IRB APPROVED
AS MODIFIED
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RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: A Phase II Pilot Trial of Nivolumab + Albumin- Bound Paclitaxel + Paricalcitol + Cisplatin + Gemcitabine (NAPPCG) in Patients with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma

PROTOCOL NO.: NAPPCG-EB 2015-001
WIRB® Protocol # 20160267

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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.

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.

You are being asked to participate because you have been diagnosed with advance pancreatic cancer and your doctor has determined that you may be a good candidate for the treatment being offered to the study participants that qualify for the study.

PURPOSE OF THE STUDY

The purpose of this study is to find out if the experimental combination of study drugs nivolumab, albumin- bound paclitaxel, paricalcitol, cisplatin, and gemcitabine given together are safe and effective.

The combination of albumin-bound paclitaxel plus 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.

In the present study, the agents paricalcitol (a synthetic vitamin D analog), nivolumab (a drug that stimulates the immune system to fight the cancer), and the anticancer agent cisplatin will be added to albumin-bound paclitaxel plus gemcitabine combination, and tested in people who have not yet had any cancer therapy for the diagnosis of advanced pancreatic cancer. The goal of this study is to improve response to treatment.

Nivolumab is approved for the treatment of advanced melanoma (an aggressive type of skin cancer), a subtype of lung cancer called squamous cell lung cancer, advanced renal cell cancer (type of kidney cancer), Hodgkin Lymphoma that has progressed after stem cell transplant, and squamous cell carcinoma of the head and neck. It is not approved by the FDA for the treatment of advanced pancreatic cancer.

Paricalcitol is a potent form of Vitamin D used to prevent bone loss is patients with advanced kidney disease. Paricalcitol is not approved by the FDA for treatment of advanced pancreatic cancer.

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.

Gemcitabine was approved by the FDA in 1996 for the treatment of pancreatic cancer. It is also an approved treatment for ovarian cancer, lung cancer, and breast cancer.

The Food and Drug Administration has determined that this study meets the requirements for Investigational New Drug (IND) Exemption.

How Many Subjects Will Take Part in the Study?
This study will be conducted at up to 2 cancer centers in the US. 10 individuals will initially be enrolled. Based upon safety and efficacy analysis, an additional 25 individuals may be enrolled for a total of 35 individuals in the US. Enrollment into this study will be competitive meaning first come first served.

PROCEDURES
The study will consist of the following parts:

- Screening Evaluation
- Study Treatment Assessments
- Office Visit after Last Dose of Study Treatment
- Continuation of Therapy Treatment Assessments
- Post-Study Follow-up

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
- Karnofsky Performance Status
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- 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 first dose, a new scan is not necessary.
- Electrocardiogram (ECG)
- Collect blood for laboratory tests. About 3 tbsp. will be taken for the following tests:
    - Hematology - Complete blood count (CBC) with differential and platelet count

  - Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
  - Thyroid Stimulating Hormone (TSH) to include reflex T3 and T4 if abnormal
  - Vitamin D levels
  - Coagulation Panel including 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
- Receive stool sample collection kit with instructions to be reviewed with study staff. **Note:** the stool sample will need to be returned to the site within 72 hours of collection.
- Review all medications taken within the last 30 days
- Collect any archived tumor tissue, if available
- Complete questionnaires regarding quality of life and pain

Study Treatment and Assessments:

If you meet the study requirements during the screening period, you will then begin the study treatment phase of the study. You will receive the following study treatment regimen over a 6 week period of time. This 6 week period is called a cycle.

- Nivolumab 240 mg will be given over one hour as an intravenous (IV) infusion on days 1, 15, and 29.
- Albumin-bound paclitaxel 125 mg/m^2 will be given over 30 minutes as an IV infusion on days 1, 8, 22 and 29
- Cisplatin - 25 mg/m^2 will be given over one hour as an IV infusion after the albumin-bound paclitaxel is completed on days 1, 8, 22 and 29. On the days you are to receive cisplatin you will be given a total of about 4 hours of hydration (IV fluid) to reduce the risk of damage to your kidneys. You will be given 2 hours of hydration prior to the chemotherapy and 2 hours of hydration after the chemotherapy is complete
- Gemcitabine 1000 mg/m^2 will be given over 30 minutes as an IV infusion after the cisplatin dose is completed on days 1, 8, 22 and 29
- Paricalcitol 25 mcg will be given intravenously on days 1, 4, 8, 12, 15, 18, 22, 26, 29, 32, 36, and 39
- On the days you are to receive albumin-bound paclitaxel, cisplatin and gemcitabine you will also receive medication to help prevent nausea and vomiting prior to the chemotherapy

During dosing in this study treatment, you will receive another medicine called granulocyte colony-stimulating factor (G-CSF) which is also known as pegfilgrastim (Neulasta). G-CSF helps your body form more white blood cells and may help some of the common side effects of the study drugs. The type, dose level, and administration of the G-CSF will be determined by your study doctor.

