IRB NUMBER: 06-12-19C
IRB APPROVAL DATE: 11/4/2019
IRB EFFECTIVE DATE: 11/4/2019
IRB EXPIRATION DATE: 11/3/2020

CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer
UH Principal Investigator: David Bajor. MD
CC Principal Investigator: Robert Pelley, MD
Sponsor: Case Comprehensive Cancer Center

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC) and/or University Hospitals (UH)

Introduction/Purpose

We are asking you to participate in a research study. The purpose of this document is to summarize your discussion with the research team and provide you with written information to help you decide whether you want to participate in research. Your decision is completely voluntary.

Your treating doctor may also be an investigator on this research study. If so, your doctor will have an interest in both your welfare and in the research study. You are not required to take part in this research study offered by your doctor. You may ask for a second opinion from another doctor who is not linked to this study. If you choose not to be in this study, the quality of your regular medical care will not be affected.

Please ask any questions you may have about the study or this consent form before signing it. Please take your time to make your decision. You will be given a copy of this form to keep.

You are being asked to take part in a clinical research study sponsored by *University Hospitals Cleveland Medical Center,* that tests metformin, which is a diabetes drug in combination with chemotherapy in Pancreatic Cancer. You are also being asked to take part in this study because you have *pancreatic cancer* and standard drugs to treat your disease are not very effective.

Before you decide whether to take part in this study, it is important for you to know why the research is being done and what it will involve. Take time to read the following information carefully and discuss it, if you wish, with friends, relatives and your personal doctor (i.e., general practitioner or primary care physician). Please ask as many questions as needed so that you can decide whether you want to take part in the study. During the study, we will tell you if we learn any new information that might affect whether you wish to continue to be in the study.

Why Is This Research Being Done?

The main goal of this research study is to find out if the combination of metformin and modified FOLFOX 6 makes patients live longer. Other purposes of this research study will be to assess if this combination of treatment can shrink the tumor size and/or can improve the duration of time

during which the cancer is not growing. The brand name for metformin is Glucophage. The brand name for oxaliplatin is Eloxatin. The brand name for Fluorouracil is Adrucil. Also, this study will assess what side effects could happen with this combination of treatments. The use of this metformin and FOLFOX 6 in combination in this clinical study is experimental and has not been approved by the Food and Drug Administration FDA for use in pancreatic cancer.

Metformin is the most widely used oral diabetes medication in the world. Recently, there have been some research studies in animals showing that metformin may kill cancer cells. Also, it has been reported that patients who are diabetics and are taking metformin may have less chance to develop cancer.

Modified FOLFOX 6 is a combination of three chemotherapy (anti-cancer) drugs, oxaliplatin, leucovorin and 5-Fluorouracil (5-FU) that are given intravenously (into a vein) at fixed doses at specific schedule. These drugs will be given in the clinic on an outpatient basis. Modified FOLFOX 6 is one of the standard regimens we use to treat pancreatic cancer.

How Many People Will Take Part In This Study?

About *43* subjects (men and women who are at least 18 years of age) will take part in this study at University Hospitals and the Cleveland Clinic.

WHAT IS INVOLVED IN THIS STUDY?

Before You Begin This Study:

You will need to have certain exams, tests or procedures (called "screening tests") to help your study doctor determine if you are eligible for this study. This is called the pretreatment "screening" period. You will be asked to sign this consent form before beginning any screening tests. Some of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. Some of the tests and procedures need to be done near the date of your first treatment. If they were done too long ago they may need to be repeated. Your doctor/study team will discuss which, if any, tests need to be repeated. You will not receive any study drugs during this time.
Screening tests to be done within 1 week before starting treatment, unless otherwise indicated:

- A review of your medical history
- You will be asked about any prescription medications, over-the-counter medications vitamins, nutritional supplements and herbal products you might be currently taking.
- You will be asked how well you are able to do your normal activities (this is called

"Performance Status").

