The Ohio State University Consent to Participate in Research

Study Title:	**A Phase II Study of the Combination of Aflibercept (VEGF-Trap) plus Modified FOLFOX 6 in Patients with Previously Untreated Metastatic Colorectal Cancer**
Principal Investigator:	**John Hays, MD, PhD**
Sponsor:	**The Ohio State University**

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

You have been asked to take part in this study because you have untreated metastatic colorectal cancer. This study is being done to see if the addition of the drug, Aflibercept in combination with a modified FOLFOX6 (mFOLFOX6) chemotherapy regimen is effective in the treatment of your cancer that has spread to lymph nodes or other organs. FOLFOX is a combination of three drugs, Oxaliplatin, Fluorouracil (5-FU) and Leucovorin. FOLFOX is approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancer, however the combination of FOLFOX with Aflibercept is not.

Aflibercept is an investigational drug (a drug that has not been approved for general use by the FDA but is under investigation in clinical trials regarding its safety and efficacy). It has been approved by the FDA for the treatment of patients with a disease of the eye called Neovascular (Wet) Age-Related Macular Degeneration (AMD). Aflibercept targets the vascular endothelial growth factor (VEGF) which is important for a tumor's blood supply.

By interfering with this growth factor, the study drug could decrease the blood supply to your tumor and possibly prevent its growth and spread.

2. How many people will take part in this study?

A total of 55 patients will be enrolled on this study at The Ohio State University.

3. What will happen if I take part in this study?

By agreeing to take part in this study, you are agreeing to follow the study requirements listed below. In order to find out if you can take part in the study, you will have a medical evaluation done after you sign the consent form. A description of tests and visits required for the medical evaluation is below.

Medical Evaluation and Pre-treatment Tests:

Before starting treatment with the study drugs, you will have the following tests and procedures to make sure that you are eligible to receive study treatment. These tests and procedures will confirm the amount of cancer that you have and they will establish your "baseline" or starting point before being treated:

- History and Physical Exam
- Vital Signs: Blood pressure, pulse rate, respiratory rate, temperature including height, weight and how well you perform everyday tasks.
- Blood tests: Complete blood count including blood clotting tests, blood chemistries to check the levels of various electrolytes and chemicals in your blood, blood test that tells how your liver is working and LDH/ Phosphorous test.
- Blood samples for pharmacodynamic blood test
- If you are a woman who is able to have children, you must have a negative pregnancy blood test in order to enroll.
- CT Scan (computed tomography - a series of pictures of areas inside the body taken from different angles. The pictures are made by a computer linked to an x-ray machine)
- Electrocardiography-(EKG- a line graph that shows changes in the electrical activity of the heart over time)
- Review the current medications you are taking
- Adverse Event Evaluation
- You will require the placement of a temporary tube into a vein in your chest or your arm during the course of your treatment. This tube will be attached to a small portable pump. The drug, 5-FU, will be given using this pump. The pump is small enough to allow it to be attached to your clothing, so it can be used without restricting most movements and activities. You will wear this pump for a 46-hour period every two weeks
- Tumor measurements on routine CT scans of the chest, abdomen and pelvis
- Serum Pregnancy test for women of childbearing potential
- Tumor biopsy- only if paraffin embedded tissue is not available

- Blood for gene analysis (to check for normal variations in DNA bases within the VEGF gene to analyze whether they predict response to therapy)
- CEA Blood Test (Tumor Test Marker)
- DCE-MRI-(dynamic contrast enhanced magnetic resonance imaging) type of MRI scan
- FDG-PET-(fluorodeoxyglucose-positron emission tomography) type of PET scan

All of the above mentioned studies are standard of care except for blood samples for pharmacodynamic blood tests, repeat tumor biopsies, blood for glucose and gene analysis, ECG, FDG-PET and DCE-MRI.

Pregnancy Prevention:
We do not know the effect of the Aflibercept in pregnant women, or the impact of Aflibercept presence in breast milk or its effects on the breast-fed child. Previous studies have shown male and female fertility are likely to be compromised during treatment with Aflibercept. Therefore, both men and women must not attempt pregnancy and women must not be pregnant or breast-feeding while participating in this study. You must agree to use an adequate form of birth control during study participation and for a 6-month period following your treatment Aflibercept. While a number of methods of birth control are acceptable for the purposes of preventing contraception while you are on this study, please remember that only birth control methods that use condoms provide adequate protection against sexually transmitted diseases.

