications with your study doctor or nurse. While you are on this study, please do not take any Vitamin C supplements.

Side Effects of G-CSF or pegfilgrastim (Neulasta®):

Pegfilgrastim will be given by subcutaneous (under the skin) injection to prevent your white blood cells from decreasing too much.

The most common side effect of G-CSF is aching in the bones and muscles. Depending on the type of G-CSF given, possible but rare side effects include the following:

- serious allergic reactions that may be life-threatening (symptoms can include rash, shortness of breath, wheezing, dizziness from a drop in blood pressure, swelling around the mouth or eyes, fast pulse, and/or sweating)
- enlarged or ruptured spleen
- adult respiratory distress syndrome (a condition caused by fluid buildup in the lungs that prevents normal breathing)
- sickle cell crisis in subjects with Sickle Cell disease.
- Swelling of the optic (eye) disc (symptoms include headache, blind spot, blurring of vision and/or loss of vision)

Side Effects of palonosetron (Aloxi®):

Palonosetron will be given by IV before the paclitaxel protein bound, cisplatin and gemcitabine to prevent nausea and vomiting that you may experience.

Less serious side effects that can occur include:

- headache
- constipation
- pain, redness swelling or a lump under your skin where the needle is placed

More serious side effects that can occur include:

- allergic reaction (symptoms include hives, swelling of the face or hands, trouble breathing, tingling in your mouth or throat and/or chest tightness)
- anxiety
- restlessness
- fever
- sweating
- muscle spasms
- nausea and/or vomiting
- diarrhea
- lightheadedness, dizziness, fainting
- chest pain and/or irregular heartbeat

Side Effects of fosaprepitant (Emend®):

Fosaprepitant will be given by IV before the paclitaxel protein bound, cisplatin and gemcitabine to prevent nausea and vomiting. In addition, you may receive fosaprepitant orally to take on your own to prevent any nausea and vomiting that you may experience at home.

Less serious side effects that can occur include:

- nausea and/or vomiting
- heartburn
- stomach pain
- diarrhea or constipation

- loss of appetite
- hiccups
- increased thirst or hot, dry skin
- weakness, dizziness, tired feeling
- headache
- ringing in your ears
- fever, chills, body aches, flu symptoms
- sleep problems (insomnia)
- pain or a hard lump where the medicine was injected.

More serious side effects that can occur include:

- feeling light-headed
- fainting
- slow heart rate
- pale skin, easy bruising or bleeding
- pain or burning when you urinate

Side Effects of dexamethasone:

Dexamethasone will be given by IV before the paclitaxel protein bound, cisplatin and gemcitabine to prevent nausea and vomiting that you may experience.

Less serious side effects that can occur include:

- upset stomach
- stomach irritation
- vomiting
- headache
- dizziness
- insomnia
- restlessness
- depression
- anxiety
- acne
- increased hair growth
- easy bruising
- irregular or absent menstrual periods

More serious side effects that can occur include:

- skin rash
- swollen face, lower legs, or ankles
- vision problems
- cold or infection that lasts a long time
- muscle weakness
- black or tarry stool

Side Effects of ondansetron (Zofran®):

Ondansetron may be given in lieu or in addition to fosaprepitant to prevent/treat nausea and vomiting. Your doctor will decide what the best course of treatment is to prevent/treat any nausea/vomiting that you may experience.

Less serious side effects that can occur include:

- headache
- constipation
- weakness
- tiredness
- chills
- drowsiness

More serious side effects that can occur include:

- blurred vision or vision loss
- rash
- hives
- itching
- swelling of the eyes, face, lips, tongue, throat, hands, feet, ankles, or lower legs
- hoarseness
- difficulty breathing or swallowing
- chest pain
- shortness of breath
- dizziness, light-headedness, or fainting
- fast, slow or irregular heartbeat
- agitation
- hallucinations (seeing things or hearing voices that do not exist)
- fever
- excessive sweating
- confusion
- nausea, vomiting, or diarrhea
- loss of coordination
- stiff or twitching muscles
- seizures
- coma (loss of consciousness)

Additional medications not listed may be given to help treat any side effects. Please talk to your study doctor regarding any questions or concerns you may have about any side effects you are experiencing.

Reproductive risks

Women of childbearing potential are women who are biologically capable of becoming pregnant. This includes women who are using contraceptives or whose sexual partner is either sterile or using contraceptives.

The study drugs may affect an unborn child or nursing infant. The risks to an unborn child or nursing infant are not fully known. These drugs may also cause changes to eggs in women.

The following information is for women who are able to become pregnant:

- It is important that you do not become pregnant while in this study. If you become pregnant, you will be taken off this study.
- You must have a negative serum (blood) pregnancy test before you start taking the study drugs.
- If you do become pregnant or suspect you are pregnant, while you are on this study or through one month after the last dose of study treatment, you must notify your study doctor immediately.
- You must not breast feed at any time you are in this study since any drugs you are taking may also affect the child.