- A physical examination, including vital signs (blood pressure, pulse, and temperature), height, and weight will be recorded.
- Blood samples (about 5 teaspoons) will be taken for routine tests to check your blood counts (numbers of each type of blood cell) and chemistries (to evaluate your overall health status by checking things such as your kidney and liver function). Blood tests may be repeated within 48 hours before starting treatment if your doctor thinks that this is necessary.
- Women of childbearing potential will be asked to have a blood test (about 1 teaspoon) to see if they are pregnant. If you are pregnant, you will not be allowed to participate in this study.
- Computed Tomography (CT) scans, or MRI (Magnetic Resonance Imaging) scans within 4 weeks before starting treatment will be taken to measure the extent of your disease.
- An electrocardiogram (ECG) to determine if there are any abnormalities with your heart.

During The Study

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, you will have a central venous catheter (a small plastic tube placed in a vein near the collar bone) such as a mediport or a PICC line, surgically inserted, if you do not have one already in place. This catheter will be used to deliver study treatment and take blood samples when possible. Insertion of mediport or a PICC line requires minor surgical procedure that is performed under local anesthesia and would require a separate informed consent.

You will take metformin tablets twice daily for the duration of the study. You should take them with meals. The tablets can be kept at room temperature.

First, you will be started on metformin alone for an "introductory period" of one-week duration. The purpose of this introductory period is to make sure that your body tolerates metformin well. Most of the patients who take this drug usually tolerate metformin without any side effects. Few patients may experience some minor side effects that usually self-resolve. Very few patients may experience side effects that require lowering the dose of metformin and rarely stopping it. Upon the end of the introductory period, your doctor will know what is the most tolerable dose of metformin in your case.

Subsequently, after the "introductory period", you will be started on chemotherapy in addition to the metformin.

Even though, you will take metformin every day, your treatment will be divided into 14-day cycles. A cycle is a treatment period. You will also receive a pill diary and instructions on how to complete the form. You will be asked to record the date, time, numbers of pills taken and any other comments you may want to note. At the end of each cycle, you will be asked to return your pill diary.

On day 1 of every cycle you will receive modified FOLFOX treatment. The oxaliplatin is given by vein over 120 minutes. Leucovorin is given by vein over 120 minutes along with the oxaliplatin. The 5-FU is given in 2 doses. The first dose is given by vein over 5-10 minutes. This is called bolus dose. Then a larger dose of 5-FU is given by vein over 46 hours. This 46 hours dose of 5-FU will be given via a small pump that you can wear in a pack around your waist. The pump will be attached to your central venous catheter. A cycle of mFOLFOX6 treatment is repeated every 2 weeks. The treatment is given on an outpatient basis and does not require an admission to the hospital.

During the study, you will have the following tests and procedures done. These tests and procedures are part of regular cancer care, so you would have them done even if you were not on this study. Each study visit is approximately 4 hours long.

NOTE: You will be asked to have a physical examination up to 6 days before day 1 of each cycle.

<u>Day 1 of every cycle:</u>

- You will be asked about any prescription medications, over-the-counter medications vitamins, nutritional supplements and herbal products you might be currently taking
- You will be asked how well you are able to do your normal activities (this is called "Performance Status").
- You will be asked about any side effects you are experiencing.
- A physical examination, including vital signs (blood pressure, pulse, and temperature), height, and weight will be recorded
- Blood samples (about 3 teaspoons)

Only at the beginning of treatment and after 4 cycles of treatment, we would ask you to give additional blood samples (total of 5 teaspoons) that we will send to a laboratory at Institute of Molecular Medicine (MED), David Geffen School of Medicine, 650 Charles E. Young Drive South, Los Angeles, CA 90025-7278 run by Dr. Dimitrios Iliopoulos, Ph.D where some additional tests will be analyzed that may help us better understand your cancer and your response to treatment. These samples may be stored indefinitely.

Every 8 weeks (4 cycles of treatment):
CT or MRI scans to measure the size of cancer and assess if it is getting smaller (you will have the same scan that you have during screening).

During this study, you should call your doctor immediately if you experience any side effects in between your treatment days while you are on study. Your dose mFOLFOX 6 may be reduced and/or your treatment with mFOLFOX 6 may be delayed. You may also be hospitalized if you have serious side effects.

