SUMMARY OF CHANGES -- Consent

NCI Protocol #: 10208
Local Protocol #: PJC-026

NCI Version Date: 23 August 2023
Protocol Date: 23 August 2023

#	Section(s)	Page(s)	Change
1.	Header	All	Version date updated to 23 August, 2023
2.	Risk **List** Nivolumab	13	Addition of new Nivolumab risk to the rare and serious risks list. Risk of *swelling of arms and legs which may cause a feeling of heaviness and tightness* added per updated Nivolumab IB.

Research Study Informed Consent Document

Study Title for Participants: Testing the combination of anetumab ravtansine with either nivolumab, nivolumab and ipilimumab, or gemcitabine and nivolumab in advanced pancreatic cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10208/PJC-026, A Phase I study of Anetumab Ravtansine in Combination with either Anti-PD-1 Antibody, or Anti-CTLA4 and Anti-PD-1 Antibodies or Anti-PD-1 Antibody and Gemcitabine in Mesothelin-Positive Advanced Pancreatic Adenocarcinoma

Overview and Key Information

This is a phase I study. Phase I means that these drugs or multiple drugs are used or combined for the first time in the clinic and you may be one of the first participants to be treated with this combination of drugs. In phase I studies we evaluate how safe it is to combine multiple medications, what is the best dose to give in combination, and look for possible signs of activity, which means see if these medications control your cancer.

In the Dose Escalation portion of the study we evaluated if anetumab ravtansine in combination with the drugs mentioned above could be safely given to participants, what was the best dose to give in combination, and if adding anetumab ravtansine to either immunotherapy (nivolumab or nivolumab and ipilimumab) or chemotherapy with immunotherapy (gemcitabine and nivolumab) will increase the effect of the immune system in participants with pancreatic cancer.

Based on safety and response data from the Dose Escalation portion of the study, the safest combination for dosing was determined to be Group 3 (anetumab ravtansine in combination with gemcitabine and nivolumab). The purpose of Dose Expansion portion of the study is to confirm the observation of the safety profile of Group 3 in both dose level 1 of anetumab ravtansine (5.5mg/kg) in combination with gemcitabine and nivolumab or dose level 2 of anetumab ravtansine (6.5 mg/kg) in combination with gemcitabine and nivolumab. Anetumab ravtansine has an expiry date of June 30, 2023 after which treatment will continue with gemcitabine and nivolumab for the duration of the subject participation.

What am I being asked to do?

We are asking you to take part in a research study because you have pancreatic adenocarcinoma that has spread outside of your pancreas, and you have already received a treatment considered effective for your disease but your cancer has now progressed. We do research studies to try to answer questions about how new medications can be combined in a safe way and how these combinations can be used to treat your cancer.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take your time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in this study. It is important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

For **Dose Escalation** portion, this study was being done to answer the following questions:

1) Are the combinations of the following medications safe when given together?
    - Group 1: anetumab ravtansine and nivolumab
    - Group 2: anetumab ravtansine, nivolumab and ipilimumab
    - Group 3: anetumab ravtansine, gemcitabine and nivolumab
2) What effect (good and/or bad) does this intervention have on you and your cancer?

For **Dose Expansion** portion, this study is being done to confirm data of safety and treatment response observed in Group 3 at two different dose levels of anetumab ravtansine:

- Group 3 Dose Level 1: 5.5 mg/kg anetumab ravtansine, gemcitabine and nivolumab
- Group 3 Dose Level 2: 6.5 mg/kg anetumab ravtansine, gemcitabine and nivolumab

You will be participating in **Dose Expansion** portion of the study

Anetumab ravtansine is a drug that targets a protein called mesothelin, which can be found in some pancreatic tumors, and we are doing this study to see if it has anti-tumor activity in your type of cancer when used in combination with other medications as described above (Group 1, Group 2 or Group 3). Your tumor was tested to see if it has mesothelin. The combinations of anetumab ravtansine and nivolumab (Group 1) or nivolumab and ipilimumab (Group 2) or gemcitabine and nivolumab (Group 3) are investigational and have not been approved by the Food and Drug Administration (FDA) for treatment of pancreatic cancer. Gemcitabine is approved by the FDA and is commercially available. Nivolumab and ipilimumab are FDA approved but not in pancreatic cancer. Anetumab ravtansine is investigational.

What is the usual approach to treat my cancer?