Birth Control Requirements for Female Participants:
If you are sexually active and able to become pregnant, you must agree to use two forms of highly effective birth control methods listed below:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

NOTE: Hormonal contraceptives alone are not considered an acceptable method of birth control for this study.

You must use birth control for the entire study and through one month after your last dose of study treatment.

Birth Control Requirements for Male Participants:
The study drugs may have a harmful effect on sperm. This can lead to damage to a fetus or embryo (developing unborn baby). If you are a fertile male, you must not impregnate a female while in this study. If you are sexually active, and able to father a child, you must agree to use two forms of birth control methods listed below:

- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Hormonal methods used by your partner, such as birth control pills, patches, injections, vaginal ring, or implants
- Intrauterine device (IUD) used by your partner
- Abstinence (no sex)

You must use birth control for the entire study and through one month after your last dose of study drug. If your partner becomes pregnant while you are on the study or through one month

after receiving the last dose of study medication, you will need to report this to your study doctor.

Risks from Study Procedures:

- **Risk of Infection:** In another study in subjects receiving the Paclitaxel Protein Bound, cisplatin, and gemcitabine combination treatment there were increased risks of infection. Subjects over the age of 80 years have a greater risk of developing this infection. Subjects that develop a fever should notify their study doctor or his team as soon as possible and may be asked to return to the study location for evaluation and possible treatment. If you develop a fever, you should begin taking the antibiotic provided to you at the first visit immediately. We will take reasonable safeguards to minimize known and potential risks but unknown and/or unanticipated side effects might occur. Some side effects go away when the study drugs are stopped. Others may be long lasting.
- **Risks with Intravenous (IV) Drug Administration**: Temporary irritation and bruising may occur at the infusion site. There may also be discomfort, pain, or bruising from the needle puncture. In rare cases, an infection may also occur at the site of the needle stick.
- **Risks of a Blood Draw:** Risks can also occur during blood draws. The risk of blood drawing may include bleeding, pain, lightheadedness, fainting, bruising, clotting, discomfort, and/or infection at the site of the needle stick. Your blood will be drawn weekly during the study. Depending on your condition, your study doctor may wish to perform additional blood draws.
- **Electrocardiogram (ECG):** This test uses small sticky pads that are placed on your chest and limbs to measure the electrical activity of your heart. There may be mild discomfort from the sticky pads and a possibility of the skin being irritated by the adhesive on the sticky pads. Chest hair may need to be shaved prior to the placement of the sticky pads.
- **CT (computed tomography) scans:** You may experience fear of being in a narrow or enclosed space while having a CT/MRI scan. You will be asked not to move during the test and to relax and breathe normally. A CT scan exposes you to a small dose of radiation. Although all radiation you receive builds up over your lifetime, this amount of radiation should not create a significant risk to your health. Contrast dye is usually injected when you get a CT scan. The contrast dye may cause pain or burning when it is injected, and may worsen kidney function in patients who already have kidney disease or who are dehydrated (have not had enough liquids that day). The contrast dye may also cause an allergic reaction, which could be severe and life-threatening.
- **MRI (magnetic resonance imaging):** There are risks from an MRI if you are pregnant or have one of the following: an artificial heart valve, pacemaker, metal plate, pin, or other metallic objects in your body (including gun shot or shrapnel). You may also become anxious from lying in a tight space without moving. The MRI scan does not cause any pain and does not expose you to x-ray radiation.
- **PET (positron emission tomography) scan**: A PET scan is an imaging technique that uses positively charged particles (radioactive positrons) to detect subtle changes in the body's metabolism and chemical activities. A PET scan provides a color-coded image of the body's function, rather than its structure. You may experience a mild skin prick when a substance called a tracer is injected into the vein. The tracer is radioactive but short lived and poses little to no risk.

- **Tumor Biopsy:** The tumor and skin biopsy procedures (to be carried out only in case an appropriate archived tumor sample is not available or if you agree to give additional samples) may be associated with pain, discomfort, bleeding, swelling, scarring, bruising, and infection. To reduce these risks, the site of the biopsy will be numbed and sterile techniques will be used.

Other Risks
In addition to the risks already described, there may be other discomforts or risks from the study drugs or study procedures which are unknown. You will be observed carefully for signs and symptoms of possible side effects. If you experience any unusual symptoms, please inform your study doctor immediately.

If you have any questions about the risks of participating in this research study, you may ask the study doctor, another study team doctor, or your regular doctor. You may ask questions now or you may call the study doctor at the phone number on the first page of this form.