We will monitor your progress while you are on the study. You will remain on the study treatment until your disease becomes worse, you experience severe or life-threatening side effects, you or your study doctor decide that it is not in your best interest to continue. You can stop participating in this study at any time. However, if you decide to stop, you should talk to your study doctor first about how to safely stop the study medications. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. You may be withdrawn from this study, even without your approval, for a number of reasons such as:

- You are allergic to one of the study drugs or are otherwise unable to tolerate it (experience severe side effects).
- Your health gets worse
- Your study doctors no longer feels that this is the best treatment for you
- You become pregnant
- You do not follow study instructions

End of study visit (4 weeks after you stop study treatment):
If you discontinue from the study for any reason, you will be asked to return to the clinic 4 weeks after you stop study treatment for an off study visit. This visit will include the following:

- You will be asked about any medications you might be currently taking
- You will be asked how well you are able to do your normal activities (this is called "Performance Status").
- You will be asked about any side effects you are experiencing.
- A physical examination, including vital signs (blood pressure, pulse, and temperature), height, and weight will be recorded
- Blood samples (about 2 tablespoons)
- CT or MRI scans to measure the size of tumors and assess your response to treatment (you will have the same scan that you have during screening).

Specimen (Correlative) studies

An additional study that we would ask you to consider participating in is allowing excess tumor specimens or biopsies previously taken to be studied so that we may better understand your cancer and your response to treatment. Those specimens will be sent (along with the blood samples drawn on day 1 of treatment) to a laboratory based at Institute of Molecular Medicine (MED), David Geffen School of Medicine, 650 Charles E. Young Drive South, Los Angeles, CA 90025-7278 run by Dr. Dimitrios Iliopoulos, Ph.D. These samples may be stored indefinitely.

POSSIBLE RISKS AND SIDE EFFECTS

Cancer is a serious disease and the medications used to treat it are also quite serious. Drugs for cancer are strong and have side effects. As with any experimental procedure, there may be adverse events or side effects that are currently unknown and some of these unknown risks could be permanent, severe, or life threatening. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study medication. In some cases, side effects can be serious, long lasting, or may never go away. As with any investigational procedure (procedures being done for experimental purposes), there may be adverse events or side effects that are currently unknown.

During your participation in this study, you should not receive any other treatment for your cancer (this includes any chemotherapy, radiation, surgery, or any other agents used to reduce or eliminate your tumors). If your study doctor decides that one of these options would be better for you, you will be withdrawn from the study.

Risks of *Metformin:*

Likely (10% or more patients experience one or more of these):

Gastrointestinal: Diarrhea, nausea/vomiting, passing gas.

Note: *In this study, you will be prescribed an extended release form of metformin.*

We believe that through the use of this form of metformin, the administration of metformin with meals, in addition to the one-week "introductory period" the possibility of gastrointestinal side effects will be much minimized.

Neuromuscular & skeletal: Weakness

Less Likely (1% to 10% of patients experience one or more of these):

Cardiovascular: Chest discomfort, flushing, increased heart rate

Central nervous system: Headache, chills, dizziness, lightheadedness

Dermatologic: Rash

Endocrine & metabolic: Low blood glucose level

Gastrointestinal: Indigestion, abdominal discomfort, abdominal distention, abnormal stools, constipation, dyspepsia/ heartburn, taste disorder

Neuromuscular & skeletal: Muscle pain

Respiratory: Shortness of breath, upper respiratory tract infection

Miscellaneous: Decreased vitamin B_{12} levels, increased perspiration, flu-like syndrome, nail disorder

Rare (Less than 1% of patients experience one or more of these):

Lactic acidosis (buildup of lactic acid in the blood stream which could affect different body systems), leukocytoclasticvasculitis (inflammation of small blood vessels), megaloblastic anemia) decreased blood hemoglobin with larger blood cells), pneumonitis (inflammation of lung tissue)

Risks of mFOLFOX6 (5-FU, Leucovorin and Oxaliplatin)

Risks of Leucovorin

Allergic reactions, including shock, have been reported when given leucovorin. No other side effects have been reported with leucovorin.

Risks of 5-FU

Likely: (occurs in 20% or more of subjects taking 5-FU)

- Loss of appetite
- An inflammation of the mucous lining of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips, throat, and roof or floor of the mouth and swelling of the esophagus which may lead to the mucous lining forming pus and/or dying and separating from the structure in the mouth (mouth ulcers).