On your first visit, you will be provided ahead of time with enough supply of an antibiotic called ciprofloxacin (or an alternative antibiotic) for use at home. If you develop a fever, you should begin taking the antibiotic when you first record a temperature of about 38.5 °C (about 101°F) or if you feel you are developing a fever and a thermometer is not available. In addition**, if you develop a fever, you should notify your study doctor immediately or his/her team as soon as possible.** You may be asked to return to the study location for evaluation and possible treatment.

With nivolumab and albumin-bound paclitaxel, or gemcitabine alone or in combination, a few patients in other studies have had a condition called interstitial pneumonitis—a very serious lung condition. Therefore, during dosing in this study treatment, if you experience shortness of breath or develop a dry cough, **you should notify your study doctor or his/her team as soon as possible.** You may be asked to return to the study location for evaluation and possible treatment.

In addition, the drug nivolumab has been associated with inflammation of the colon. If you have more than 3 stools per day, **you should notify your study doctor or health team as soon as possible.** Nivolumab has also been associated with inflammation of the thyroid, liver and/or kidneys. The blood testing that is done for you by the study team will be used to monitor for that inflammation.

<u>The following evaluations will be performed prior to dosing on **Day 1, 22 and 29 of each cycle**</u>

- Directed physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight
- Body Surface Area (BSA) calculation prior to dosing
- Karnofsky Performance Status
- Collect blood for laboratory tests. About 2 Tbsp will be taken for the following tests:
    - Hematology: CBC with differential and platelet count
    - Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
    - CA 19-9 (or CA 125 or CEA if not expressers of CA 19-9)
    - Thyroid Stimulating Hormone (TSH) to include reflex T3 and T4 if abnormal
    - Peripheral Blood BioMarker
    - Serum Pregnancy (if applicable)
- 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

The following evaluations will be performed on **Day 8, 15 and 36 of each cycle**

- Directed physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight (weight will not be measured on Day 15 and 36)
- Karnofsky Performance Status (KPS)
- Collect blood for laboratory tests. About 1 Tbsp will be taken for the following tests:
    - Hematology: CBC with differential and platelet count
    - Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
- 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 (Days 8 and 15 only)

The following evaluation will be performed on **Day 39 of each cycle**

- Receive stool sample collection kit with instructions to be reviewed with study staff. **Note:** the stool sample will need to be returned to the site within 72 hours of collection.

Every 6 weeks prior to each cycle

- CT scans of the chest, abdomen, and pelvis or any other studies required for tumor imaging (such as MRI), will be done every 6 weeks while you are on treatment. This will be the same type of imaging that you had at the screening evaluation
- It will also be determined by your physician/nurse if a PET scan is necessary depending on your tumors response to the treatment.

You will be treated until one or more of the following occur:

- 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.

Office Visit after Last Dose of Study Treatment:

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:

- Directed physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).

- Measurement of weight
- Karnofsky Performance Status
- Collect blood for laboratory tests. About 2 Tbsp will be taken for the following tests:
    - Hematology: CBC with differential and platelet count
    - Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
    - CA 19-9
    - Thyroid Stimulating Hormone (TSH) and any reference tests as required
    - Serum Pregnancy (if applicable)
- Collect a urine sample for a urinalysis
- CT scan of chest, abdomen, and pelvis and any other studies required for tumor imaging (only if your previous CT scan was >5 weeks ago)
- 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

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 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 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:

- Directed physical exam
- Vital signs (blood pressure, pulse, respiratory rate, and temperature).
- Measurement of weight
- Karnofsky Performance Status
- Collect blood for laboratory tests. About 1 Tbsp will be taken for the following tests:
    - Hematology: CBC with differential and platelet count
    - Serum chemistries (for hepatic and renal function tests) including: blood urea nitrogen (BUN), phosphorus, magnesium, creatinine, creatinine clearance, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and electrolytes (chloride, sodium, potassium, and bicarbonate).
- Review any changes to your health since the last visit
- Review any changes to your medications since the last visit

Other Study Requirements:
You must not use any prescription medication during the study without first checking with the study doctor. You must agree to not participate in any other research study while participating in this study. You must have stopped taking any research medications at least 4 weeks prior to enrolling in this study. You must have also stopped all other anti-cancer medications for this research study. Your study doctor will inform you of how long you must be off those medications to participate in this research study.