If you or your partner become pregnant while taking the study drug, it is important that you notify your study nurse/physician immediately. If you are a woman of child-bearing potential, you will have a pregnancy test done before you begin the study to make sure that you are not pregnant. Pregnancy tests will be performed if you or your doctor suspect you may be pregnant. If you become pregnant, you will be required to stop the study treatment at which time other treatment options will be discussed with you. If you require more information about preventing pregnancy, ask your study doctor.

My initials below indicate that I have read and understand the reproductive risk section and agree to use adequate birth control to prevent pregnancy as stated above:

_____ (Initials) _____ (Date)

During The Study
If the exams, tests and procedures show that you can be in the study, and you choose to participate, then you will have treatment cycles which last 28 days. The following tests and procedures will occur:

<u>Day 1 and 15 of each cycle</u>

- Physical exam, weight and performance status- including how well you perform everyday tasks

- Vital Signs: Blood pressure, pulse rate, respiratory rate, temperature
- Blood tests: complete blood count including blood clotting tests, blood chemistries to check the levels of various electrolytes and chemicals in your blood, blood test that tells how your liver is working.
- You will be asked about any side effects that you may have experienced while on treatment
- Review the current medications you are taking
- Aflibercept and modified FOLFOX6 (mFOLFOX6) will be administered intravenously (through a needle in your vein), followed by continuous infusion (through a needle in your vein) 5-FU over 46 hours.
- CEA Blood Test (Tumor Test Marker) -This test will only be performed on Day 1 of each cycle.

Unless you have one, a portable blood pressure device will be given to you to check your blood pressure at home and report the lower number back to the study coordinator by phone on the following days:
Cycle 1 Day 8, Cycle 1 Day 22 and Cycle 2 Day 8.

Every 8 weeks
You will have a CT scan to measure your tumors prior to starting the next cycle.

Correlative Studies
After week 8 (cycle 2), you will have a FDG-PET and DCE-MRI scan done.

Blood samples for pharmacodynamic tests will be done at day 1 of weeks 1, 3, 9 13 and 4 weeks after you go off study.

Optional Tests

At 8 weeks after starting treatment, you will have the option to undergo a tumor biopsy to assess for changes in your tumor. This is an optional biopsy. You may opt to not have the extra biopsy done. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits.

YES ☐ Check this box if you would like to have the biopsy done.

NO ☐ Check if you would not like to have the biopsy done.

Future Research with your Tissue and Blood Samples

The researchers would like to keep any of the extra tissue and blood that was left over for future research. If you agree, this tissue will be kept and may be used in research to learn

more about cancer and other diseases. Any future research that may be done with your tissue or blood is not designed specifically to help you. Your tissue will be used only for research and will not be sold.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits.

YES ☐ Check this box if we may keep/use your tissue and blood for future unknown use in research to learn about, prevents, treat, or cure cancer or other health problems.

NO ☐ Check this box if you would not like your samples kept/used for future unknown research.

When you are finished with the study treatment:
When you have completed your treatment on this regimen you will be asked to come back and complete an End of Study visit (EOS). This visit will consist of the following tests and procedures:

- Physical exam- including how well you perform everyday tasks.
- Vital Signs: Blood pressure, pulse rate, respiratory rate, temperature) including weight
- Blood tests: complete blood count including blood clotting tests, blood chemistries to check the levels of various electrolytes and chemicals in your blood, blood test that tells how your liver is working.
- CEA Blood Test-(tumor marker test)
- Tumor measurement (CT scan)
- You will be asked about any side effects that you may have experienced while on treatment.

4. How long will I be in the study?

If you are responding to therapy or if your disease is stable (not getting worse), you will continue to be treated until one of the following occurs: your disease gets worse, you have a severe side effect that would require you to come off study, you refuse to continue with study, the study doctor decides it is in your best interest for you to stop the study, the study ends, or you are removed from the study to undergo surgical removal of your cancer. .

You will be followed for survival after being removed from the study as long as you live. If you are removed from the study for a severe side effect, you will be followed until this gets better. .

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. You can request the destruction of all your samples if you withdraw from the study. Your decision will not affect your future relationship with The Ohio State University.