The usual approach for participants who have pancreatic cancer that has spread outside of the pancreas and cannot be removed with surgery is chemotherapy. The usual medications used and approved by FDA are:

- Gemcitabine
- Gemcitabine and nab-paclitaxel
- Gemcitabine and erlotinib

- Oxaliplatin, irinotecan, leucovorin, and fluorouracil (5-FU)

When the disease grows (progresses) despite one of these interventions, there is no standard option but some of the above-mentioned medications can be tried. Other options include radiotherapy, surgery or comfort care, also called palliative care to relieve the symptoms from the cancer. This option is defined as best supportive care.

What are my choices if I decide not to take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- You may choose to have the usual approach described above
- You may choose to take part in a different study, if one is available
- You may choose not to be treated for cancer. You may choose to get comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

What will happen if I decide to take part in this study?

If you decide to take part in this study, till June 30, 2023 you will get either 5.5 mg/kg or 6.5 mg/kg anetumab ravtansine with gemcitabine and nivolumab (Group 3). After June 30, 2023, if you would be benefitting from the study, you will continue receiving gemcitabine and nivolumab for up to 1 year or until progression of your cancer. As the safety of both dose levels has been established, the expansion portion of the study for both dose levels will be open simultaneously and you will be informed of the dose level you will be participating in at the time of signing the consent.

After you finish your study intervention, your doctor and study team will watch you for side effects or until your cancer has progressed if you did not come off intervention for progression. This will be completed over the phone or in clinic every 8 weeks.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that:

- The study drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

- There is also a risk that you could have side effects from the study drugs. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

The tables below show the most common and the most serious side effects that researchers know about. If important new side effects are found, the study doctor will discuss these with you.

Anetumab:
- Diarrhea, nausea
- Tiredness

Nivolumab
- Tiredness

Gemcitabine:
- Flu-like symptoms (muscle pain, fever, headache, chills, fatigue)
- Fever (within 6-12 hours of first dose)
- Fatigue
- Nausea (mild)
- Vomiting
- Poor appetite
- Skin rash
- Low blood counts.

There may be some risks that the study doctors do not yet know about.

Benefits

If you agree to take part in this study, the experimental intervention may or may not be of direct benefit to you. It is unlikely that this combination and dose level of intervention will help you live longer. This study may help the study doctors learn things that may help other people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. If you stop, you can decide if you want to keep letting the study doctor know how you are doing and provide your medical information to the organization running the study.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor. The study sponsor is the organization that oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to test the safety of the drug combinations of two dose levels of anetumab ravtansine with gemcitabine and nivolumab (Group 3). This study tests different doses of the drug to see which dose is safer for people with pancreatic cancer.

This particular study focuses on participants like you who have pancreatic cancer and have received at least a systemic therapy, such as chemotherapy.

Anetumab ravtansine is a new drug that targets a protein called mesothelin. This protein is found only on a few normal cells, but can be found in certain types of cancer. Pancreatic cancer often expresses the mesothelin protein (expressed in 80% or more of cases). This drug functions only where it can find the mesothelin protein. Your saved tumor tissue has already been tested and expresses the mesothelin protein.

Anetumab ravtansine has already been used in the clinic alone but in this study will be combined with immunotherapy (nivolumab) and chemotherapy (gemcitabine) till June 30, 2023 after which only nivolumab and gemcitabine will be administered.

There will be about 20 people taking part in the **Dose Expansion** portion of this study.

What are the study groups?

There were two parts in this study, a dose escalation part and a dose expansion part. Dose Escalation has been completed and you will be participating in Dose Expansion portion of the study.