- Loose stools
- Nausea, and vomiting
- Hair loss and dermatitis (inflammation of the skin) may be seen in a substantial number of cases. The dermatitis most often seen is a rash usually appearing on the extremities
- Leukopenia (low white blood cell count, which can increase your risk of infection) usually follows every course of therapy with 5-FU. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of treatment. By the 30th day, the count has usually returned to normal.
- Low blood cells which can increase your risk of infection, cause fatigue or shortness of breath, and increase your risk of bleeding
- Low hemoglobin levels which can cause fatigue and/or shortness of breath

Less Likely: (occurs in 3-19% of subjects taking 5-FU)

- When given 5-FU, subjects have reported something known as hand-foot syndrome. This syndrome has been described as a tingling sensation in the hands and feet which may turn into pain when holding objects or walking over the next few days. The palms and soles may become swollen on both sides with redness of the skin and sensitivity of the fingers or toes, possibly including peeling of the skin. These symptoms may resolve over 5 to 7 days when you stop the drug. You must contact the study staff immediately if you experience any of these symptoms.
- Nail changes (including loss of nails)
- Dry skin
- Cracking skin
- Vein coloring
- Light sensitivity; increased sensitivity to the sun

Rare but Serious: (occurs in less than 3% of subjects taking 5-FU)

- Tear duct narrowing
- Visual changes
- Increased tears
- Eye twitching
- Headache
- Disorientation
- Confusion
- Euphoria (an exaggerated feeling of happiness, confidence, or well-being)
- Decrease in blood flow which can cause dizziness, blurred vision, confusion, fainting, light-headedness, sleepiness and weakness
- Angina (an attack of painful spasms that cause you to feel like you are choking or

suffocating, and can lead to a heart attack)
- Acute cerebellar syndrome, which can cause inability to walk without assistance and difficulty speaking, which may be permanent.
- Blood clots
- Nose bleeds

Risks of Oxaliplatin

Likely: (occurs in more than 20% of subjects receiving Oxaliplatin)
- Lack of enough red blood cells (anemia, which may make you short of breath, weak, fatigued or tired)
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Increased blood level of a liver enzyme (ALT/SGPT and AST/SGOT) which may indicate that your liver is not working properly
- Decreased number of a type of blood cell that helps to clot blood (platelet) which may result in easy bruising or bleeding
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of the brain and spinal cord) causing numbness, tingling, or burning

Less Likely: (occurs in 3-20% of subjects receiving Oxaliplatin)
- Abnormal blood clotting and/or bleeding
- Fever associated with dangerously low levels of a type of white blood cell (neutrophils)
- Destruction of red blood cells
- Abnormally fast or slow, regular or irregular heartbeat involving the upper chambers of the heart (atria)
- Period of very rapid and regular heartbeats that begins and ends suddenly
- Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle) and results in uncoordinated muscle movement of the ventricles, making them tremble rather than contract properly. This can be life-threatening and needs immediate attention.
- Rapid heartbeat in or above one of the lower chambers (ventricles) of the heart, with a regular rhythm. This can also be life threatening and needs immediate attention.
- Hearing loss that is usually temporary and should resolve once study treatment has ended. However, there is a possibility that it may be permanent.
- Inflammation (swelling and redness) to the middle ear

- Inflammation (swelling and redness) of the conjunctiva (the outermost layer of the eye and the inner surface of the eyelids). This is commonly called "pink eye."
- Dry eyes
- A situation in which one has temporary blindness of one eye, due to a blockage (or decreased blood flow) in the blood vessels leading to that eye
- Temporary vision problems caused by the cold
- Problems with the eyelid(s)
- Swelling around the nerve in the back of the eye which is responsible for vision
- Belly pain
- Fluid collection in the abdomen
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Dry mouth
- Heartburn
- Difficulty swallowing
- Inflammation (swelling and redness) of the small and large bowel
- Inflammation (swelling and redness) of the esophagus (gullet or the tube the goes from the mouth to the stomach, through which food passes)
- Excess passing of gas
- Inflammation (swelling and redness) of the stomach lining
- Bleeding in some organ(s) of the digestive tract
- Death of tissue somewhere in the digestive tract (stomach or intestines). Surgery may be required to remove the dead tissue.
- Sore (ulcer) somewhere in the digestive tract
- Partial or complete blockage of the small and/or large bowel, called ileus. Ileus is a functional rather than an actual blockage of the bowel, but may require surgery to repair.
- Irritation or sores in the lining of the mouth
- Inflammation (swelling and redness) of the pancreas
- Blockage of the small bowel
- Chills
- Swelling of the face
- Swelling of the extremities (arms and/or legs)
- Fever
- Limp or difficulty walking
- A condition in which both the liver and kidneys fail
- Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected (administered)
- Chest pain, not heart-related