Tell your study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

6. What risks, side effects or discomforts can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

RISKS OF AFLIBERCEPT

Likely: occurs in more than >10% of people receiving Aflibercept:

- Anemia (low red blood cell count)
- Nausea
- Vomiting
- Diarrhea
- Asthenia (feeling weak)
- Fatigue (tiredness)
- Arthralgia (joint pains)
- Myalgia (muscle pains)
- Headache
- Dizziness
- Proteinuria (including nephrotic syndrome) (kidney damage causing protein in the urine)
- Epistaxis (Nose bleeds)
- Hypertension-(high blood pressure) (including malignant hypertension- Malignant hypertension is very high blood pressure that comes on suddenly and quickly. The lower (diastolic) blood pressure reading, which is normally around 80 mmHg, is often above 130 mmHg.

Less Likely: occurs in 1-10% of people receiving Afilbercept:

- Thrombocytopenia (low platelet count that may lead to an increase in bruising or bleeding)

- Hyponatremia (low sodium levels in blood, if severe these low levels can lead to abnormal function of nerves, muscles or brain)
- Hypomagnesemia (low magnesium levels in blood, if severe these low levels can lead to abnormal function of nerves, muscles or brain)
- Hypokalemia (low potassium levels in blood, if severe these low levels can lead to abnormal function of nerves, muscles or brain)

Rare: occurs in less than 1% of people receiving Afilbercept:

- Thrombotic microangiopathy (breakdown of red blood cells in the arteries)
- Neutropenia including neutropenia with fever (low white blood count)
- Neutropenic colitis (irritation of the colon with low blood counts)
- Sepsis (severe infection of the bloodstream)
- Cardiac failure (heart failure)
- Belly pain
- Gastrointestinal hemorrhage (bleeding from the stomach or bowel)
- Intestinal perforation (a hole in the bowel)
- Intestinal obstruction (blockage of the bowel)
- Enteric fistula (leakage of bowel fluid into other organs)
- Peritonitis (irritation of the lining of the abdomen)
- Pneumatosis intestinalis (air accumulation in the intestines)
- Mucosal inflammation or ulceration (irritation of the lining of the digestive tract anywhere from mouth to rectum)
- Stomatitis (mouth sores)
- Hepatic enzymes increased (liver inflammation)
- Musculoskeletal pain
- Injection site reaction
- Hypersensitivity (allergic reaction)
- Dehydration
- Osteonecrosis (bone damage)
- Posterior Reversible Encephalopathy Syndrome (irritation of the brain), (including reversible posterior leukoencephalopathy syndrome, is a syndrome that can cause: headache, confusion, seizures and visual loss. It may occur due to a number of causes, one being malignant hypertension
- Cerebral ischemia (decreased blood going to the brain)
- Cerebral hemorrhage (bleeding in the brain)
- Cerebral venous thrombosis (blood clot in the brain)
- Hematuria (blood in the urine)
- Renal failure (kidney failure)
- Dysphonia (altered voice)
- Dyspnea (shortness of breath)
- Hemoptysis (coughing blood)
- Pulmonary embolism (blood clot in the lungs)
- Tracheo-esophageal fistula (a hole between the swallowing tube and breathing tube)

- Palmar-plantar erythrodysaesthia syndrome (sore and red skin of the palms and soles)
- Erythema (red skin)
- Deep vein thrombosis, (Blood clots)
- Phlebitis (irritation of the veins)
- Anxiety
- Female genital tract fistula (a hole between the genital tract and another organ or skin)
- Pyrexia (fever)
- Hypertriglyceridemia (high blood levels of fat)
- Hypercholesterolemia (high blood levels of cholesterol)

People who start Aflibercept after a recent surgery or who undergo surgery after receiving Aflibercept are at an increased risk of breakdown of the wound (wound dehiscence) and of having wound healing problems.

Risks of modified FOLFOX6 (mFOLFOX6) (5-FU, Leucovorin and Oxaliplatin)

Risks of Leucovorin
The following risks have been reported when leucovorin was given (occurs in 20% of people receiving leucovorin): allergic reactions (which may be severe and life threatening), shock (low blood pressure), nausea, diarrhea, thrombocytosis (high platelet count), rash, hives, pruritus (itching), headache, and wheezing.

Risks of 5-FU

Likely: (occurs in 20% or more of people receiving 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).
- diarrhea
- 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 people receiving 5-FU)

- When given 5-FU, subjects have reported something known as Hand-foot syndrome. This causes 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 people receiving 5-FU)

- Tear duct narrowing (this may cause increased tearing of the eyes)
- 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
- Increased sensitivity to light

Risks of Oxaliplatin

Likely: (occurs in more than 20% of people 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 the liver enzymes (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 people 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 cold temperatures
- 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 that is 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 narrowing 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)

Rarely: (occurs in less than 3% of people receiving Oxaliplatin)
- 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.