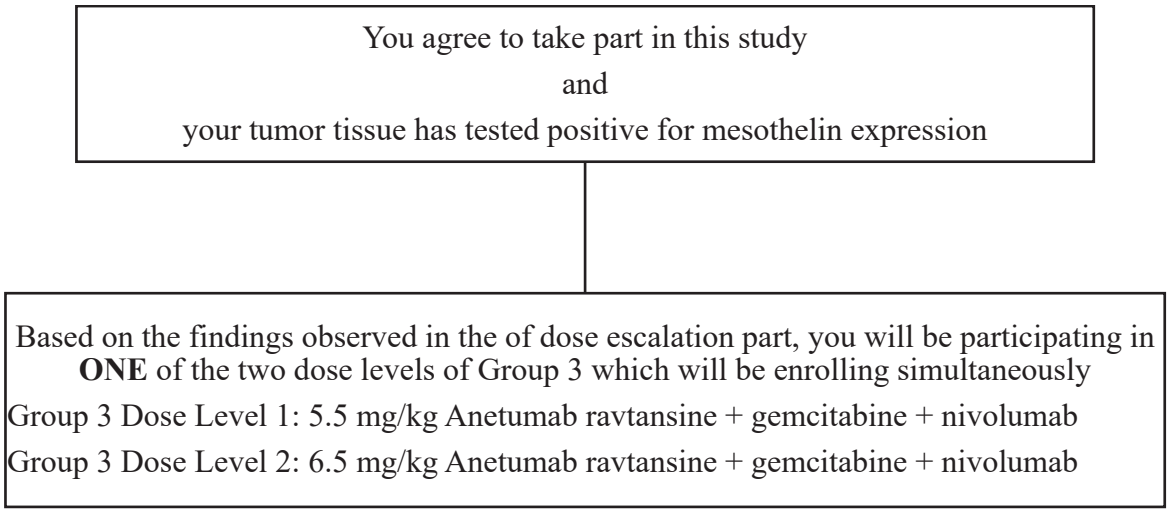
This part of the study will have a lead-in phase of 1 week where participants receive either:

- 5.5 mg/kg Anetumab ravtansine with gemcitabine and nivolumab
- 6.5 mg/kg Anetumab ravtansine with gemcitabine and nivolumab

In this part of this study, people with mesothelin positive pancreatic cancer (as identified by the pre-screening tests completed on your tissue) will be placed into ONE of the Group 3 dose levels. The study drug combination will be given to 10 people in each dose level (total 20). This will help study doctors to better understand the side effects that may occur with these drugs, compare and evaluate the potential effect of the dose level and combination on pancreatic cancer.

In this Group, you will get anetumab ravtansine with gemcitabine and nivolumab. All three drugs are given through the vein in the arm. Anetumab ravtansine will be given every three weeks till June 30, 2023, nivolumab and, gemcitabine are given every 3 weeks as follows: once a week for 2 weeks while the 3rd week is considered the resting week. The drugs, except Anetumab ravtansine, will be given for a maximum of 1 year or until progression of your cancer. Anetumab ravtansine and nivolumab are not approved by the FDA for your type of cancer, while gemcitabine is commercially available.

Another way to find out what will happen to you during the dose expansion part of the study is to read the chart below. Start reading from the top and read to the bottom.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Before you begin the study:
Your tumor sample must be tested for mesothelin and be positive. You will need to have the following extra exams, tests and/or procedures to find out if you can be in the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Review your medical and surgical history: This includes questions about medical illnesses, medications, past radiation or anti-cancer therapy you have received, past surgeries, and allergies. You will also be asked to list what medications and/or dietary supplements you are taking.

- Your doctor will do a physical exam that includes collection of vital signs (blood pressure, temperature, heart rate and level of oxygen in your body, height and weight).
- You will be asked to provide blood samples for checking bone marrow, liver, kidney, coagulation (how easy or not your blood can clot) function. A blood test to check for hepatitis will also be performed.
- You will be asked to provide a urine sample for safety laboratory tests
- You will be asked to provide blood samples for the following tests (mandatory):
  - Blood test to look at biomarkers (proteins or genes in your system) that might tell us about what the study drugs have on your tumor
  - Pregnancy test (only if you are a woman who is able to get pregnant)
- You will have an eye exam to check the health of your eyes
- You will be asked to provide saved (tumor tissue collected at the time of your diagnosis) tumor tissue (mandatory): A sample of your tumor tissue that was removed previously by biopsy or surgery prior to your participation in this study will be collected. The tumor tissue will be tested to see what effects the study drugs have on your tumor.
- You will have an electrocardiogram (ECG): This involves attaching small wires to your arms, legs and chest to read the electrical activity of your heart.
- You will have a MUGA scan (a special x-ray to study the heart) or echocardiogram (EchoCG): An echocardiogram is an ultrasound of your heart and uses sound waves to create a picture of your heart and show how it is working.
- You will have a computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan of your tumor:
  - CT scan is a series of x-rays of the body from many angles that are turned into 3-dimensional pictures on a screen. CT scans often involve injecting a dye into your vein.
  - MRI is a scan that uses a strong magnet to produce pictures of areas inside the body such as organs and other tissue, and inside of bones. MRI scans often involve injecting a dye into your vein.

If the results of your tests show that you can take part in the study, you will enter the intervention period, which will be 28 days for cycle 1 and 21 days for cycle 2 onwards) and start the study drug.