There may be side effects that are not known at this time. Your condition may get better or may get worse during this study. Your chemotherapy regimen may be interrupted or reduced if you experience any side effects that are caused by the medications you are receiving while you are enrolled in this study. It is not known how the addition of the high dose Vitamin C to the standard chemotherapy regimen for this study will affect your treatment. It is important to report any changes in your health immediately to the study doctor or a member of the study team and to follow all instructions provided to you.

It is important to discuss any changes in your medications before any changes are made. While you are receiving treatment on this study, you are not allowed to take the following medications/treatments:

- Acetaminophen and all acetaminophen-containing products (within 72 hours of first dose of vitamin c 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.

You must use caution with using the following medications while receiving vitamin C infusions:

- Aluminum-containing antacids – Vitamin C may increase the absorption of aluminum hydroxide.
- Amphetamines - Vitamin C 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).

- Any drugs that could cause damage to your liver (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs). Cisplatin nephrotoxicity may be exacerbated by treatment with these medications.

NEW INFORMATION
You will be told about anything new that might change your decision to be in this study. If there is new information, you may be asked to sign a new consent form.

BENEFITS
It cannot be promised that you will receive any medical benefits from being in this study.

There may be no direct medical benefit to you from participating in this study, except you may gain information about your health from the different tests that are done as part of the study. Information obtained from this study will benefit the sponsor. It might also lead to treatments that help others in the future.

COSTS
The sponsor will pay for all procedures and tests done specifically for this research study. Those treatments, procedures (including drug infusions) and tests that you would be likely to receive whether you were in the study or not, are not paid for by the study sponsor, and are considered "standard of care" for your medical condition. If you have health insurance, the cost of these "standard of care" services will be billed to your insurance company. Your health insurance may not cover these costs because of your participation in this research study. If it does not, the costs will be your responsibility. If you do not have health insurance, the cost of these "standard of care" services will be billed to you.

You might have unexpected expenses from being in this study. Ask your Patient Financial Counselor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

You may need to receive medical care that is not listed in this document. HonorHealth will not cover the costs of that care.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

PAYMENT FOR PARTICIPATION
You will receive a $100 stipend to help with costs of your time and travel at Day 1 of Cycle 1 and at your EOT visit. Total stipend for completing the study is $200.

ALTERNATIVE TREATMENT
There are other treatment options for locally advanced pancreatic cancer. These options include other chemotherapy regimens, radiation, or other experimental therapy. You could receive paclitaxel protein bound, gemcitabine, and cisplatin without being in the study. Other options include chemotherapy such as 5-Fluorouracil (5-FU) alone or in combination with other drugs such as irinotecan and/or oxaliplatin. Your study doctor will explain the other options available

to you. You do not have to participate in this study to receive treatment for your condition. You may also choose to receive no treatment for your cancer.

If you decide that you don't want any more active treatment, one of your options is called "comfort care." Comfort care includes pain medication and other support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home.

If you think you might prefer comfort care, please discuss this with your family, friends and your doctor.

CONFIDENTIALITY OF YOUR INFORMATION COLLECTED DURING THE STUDY
As required by the Federal Health Insurance Portability and Accountability Act (HIPAA), every effort will be made to safeguard the confidentiality of information that identifies you and relates to your past, present and future physical and mental health. We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law.

Unless required by law, you will not be identified on any electronic form by name, social security number, address and telephone number or any other information that can directly identify you. The information shared with the Sponsor is protected by the use of a code, which is a number specifically assigned to you. The study doctor is in control of the code needed to connect your data to you, but the study doctor will not send the list with the code to the Sponsor. However, the study forms may contain other information about you, such as your age, sex and medical history. It is possible that this other information could be used to identify you even though your name does not appear.

The results of this study may be published by the Sponsor, including in a medical journal and shown at medical meetings. You will not be identified (by name or any other means, e.g., photo) in any of these publications.

Because this research is regulated by the Food and Drug Administration (FDA), the FDA may inspect records related to this research, which may include your protected health information or other information about you derived or maintained as part of this study. The Institutional Review Board will also have access to your research records.

Information derived from this study may be used for research purposes that may include publication and teaching. However, information used for publication and teaching will not disclose your identity.

COMPENSATION FOR INJURY
We will make every effort to prevent study-related injuries and illness. If you are injured or become ill while you are in the study and the illness or injury is due to your participation in this study, you may go to any emergency room or urgent care facility to seek medical treatment. The costs of this care will be charged to you or to your health insurer. No funds are available from HonorHealth to compensate you for a study-related injury or illness.

The study doctor will provide you medical care if you need it, and will also treat you for any complications that may occur during your participation in the study. If you become ill or are injured as a direct result of your participation in this study, you will be provided the reasonable and necessary treatment for that injury or illness. The bills for the injury or illness not caused by study participation may be billed to your medical insurance or to your third party or governmental programs in which you participate.