- Liver failure
- Increase in the size of the liver
- A condition in which there is blockage of the veins of the liver. This can lead to liver damage.
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Infection
- Test that shows a problem in blood clotting
- Increased blood level of a liver or bone enzyme (alkaline phosphatase)
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)
- Increased blood level of a liver enzyme (GGT)
- Increased INR (measure of the ability of the blood to clot properly) which increases the risk of bleeding
- Decreased number of a type of white blood cells (lymphocyte), which may make you more vulnerable to infection which could be serious even life threatening
- Decrease in the number of a type of white blood cell (neutrophil/granulocyte) which can increase the risk of serious infection
- Weight gain
- Weight loss
- Decrease in the total number of white blood cells (leukocytes) which can increase your risk of infection
- More acid than normal in the blood, which may indicate that your kidneys are not working properly
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Increased blood sugar level, which can cause you to be thirsty, or have headaches or blurred vision
- Increased blood level of uric acid, a waste material from food digestion, which may indicate that your kidneys are not working properly
- Decreased levels of a blood protein called albumin, which may indicate that your liver is not working properly
- Decreased blood level of calcium, which can cause a tingling sensation in the extremities of the hands and feet
- Decreased blood sugar level, which may cause you to lose your appetite
- Decreased blood level of potassium, which can cause weakness, nausea, vomiting, and abdominal pain or constipation

- Decreased blood level of magnesium, which could cause muscle weakness, confusion and decreased reflexes.
- Decreased blood level of sodium, which can cause nausea, headache, or confusion
- Decreased blood level of phosphate, which in some cases can cause you to become mildly short of breath
- Joint pain
- Back pain
- Bone pain
- Muscle pain
- Difficulty or limitation in ability to open mouth
- Loss of muscle coordination; awkward, uncoordinated walking; unsteadiness when walking
- Sleepiness
- Dizziness (or sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking)
- Taste changes
- Speech problems
- Restless, repetitive, or involuntary movements and rapid speech
- Headache or head pain
- Bleeding in the brain
- Decreased blood flow to the brain which may lead to stroke
- A malfunction of the nerves within the head and neck, which can cause increased sensitivity or pain
- Paralysis of facial muscles due to problems with the nerves that supply them
- Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those outside of the brain and spinal cord)
- Convulsion or seizure
- Anxiety, feelings of dread or danger
- Confusion
- Feelings of sadness, worthlessness, thoughts of suicide or death (depression)
- Difficulty sleeping or falling asleep
- Blood in the urine
- Bleeding in the kidney
- Need to urinate often
- Difficulty emptying the bladder
- Presence of blood in a fallopian tube (the tube between the ovary and uterus [womb])
- Bleeding in the ovary
- Bleeding in the prostate
- Bleeding in the spermic cord (a structure resembling a cord that suspends the testes

within the scrotum and contains the vas deferens [the tube that carries sperm] and other vessels and nerves)
- Bleeding in the testis
- Bleeding in the uterus (womb)
- Bleeding in the vagina
- Stuffy or runny nose, sneezing
- Bleeding from the lungs
- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Hiccups
- Inflammation (swelling and redness) of the lungs that may cause difficulty breathing and can be life-threatening
- Scarring of the lungs that can cause shortness of breath and interfere with breathing
- Problem of the sinuses
- Voice changes
- Hair loss
- Dry skin
- Excess sweating
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives
- Sudden reddening of the face and/or neck
- Hot flashes
- High blood pressure
- Low blood pressure
- Inflammation (swelling and irritation) of a vein, blood clot
- Formation of a blood clot that plugs the blood vessel; the blood clot(s) may break loose and can be carried by the blood stream to plug another place, such as the lung
- Bleeding with a decreased number of blood cells that help to clot blood (platelets)