During the intervention period, you will be asked to attend a number of visits to the hospital so that the study doctor can see how the study drug is affecting your condition and check the status of the disease.

<u>During the</u> intervention period the following exams, tests, and procedures will be performed to monitor your safety and health:

- Physical exam, vital signs, weight check (at every required visit)
- Evaluation of symptoms you may have developed during intervention (at every required visit)
- Blood tests done weekly during the first cycle, at the beginning of each cycle and at day 15 on cycle 2
- Blood sample to test for pregnancy prior to the start of Cycle 2, and then every 6 weeks
- Blood test to check liver, kidney, thyroid function, electrolytes weekly during cycle 1 and 2, and on day 1 of each new cycle.

- Computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan of your tumor every 6 weeks for the first 4 cycles and then every 12 weeks thereafter.
- Two research biopsies (mandatory) will be performed after anetumab single agent lead-in period or anetumab and gemcitabine lead-in period (cycle 1 day 7 with -1 day window), and after cycle 2 (cycle 2 day 7 with -4 day window). The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer.
- Research blood tests to measure the level of study drug in your blood (called pharmacokinetics). **A study calendar** is included below **that shows how often these will be done.**
- Urinalysis of day 1 of each cycle. Blood for sample for biomarkers (proteins or genes in your system) that might tell us about what the study drugs have on your tumor. A study calendar is included below that shows how often these will be done.

Other tests will be performed only if your doctor considers it appropriate. These tests will include:

- MUGA scan (a special x-ray to study the heart) or echocardiogram (EchoCG): An echocardiogram is an ultrasound of your heart and uses sound waves to create a picture of your heart and show how it is working.
- Computerized tomography (CT) scan or magnetic resonance imaging (MRI) scan of your tumor.
- Eye exam
- Any other of the above-mentioned tests.

At the end of intervention, you will have:

- Physical exam, vital signs, weight check.
- Evaluation of symptoms you may have developed and how active you are.
- Blood test to check liver, kidney, thyroid function, electrolytes.

Study Calendar

Tests and Procedures	**Screening (Day-28 to -1)**	**C1 D1**	**C1 D7**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D7**	**C2 D8**	**C2 D15**	**C3 D1**	**C3 D8**	**C3 D15**	**C4 D1**	**C5 -17 D1**	**C4-17 D8**	**PD**	**FU**
Receive Anetumab administration[1]		X					X				X			X	X			
Receive Nivolumab				X			X				X			X	X			
Receive Gemcitabine[2]		X		X			X		X		X	X		X	X	X		
Medical history	X																	
Review of side effects and medications	X	Continuous assessment throughout study																
Physical exam	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X
Measure weight, vital signs, oxygen levels	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X	X
ECG	X	X					X				X			X	X			
Eye exam	X	As clinically indicated																
MUGA/Echocardiogram	X	As clinically indicated																
Blood Tests (checking bone marrow, liver, kidney, coagulation (how easy or not your blood can clot)	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X
Urine	X	X					X				X			X	X			
Blood sample for pregnancy test for women who are able to have children	X	Prior to the start of C2, and then every 6 weeks																X
Blood tests to measure the level of drug in your blood		X		X														
Blood sample for biomarker	X	X	X	X			X	X			X	X		X	X		X	
Research tumor biopsy	X[3]		X					X									X[3]	

1. Anetumab given for visits up until June 30, 2023
2. Gemcitabine given on Day 1 and 8 of each cycle
3. Optional

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the study drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- You may be asked sensitive or private questions which you normally do not discuss.
- May not be able to take part in future studies.

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and do all the above-mentioned tests and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:
• The study doctors do not know who will or will not have side effects.
• Some side effects may go away soon, some may last a long time, or some may never go away.
• Some side effects may make it hard for you to have children.
• Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

• If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
• Your study doctor will work with you to treat your side effects.
• Your study doctor may adjust the study drugs to try to reduce side effects.
• The study doctor will provide you with information about other drugs you may need to avoid while receiving the study drug.

Drugs Risks

The tables below show the most common and the most serious side effects that researchers know about. Keep in mind that there might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you. These risks apply to all Groups.