How Long Will the Study Last?
The length of time that you participate in the trial will depend on whether your cancer gets better or worse in response to the study treatment. It is expected that you will stay on study treatment as long as your cancer improves or is stable or until your cancer gets worse, side effects become intolerable, or you or your study doctor decide to not continue in the study. Long term follow-up will take place for 24 months after you stop study treatment.

RISKS AND DISCOMFORTS
Participation in this research study may involve added risks and discomforts, including the possible side effects of the study treatments described in this form, (see table below). There also may be other potentially serious side effects that are not yet known. Let your study doctor know about any side effects you are experiencing. Your study doctor may be able to give you other drugs to make side effects less serious or uncomfortable. Many side effects go away after the study treatment is stopped but, in some cases, these side effects may be serious and/or long lasting. Rarely, side effects could be fatal (causing death).

Nivolumab
Common side effects related to Nivolumab:
- Adrenal disorders
- Anemia (low red blood cell count – which may cause you to feel tired, look pale, and have shortness of breath)
- Appetite loss
- Diarrhea
- Difficulty breathing
- Fatigue
- Fever
- Joint and muscle pain
- Nausea
- Rash - * skin reactions including rash, itching, hives, redness and dry skin toxic epidural necrolysis, a potentially life threatening disease characterized by blistering and peeling of the skin resembling a severe burn has been seen in one patient receiving ipilimumab after nivolumab.

Less common side effects related to Nivolumab:
- Constipation
- Abnormal liver function tests
- Low platelet count (which can lead to bruising or bleeding)

- Thyroid abnormalities
- Vomiting

Rare but potentially serious side effects related to Nivolumab:

- Allergic reaction
- Blood and protein in the urine
- Cough
- Difficulty breathing
- Abnormal kidney function / failure
- Low blood oxygen level
- Acute lung injury or failure
- Collection of fluid around the lungs
- Inflammation of the appendix
- Increase in inflammatory blood proteins (e.g. lipase)
- Adrenal gland abnormalities
- Pituitary gland inflammation
- Changes in vision (including decreased or blurry vision), inflammation of the eye or bleeding into the eye
- Liver inflammation
- Acute kidney injury or failure
- Abnormal blood cell production
- Inflammation of the mouth and lining of the digestive tract
- Swelling of the face, arms or legs
- Inflammation of the pancreas
- Back pain
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Chest discomfort
- Heart palpitations
- Inflammation of the heart or its lining
- Collection of fluid around the heart
- Increased blood sugar
- Dehydration
- Infections: including sepsis, lung infections, and skin infections
- Decreased movement of the intestines
- Disorientation
- Swelling of the optic disc
- Inflammation of the optic nerve
- Inflammation of the lining of the brain and spinal cord
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Myasthenia Gravis, a nerve disease which may cause weakness of eye, face, breathing, and swallowing muscles.
- Abnormal brain function due to brain inflammation

- Rhabdomyolysis (muscle fiber released into the blood stream which could damage your kidneys) and polymyositis (chronic muscle inflammation with muscle weakness) has been reported in one patient

Albumin-Bound Paclitaxel
Common side effects of Albumin Bound Paclitaxel:

- 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 Albumin Bound Paclitaxel:

- 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 Albumin bound Paclitaxel:

- Allergic reaction
- Cough
- Difficulty breathing
- Heart 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
- Low platelet count (which can lead to bruising or bleeding)
- 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)
- Cough
- 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

Paricalcitol
Rare toxicities related to Paricalcitol:

- High blood calcium
- Kidney stones

Risk of Infection:
In another study in subjects receiving the albumin bound paclitaxel, 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.

Other Medications
Before each dose of study drug(s), your study doctor may decide to 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.

Side Effects of G-CSF or pegfilgrastim (Neulasta®):
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 disc (symptoms include headache, blind spot, blurring of vision and/or loss of vision)

Side Effects of palonosetron (Aloxi®):
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®):
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:
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®):
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)

Risks with Intravenous (IV) Drug Administration:
Nivolumab, albumin bound paclitaxel, cisplatin, and gemcitabine are given as IV infusions. 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.

Risks of CT Scans, MRI Scans and PET Scans:
CT scanning uses X-rays to create images of tissue below the skin. The risk of X-rays is slight. The amount of X-ray exposure that most people receive in a lifetime is not known to produce any illness. An allergic reaction to the dyes used to perform the CT scans is a possible risk of the procedure.