<u>Rarely: (occurs in less than 3% of subjects receiving Oxaliplatin)</u>
- Formation of blood clots in small blood vessels around the body that leads to a low platelet (a type of blood cell that helps to clot blood) count
- Gas in the intestinal (bowel) wall, which can result in a blood clot, or death of the cells in the wall.
- Inflammation (swelling and redness) of the gall bladder possibly associated with gall

stones
- Sudden decrease of kidney function
- Severe, potentially life-threatening damage to the lungs which can lead to fluid in the lungs
- Swelling and redness of the skin on the palms of the hands and soles of the feet

The nerves that affect your throat may be affected and cause a strange sensation when swallowing cold liquids. You should avoid cold beverages while you are participating in this study. You may also notice a tingling and numbness or pain in your hands and feet that worsen on exposure to cold. Extra layers of clothing (gloves, mittens and warm socks) may help these symptoms become less severe.

Additional risks of oxaliplatin:

If you should develop throat tightness, shortness of breath, or a choking sensation, contact your doctor immediately. Scarring of the lung, which may be fatal, was observed in less than 1% of over 4,000 patients treated with oxaliplatin on clinical research studies.

Inflammation of the nerves can become worse during the time you are receiving treatment, and the risk of developing it increases with the amount of oxaliplatin you receive. This inflammation usually goes away.

IN SOME CASES, THE COMBINATION OF OXALIPLATIN AND 5-FU CAN CAUSE A SEVERE INFECTION OFTEN ASSOCIATED WITH DIARRHEA. THIS INFECTION IS SERIOUS AND CAN BE LIFE THREATENING. CONTACT YOUR PHYSICIAN IMMEDIATELY IF YOU ARE EXPERIENCING SEVERE DIARRHEA, FEVER, AS WELL AS NUMBNESS OR TINGLING IN YOUR HANDS, FEET OR THROAT, OR WEAKNESS.

A few patients treated with oxaliplatin have developed a condition known as “Tumor Lysis Syndrome.” Tumor Lysis Syndrome is a complication that can occur when cancer cells are destroyed by treatment. The destruction of cells may damage the kidneys and change calcium levels in the body. This complication may lead to the need for kidney dialysis usually on a temporary basis. You may also develop a condition associated with the dysfunction of your kidneys called Hemolytic Uremic Syndrome. This syndrome can be serious and may lead to seizures, problems with the central nervous system, or coma.

Platinum drugs like oxaliplatin have been known to cause leukemia in a small number of patients. It is not known whether risk of future development of leukemia is a side effect of oxaliplatin. One case of leukemia and one case of myelodysplastic syndrome, a condition which could lead to leukemia, have been seen following oxaliplatin chemotherapy, although it is not certain that oxaliplatin caused these blood disorders.

It is possible that not all side effects of this combination may be known. You may experience side effects other than those listed previously.

Potential Risk or Discomfort from Procedures

Blood Draws
The insertion of the needle to draw blood is painful; however, the discomfort is brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

CT Scans
A liquid solution known as a contrast is frequently used in CT scans. The contrast is a solution used to make certain organs, blood vessels and tissues "stand out" to better image your disease. It is possible that you may develop an allergic response to the contrast agent. You may experience nausea, flushing, warmth and a salty taste. You will be asked not to move during the test, but relax and breathe normally. You might be uncomfortable while you are in the tunnel-shaped machine. Some patients have felt claustrophobic during this test.

Echocardiogram
Uses sound waves to evaluate your heart. These high-frequency sound waves have not been shown to have any harmful effects

MRI
An MRI uses magnetic energy and radio waves rather than x-ray radiation. A small amount of patients may experience claustrophobia, or an inability to be in a confined space without being given a sedative (a drug used to calm them). In addition, you will hear loud, knocking noises. Occasionally, subjects will report a mild headache from the "knocking" sound. Temporary hearing loss has been reported from this loud noise. You will be asked to wear ear plugs. At certain times during the MRI, you may be asked not to swallow for a while, which can be uncomfortable.

Watches and credit cards should also be removed as these could be damaged. You will be provided a way to secure these items.