COMMON, SOME MAY BE SERIOUS In 100 people receiving anetumab ravtansine (BAY 94-9343), more than 20 and up to 100 may have:
• Tear on the surface of the eye • Diarrhea, nausea • Tiredness • Loss of appetite

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving anetumab ravtansine (BAY 94-9343), from 4 to 20 may have:
• Anemia which may require blood transfusion • Blurred vision • Dry eye • Swelling and redness of the eye • Pain • Constipation, heartburn, vomiting • Fever • Reaction during or following a drug infusion which may cause chills, low blood pressure • Bruising, bleeding • Weight loss • Infection, especially when white blood cell count is low • Changes in taste • Muscle weakness • Feeling of "pins and needles" in arms and legs • Numbness, tingling or pain of the arms and legs • Shortness of breath • Rash

Nivolumab is an agent involved in the inhibition of “immune checkpoints,” and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving nivolumab. In clinical trials, most immune-mediated side effects were reversible and managed by stopping nivolumab temporarily, administration of corticosteroids and supportive care. Possible risks of nivolumab are summarized below:

Special precautions
Side effects of BMS-936558 (Nivolumab, MDX-1106) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 (Nivolumab, MDX-1106) is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS In 100 people receiving BMS-936558 (Nivolumab, MDX-1106), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving BMS-936558 (Nivolumab, MDX-1106), from 4 to 20 may have:
• Anemia which may require blood transfusion • Swelling and redness of the eye • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection • Bruising, bleeding • Pain or swelling of the joints • Loss of appetite • Reaction during or following a drug infusion which may cause fever, chills, rash BMS-936558 (Nivolumab, MDX-1106) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness. • Skin: itching; rash, blisters including inside the mouth; loss of skin pigment • Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly • Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urination; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving BMS-936558 (Nivolumab, MDX-1106), 3 or fewer may have:

- Swelling of arms and legs which may cause a feeling of heaviness and tightness
- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the bowels

BMS-936558 (Nivolumab, MDX-1106) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 (Nivolumab) therapy, since the risk and severity of transplant-associated complications may be increased.

Gemcitabine is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. Gemcitabine is classified as an antimetabolite. It is routinely used for the treatment advanced cancer such as:

- pancreatic cancer
- lung cancer
- bladder cancer
- sarcoma
- breast cancer
- ovarian cancer

The following side effects are common (occurring in more than 30%) for patients taking Gemcitabine:

- Flu-like symptoms (muscle pain, fever, headache, chills, fatigue)
- Fever (within 6-12 hours of first dose)
- Fatigue
- Nausea (mild)
- Vomiting
- Poor appetite
- Skin rash
- Low blood counts. Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia and/or bleeding.

Less common side effects (occurring in 10-29%) for patients receiving Gemcitabine include:

- Diarrhea
- Weakness
- Hair loss
- Mouth sores
- Difficulty sleeping
- Shortness of breath (see lung problems)

Not all side effects are listed above, some that are rare (occurring in less than 10% of patients) are not listed here.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Additional Drug Risks

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

No additional risks have been described in terms of drug-drug interaction with combination therapy of Group 3.

Reproductive risks: Because the drugs in this study can possibly affect an unborn baby and infants, you should not become pregnant or father a baby or breast-feed while you are on this study. Also, because these drugs remain in your body for weeks to months, you should continue to use adequate contraceptive measures and avoid nursing a baby for at least 6 months after your last dose of the medications, although the optimal or the maximal time required for drug clearance cannot be precisely predicted. Please notify your treating physician immediately if you become pregnant or suspect that you may be pregnant. In addition, women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Study Procedure Related Risks

Eye Exam
The eye exam will involve a slit lamp and an ophthalmoscope. You will have a strong light pointed in your eyes and this may cause mild and short-lived discomfort which is completely reversible and doesn't cause damage. The exam will require dilatation (widening) of your pupils (dark part in the front of the eye) by medicated eye drops. This dilatation of the pupils will prevent you from driving or operating machines for several hours after the exam, and will make your eyes sensitive to bright daylight and sunshine. Wearing sunglasses may be necessary for several hours after. These effects of dilatation of the pupils are completely reversible after several hours. In order to test your tear production, you may be asked to remove your contact lenses and you may receive a local anesthetic eye drop.

Blood Samples
The most common risks related to drawing blood from your arm are brief pain and possibly a bruise. You may also experience lightheadedness, and rarely, infection.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Imaging Risks

The CT-scans
This test will expose you to more radiation than you get from everyday background radiation. The amount of radiation from this scan is the same as 3 years' worth of natural background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

MUGA Scans
During the test, a small amount of a radioactive tracer is injected into your vein. The tracer binds to the red blood cells in your bloodstream and helps us to take pictures of your heart with a special camera. The tracer is radioactive and delivers a small amount of radiation. The amount of radiation is comparable with what you would receive during a CT scan. An allergic reaction to the tracer may rarely occur. Drinking a lot of water will help flush the tracer out of your system. It may take a day or two for it to be completely eliminated.