MRI uses magnetic fields to produce high-quality images of tissue below the skin. Therefore, subjects with metal in their bodies (such as cardiac pacemakers, metal prostheses [artificial body parts] and magnetic clips) will not be imaged. Otherwise, the risk of MRI is slight.

PET (positron emission tomography) 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.

Risks to Women of Child Bearing Potential:
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.
- 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 for 5 months after the last dose of study drug, you must notify your study doctor immediately.
- If you become pregnant, you will be taken off this study.
- You must agree to use **two** forms of highly effective birth control at the same time that are medically acceptable to your study doctor, throughout the study and for 5 months after the last dose of study medications. The study doctor will discuss the appropriate methods of contraception with you. **NOTE: Hormonal contraceptives alone (the "pill") are not considered an acceptable method of birth control for this study.**

You must not breast feed at any time you are in this study since any drugs you are taking may also affect the child.

Risks to Men of Reproductive Potential:
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. You must agree to use a form of birth control, along with the method your partner is using, that is medically acceptable to your study doctor during the study. You should continue the use of your birth control methods following your last dose of study drugs and for 5 months after your last dose. If your partner becomes pregnant while you are on the study or within 5 months of receiving the last dose of study medication, you will need to report this to your study doctor.

Unknown 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 not get better or may get worse during this study.

NEW INFORMATION
You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
There may or may not be direct medical benefits to you from taking part in this study, except you may gain information about your health from the different tests (ECGs, laboratory tests, and physical exams) that are done. The expected benefit of taking part in the study may be similar to that of getting commonly used chemotherapy. Gemcitabine combined with albumin bound

paclitaxel has been shown to be effective in patients with metastatic pancreatic cancer. However, it is unknown if nivolumab plus albumin bound paclitaxel plus paricalcitol plus cisplatin given together with gemcitabine will be as effective, more effective, or less effective than other commonly used chemotherapies.

The information learned from this study may help future patients with metastatic pancreatic cancer.

COSTS
The sponsor, HonorHealth, 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 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.

You might have unexpected expenses from being in this study. Ask your study doctor 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.

PAYMENT FOR PARTICIPATION
You will not be paid for being in this study.

ALTERNATIVE TREATMENT
There are other treatment options for metastatic pancreatic cancer. These options include other chemotherapy regimens, radiation, or other experimental therapy. You could receive nab-paclitaxel, gemcitabine, and cisplatin without being in the study.

Other options include capecitabine. 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.

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.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES
The United States government has issued a privacy rule to protect the privacy rights of patients. This rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your protected health information (PHI). The document you are reading, called an "Authorization," explains how your PHI will be used and disclosed (shared) for purposes of the research study and describes your rights with respect to such information.

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- 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 the 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, the Sponsor
- HonorHealth Research Institute, the study site

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, and
- Western Institutional Review Board® (WIRB®)
- HonorHealth Human Subjects Research Protection Program (HSRPP)
- Bristol Myers Squibb who is supplying the drug and supporting some of the costs of the study

The HonorHealth HSRPP 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 if I decide not to give permission to use and give out my health information?
Then you will not be able to 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 my 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.

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 routinely available from HonorHealth to compensate you for a study-related injury or illness. This does not mean that you are giving up any of your legal rights.

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 will be billed to your insurance or to your third party or governmental programs in which you participate.

If you have out of pocket expenses not covered by your insurance, the Sponsor **may** reimburse you. Please speak with your study doctor to make sure you understand your options regarding compensation for injury.

LABORATORY SAMPLES FOR FUTURE RESEARCH
HonorHealth would like to use any leftover blood and tissue samples for biomarker testing and for future research. By agreeing to participate in this study you are authorizing HonorHealth to use any leftover blood and tissue samples for biomarker testing and for future research, not defined at this time. If your samples are used in future research, they may be shared with researchers who are not part of HonorHealth. All samples will be stored with no identifying information attached to the sample.

In addition, HonorHealth will be collecting stool samples from you for gut microbiome and/or mycobiome testing. By agreeing to participate in this study you are authorizing HonorHealth to collect and send your stool samples for microbiome testing and for future research, not defined at this time. All samples will be send with no identifying information attached to the sample.

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:

- serious side effects of the study drug;
- worsening of your cancer despite treatment with the study drug;
- a change in your condition that prevents you from continuing with the study;
- your being unable to follow the schedule or procedures required by the study;
- the sponsoring company may stop your participation if study drug ceases to be available or for other reasons;
- You become pregnant;
- you do not consent to continue in the study after being told of changes in the research that may affect you;
- at the discretion of the study doctor for any reason

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.

QUESTIONS
Contact Erkut Borazanci, MD at 480-323-1350 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 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 (toll free) 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.

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.

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

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date