The sponsor **may** reimburse costs for documented medical expenses for injury or illness caused by administration of study drug in accordance with the protocol or any properly performed procedures required by the protocol including if a deviation from the protocol is necessary to protect your rights, safety or welfare. The Sponsor will not reimburse costs for injury caused by your failure to follow your study doctor's or study staff's instructions for the study. The Sponsor will not offer to pay costs of medical care for such an injury or items such as lost wages, expenses, compensation for pain and suffering, discomfort and disability. Please speak with your study doctor to make sure you understand your options regarding compensation for injury.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to take part or you may leave the study at any time. Your decision will not cause any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any of the following reasons:

- your cancer becomes worse
- side effects arise which prevent further study treatment
- you decide to withdraw from the study
- changes in your condition occur that lead your study doctor to believe that it would be harmful for you to receive further study treatment
- you become pregnant or fail to use adequate birth control (if you are of child-bearing potential)
- another anticancer medication is started
- you cannot or will not follow the instructions for participation in the study
- the study doctor decides it is in your best interest not to continue in the study.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

HonorHealth has received funding from the Translational Genomics (TGen) Foundation, Stand Up to Cancer (SU2C), Cancer Research UK, and Lustgarten Foundation to conduct this research study. Your study doctor is receiving a salary from HonorHealth as an employee but will not receive any additional payments for conducting this study.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information will be collected by the study doctor and his research staff for this study?
The study doctor will collect your personal and medical information. This may include:

- Past and present medical records,
- Research records,
- Records about phone calls made as part of this research,
- Records about your study visits.

Who may use and give out information about you?
The study doctor and his research staff conducting the research.

Who will receive your personal and medical information collected?
Information from this study will be given to the study sponsor. "Sponsor" is the person or entity that initiates, provides oversight of activities within the study, and includes any persons or companies that are contracted by the sponsor to have access to the research information during and after the study. Medical records which identify you and the consent form signed by you will be looked at and collected for research purposes by:

- HonorHealth Research Institute including facilities affiliated with HonorHealth, the Sponsor and study site
- Stand Up to Cancer (SU2C), providing funding for the study
- Translational Genomics (TGen) Foundation, providing funding for the study

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported,
- Western Institutional Review Board (WIRB®),
- HonorHealth Institutional Review Board.

The HonorHealth IRB and the HonorHealth Research Institute have the authority to review and monitor all records related to this research.

Why will this information be used and/or given to others?

- for research purposes as described in this consent form,
- for consideration by the FDA or any governmental agencies in other countries for drug approval,
- to make sure the study was conducted as approved by the FDA and IRB,
- to be used for future research purposes.

What will happen if you decide not to give permission to use and give out your private health information?
You cannot be in this research study.

Will you have access to the information collected during the study?
To maintain the integrity of this research study, you will not have access to your personal health information related to this research until the study is complete. At the conclusion of the research and at your request, you may request access to your health information that HonorHealth maintains in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at HonorHealth. If it is necessary for your care, your health information will be provided to you or your physician.

Does this authorization expire?
This authorization does not expire unless it is canceled by you in writing.

Can this authorization be withdrawn or canceled?
You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is your health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission. Absolute confidentiality cannot be guaranteed because of the need to give information to these parties.

QUESTIONS
Contact Gayle S. Jameson, RN, MSN, ACNP-BC, AOCN at 480-323-1350 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if at any time you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns, or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns, input, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE, Suite 120
Puyallup, Washington 98374
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

ClinicalTrials.gov
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Genetic Information Nondiscrimination Act (GINA)
A federal law (2009), called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information.

Health insurance companies and health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. This federal law protects you against genetic discrimination by companies that sell insurance including life, disability, or long-term care insurance.

LABORATORY SAMPLES FOR FUTURE RESEARCH
HonorHealth will use any leftover bio-specimens including blood, urine, fecal and/or tissue samples for additional biomarker testing and for long term storage for future research. This is not optional. Please initial below to document your consent to this research.

_____ I DO agree to allow HonorHealth to use my leftover bio-specimens as described above.

_____ I DO NOT agree to allow HonorHealth to use my leftover bio-specimens as described above. I understand that if I do not agree to this, I cannot participate in this study.

REPEAT TUMOR BIOPSY AT CYCLE 2, DAY 15 - OPTIONAL
Please initial below to document your consent to the optional tumor biopsy at your Cycle 2, Day 15 visit. This is completely optional. If you do not wish to have an additional biopsy done, you can still participate in this study.

_____ I DO agree to the optional tumor biopsy at Cycle 2, Day 15.

_____ I DO NOT agree to the optional tumor biopsy at Cycle 2, Day 15.

CONSENT

I have read this consent form and understand what has been discussed. All my questions about the study and my part in it have been answered. I voluntarily consent to be in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

_____
Name of Person Conducting Informed Consent Discussion (printed)

_____ _____
Signature of Person Conducting Informed Consent Discussion Date