MRI Scans
This scan is painless but noisy. There is no radiation involved. There are no harmful effects from the strong magnetic field used for MRI however, the magnet may affect any metals in the body. Discuss any metal in your body with the study staff. Some individuals with claustrophobia (fear of closed spaces) may feel discomfort from lying still on the enclosed scanning table for the MRI scan.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study.
For men: Do not father a baby while taking part in this study. If you are sexually active with a woman who is able to get pregnant, you must use adequate contraceptive measures during the study and for 7 months after the last dose of medication.
For all: Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 7 months after your last dose of study drugs.

What are the costs of taking part in this study?

The study drugs anetumab ravtansine and nivolumab will be given to you free of charge unless you stop participating in this study.

The costs of your medical treatment will be paid for by your medical plan to the extent that such coverage is available. There may be extra costs that are not covered by your medical plan that you will have to pay yourself; some examples may be physiotherapy or certain pain medications.

Taking part in this study may result in added costs to you (i.e. transportation, parking, meals, or unpaid leave from work). You may have to pay for medication prescribed to treat or prevent side effects, and you may have to visit the hospital more often than if you were not participating in this study.

If you have insurance, talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

You and/or your insurance provider will not have to pay for research exams and procedures done that are covered by the study. These include:

- Eye exams
- Biopsy for testing mesothelin expression and on study biopsies

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study drugs now or in the future.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research. Health Canada will also have access in Canada.
- The NCI and the groups it works with to review research.

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other participants to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information until the study has not completed. If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).
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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____(*insert name of study doctor[s]*) at _____ (*insert telephone number and email address if appropriate*).

For questions about your rights while in this study, call the _____ (*insert name of organization or center*) Institutional Review Board at _____ (*insert telephone number*).

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your

health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say "no" to any or all of these studies. There is no penalty for saying "no." You and your insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies

Researchers are trying to learn more about cancer and other health problems using tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to intervention. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

There are two optional studies that you can choose to take part in. You can take part in any or none of these studies.

1. The first optional study is to collect some tumor tissue before you start intervention with the combinations of anetumab ravtansine with gemcitabine and nivolumab (Group 3) if you are in the dose expansion part of the study. This tumor tissue will be tested for exploratory purposes. The research will be able to compare this additional tissue with the one collected while you are on intervention to evaluate if and how the different dose levels of anetumab ravtansine can increase the effect of the immune system in participants with advanced pancreatic cancer.

2. The second optional study is to collect some tumor tissue after you have been treated and your disease has progressed with the combinations of anetumab ravtansine with gemcitabine and nivolumab (Group 3) if you are in the dose expansion part of the study. This tumor tissue will be tested for exploratory purposes. The research will be able to compare this additional tissue with the one collected while you were on intervention to evaluate if and how the different dose levels of anetumab ravtansine can increase the effect of the immune system in participants with advanced pancreatic cancer.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. To take part in the first optional study: A sample of tissue will be collected from a fresh tissue biopsy before you start intervention
2. To take part in the second optional study: A sample of tissue will be collected from a fresh tissue biopsy after you have been treated and your disease has progressed on study intervention.
3. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- If you have a biopsy, you may experience pain or discomfort at the biopsy site. Irritation, redness, swelling and/or bleeding may also occur. There is a risk of abnormal healing, fever, infection or of an allergic reaction to the anesthetic agent (numbing medicine) used to anesthetize the skin at the biopsy site.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*).

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

1. I agree to have my tumor tissue collected before I start intervention with the combination of anetumab ravtansine, gemcitabine and nivolumab (Group 3) if I am in the dose expansion part of the study, and I agree that my specimen samples and related information may be used for the laboratory studies described above.

   YES NO

2. I agree to have my tumor tissue collected after I have been treated with have been treated and have progressed with the combinations of anetumab ravtansine, gemcitabine and nivolumab (Group 3) if I am in the dose expansion part of the study, and I agree that my specimen samples and related information may be used for the laboratory studies described above.

   YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature: _____

Date of signature: _____

Signature of person(s) conducting the informed consent discussion: _____

Date of signature: _____