If you have any metal implants within the body you will not be able to undergo an MRI since metal implants interfere with the MRI system's magnetic field. You will still be able to participate in this study, but would have a CT scan instead of an MRI. Before you have the MRI scan, make sure to tell the operator/investigator if you have any of the following:

- A cardiac pacemaker or any other biomedical device in or on your body,
- Any metal objects (especially surgical clips), devices, or implants that are in or on your body. In some cases, having those devices means you should not have an MRI scan performed.
- If you have metal-containing pigment in tattoo dye or permanent makeup. There have been reports of people with tattoos or permanent makeup who experienced swelling or burning in the affected areas. This seems to occur only rarely and apparently without lasting effects.
- Any history of head or eye injury involving metal fragments,
- If you have ever worked in a metal shop,
- If you could be pregnant,
- if you are claustrophobic (the fear of being in a narrow or enclosed space).
- If you have had a previous reaction to Gadolinium-based contrast agents or a history of severe allergies. Subjects with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenicsclerosing fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life threatening. There are no reports of NSF in subjects with normal kidney function. Before you have a MRI or CT scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI or CT scans.

Reproductive Risks

Women who are pregnant or breastfeeding cannot take part in this study, because we do not know what effect *Modified FOLFOX 6*will have on an unborn child or whether the drugs are passed to a baby through mother's milk. To avoid risk to the fetus, it is important that you not be pregnant while participating in this study. If applicable, you must stop breastfeeding if you are being treated with the study drug. If you are a woman capable of having children, you will be given a pregnancy test before you begin the study, which must be negative in order for you to take part. Men who are able to father children should use adequate contraception. We also

advise that you (or your female sexual partner) not become pregnant while involved in this study.

Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you should use an appropriate "double barrier" method of birth control: female use of a diaphragm, intrauterine device (IUD), contraceptive sponge, prescribed "birth control" pills, injections, or implants, in addition to male use of a condom. You should use contraceptives during treatment, and for 4 weeks after you stop treatment. If you choose to be sexually active during this study, you understand that even with the use of these birth control measures pregnancy could still result.

If you become pregnant while you are taking part in this study, you must notify one of the study doctors so that management of the pregnancy and the possibility of stopping the study drug can be discussed. You should continue to use birth control for 4 weeks after finishing the study.

BENEFITS

You may or may not benefit from participating in this study. Your physician cannot predict whether this treatment can shrink your tumor or prolong your life. Information learned from this study may benefit other patients with cancer in the future.

ALTERNATIVES TO PARTICIPATION

If you do not wish to take part in this research study, your study doctor will discuss alternate treatment options with you, including their benefits and risks. These may include:

- Getting treatment or care for your cancer, if available, without being in a study.
- Taking part in other investigational studies if they are available.
- Getting comfort care, also called palliative care, for your symptoms. 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.

Talk to your study doctor about each of these choices before you decide if you will take part in this study. If you decide not to participate, withdraw your participation after starting the study, or are taken off the study, your study doctor will discuss all other treatment options with you.

CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer
UH Principal Investigator: David Bajor. MD
CC Principal Investigator: Robert Pelley, MD
Sponsor: Case Comprehensive Cancer Center

COSTS AND COMPENSATION

Your involvement in this research study is voluntary and you will not be paid for your participation.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures. The blood work and specimen tests that are done for research purposes will not be charged to you. It will be paid for by the research study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

RESEARCH-RELATED INJURY

If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If you experience physical injury or illness as a result of participating in this research study, medical care is available at University Hospitals and/or the Cleveland Clinic; however, University Hospitals and the Cleveland Clinic have no plans to provide free care or compensation for lost wages. You or your insurance company will be charged for treatment of research-related injuries.

Further information about research-related injuries is available by contacting the University Hospitals Institutional Review Board at (216) 844-1529.

CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer
UH Principal Investigator: David Bajor. MD
CC Principal Investigator: Robert Pelley, MD
Sponsor: Case Comprehensive Cancer Center

CONFIDENTIALITY

The medical and research information recorded about you will be used within University Hospitals and/or the Cleveland Clinic and/or disclosed outside University Hospitals and/or the Cleveland Clinic as part of this research. Some of the tests and procedures done solely for this research study also maybe placed in your medical record so your other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in the medical chart.

Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by name in any publication of the research results unless you sign a separate consent form giving your permission (release).

This research study will involve the recording of current and/or future identifiable (pertaining to only you) medical information from your hospital and/or other health care provider (for example, your physician's office) records. This information that will be recorded will be limited to information concerning treatment of your cancer (for example, diagnostic information, lab and scan results, medications, medical history). This information will be used to determine your eligibility for this study and to follow your response once you are enrolled in the study.

Parts of your identifiable medical record information that pertain to your participation in this study may be sent to a central location for review (photocopied and mailed, or electronically transmitted, such as by fax or email). The organizations receiving your identifiable medical record information may not have the same obligations to protect your information and may further disclose it to groups not named here. Information released to these parties is no longer under the control of the study doctor and can no longer be protected by Federal Privacy Rules.

The purposes of disclosing your medical record information to the organizations are to collect the data necessary to complete the research, to properly monitor how this study is carried out, and to answer research questions related to this research study.

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. To protect your privacy, the study staff will use your study number and initials rather than your name on any photocopies of your study records, and on any blood samples that are sent outside of the local research institution(s) for review or testing. If information from this study is published in scientific journals or

presented at scientific meetings, your name and other personal information will not be used.

Privacy and Confidentiality

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to David Bajor, MD and the research staff at University Hospitals and/or Robert Pelley, MD and the research staff at Cleveland Clinic for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, University Hospitals Institutional Review Board and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- The researchers and collaborators at other hospitals and medical centers taking part in this study
- The study's Data Safety Monitor
- The Food and Drug Administration (FDA) and any other regulatory authorities to which the results of this study will be submitted to review the study findings
- University Hospitals Cleveland Medical Center and/or the Cleveland Clinic
- Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer
UH Principal Investigator: David Bajor. MD
CC Principal Investigator: Robert Pelley, MD
Sponsor: Case Comprehensive Cancer Center

David Bajor, MD
Case Comprehensive Cancer Center
University Hospitals Cleveland Medical Center
11100 Euclid Ave.
Cleveland, OH 44106

or

Robert Pelley, MD
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic and/or University Hospitals cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic and/or University Hospitals will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) and/or University Hospitals Institutional Review Board assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

SUMMARY OF YOUR RIGHTS AS A PARTICIPANT IN A RESEARCH STUDY

Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer
UH Principal Investigator: David Bajor. MD
CC Principal Investigator: Robert Pelley, MD
Sponsor: Case Comprehensive Cancer Center

Questions About the Research
If you have any questions, you can ask the Principal Investigator David Bajor, MD and/or her research staff at 216-844-3951 or Robert Pelley, MD and/or his research staff at 216-445-6720.

If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-2924 or the University Hospitals Cleveland Medical Center's Research Subjects Rights Phone line at 216-983-4979.

Emergency or after-hours contact information
If you are a University Hospitals patient, and you need to contact study staff outside normal business hours, you may contact 216-844-3951 and you will be transferred to the answering service, which can put you in contact with *Dr. Bajor* or the oncologist (cancer doctor) on call.

If you are a Cleveland Clinic patient, you should contact the page operator at 216-444-2200 or toll free, 1-800-223-2273, and ask for the oncologist (cancer doctor) that is on call.

Where Can I Get More Information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

US National Institutes of Health (NIH) Clinical Trial Database:

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time to find out information about the trial and basic results.

SIGNATURE

Signing below indicates that you have been informed about the research study in which you

CONSENT FOR CANCER RESEARCH

Project Title: A Phase II Study of Metformin plus modified FOLFOX 6 in Patients with Metastatic Pancreatic Cancer
UH Principal Investigator: David Bajor. MD
CC Principal Investigator: Robert Pelley, MD
Sponsor: Case Comprehensive Cancer Center

voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

X	
Signature of Participant	*Date*
X	
Printed Name of Participant	

Study personnel (only individuals designated on the checklist may obtain consent)

X	
Signature of person obtaining informed consent	*Date*
X	
Printed name of person obtaining informed consent	
X	

X	
Signature of Witness	*Date*
X	
Printed Name of Witness	