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 over time.

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.

Risks associated with study procedures/tests

Blood Collection
During your participation in this study, you will have blood draws. Possible risks associated include pain, bleeding, bruising, infection, or inflammation at the site where the blood is taken.

MRI Scan
When having an MRI (magnetic resonance imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your study doctor. Your study doctor may give you a medication to make you feel more comfortable in a confined space. MRIs use powerful magnets to make images. Therefore, persons with certain metal implants, such as pacemakers, should not have an MRI. If you have an implant or any metal in your body, please check with your study doctor to find out whether or not you can have an MRI. For people without metal implants, there are no known health risks associated with exposure to the magnet.

The contrast solution that may be given for an MRI scan may cause a metallic taste or warm feeling in your mouth. Rarely, it causes, nausea, vomiting, and/or an allergic reaction that can involve itching, rash, or in severe cases, difficulty breathing and dangerous lowering of blood pressure.

The nephrogenic systemic fibrosis (NSF) associated with gadolinium-based contrast media, as well as the cardiac dose used during the cardiac magnetic resonance imaging (CMR) procedure:

- A rare, serious condition called neprogenic systemic fibrosis (NSF) has been linked to gadolinium-based contrast agents used to improve MRI images. Nephrogenic systemic fibrosis has occurred in patients in the period just before or just after liver transplantation.
- NSF may result in a fatal or debilitating condition that affects the skin, muscles, and internal organs. The most common serious side effect from gadolinium-based contrast agents is an allergic reaction that is usually mild but is occasionally severe and even results in fatalities. Some patients have developed skin conditions such as rash, sweating, itching, hives and facial swelling. You will be screened through your medical history and/or lab tests for these conditions.

- A blood test will be done on the day of your MRI scan before the administration of gadolinium. If your test results are significantly abnormal, you will not be able to have the gadolinium-based, contrast-enhanced MRI scan.
- Although the contrast dose is twice that recommended by FDA guidelines, it is the standard cardiac dose.

PET Scan

During the PET scan you will be asked to lie very still on a comfortable table that moves through a ring-like scanner. You should not feel anything during the scan which can last between 45-60 minutes. A special sugar plus a radioactive tracer is injected into your vein before the scan. Active cells, like cancer cells, use sugar for energy and the scan will pick up the tracer and show any collection of abnormal cells. The risk of side effects after the PET scan is very low, but there may be a risk of having an allergic reaction to the administered radiation-labeled sugar. However, this reaction has only been rarely observed.

The PET/CT scan will also expose you to low doses of radiation. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. Two PET/CT scans will give your body the equivalent of about 20 extra years' worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

CT Scan

There is a slight risk of developing an allergic reaction to the iodine contrast material (is a form of intravenous contract, which enhances the visibility of vascular structures and organs during radiographic procedures). The reaction can be mild (itching, rash) or severe (difficulty breathing or sudden shock). Death resulting from an allergic reaction is rare. Most reactions can be controlled using drugs. Be sure to tell your study doctor if you have allergies of any kind (such as hay fever, iodine allergy, eczema, hives, or food allergies). The contrast materials used during CT scanning can cause water loss or damage to the kidneys that may lead to kidney failure. This is a concern if you have poor kidney function, dehydration or diabetes, especially if you take Metformin® (Glucophage) to control your diabetes.

You will be exposed to a limited and medically acceptable dose of radiation during this procedure. There is always a slight risk from being exposed to any radiation, including the low levels of x-rays used for a CT scan.

You may also experience discomfort related to lying still in an enclosed space for a prolonged period of time.

Electrocardiogram

An electrocardiogram generally has no risks. Because this procedure only records the electronic activity of the heart and does not send out electricity, there is no risk of shock. Occasionally, there may be some minor skin irritation or slight discomfort from ECG electrodes (disposable adhesive tabs placed on top of the skin in the chest area and then removed from the skin at the end of the procedure).

Risk of Tumor Biopsy
A tumor biopsy procedure may cause pain, bleeding, and possibly infection and discomfort at the site of the biopsy.

7. What benefits can I expect from being in the study?

Taking part in this study may or may not make your health better. While researchers hope that the combination of Aflibercept with modified FOLFOX6 (mFOLFOX6) will be more useful against your type of cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about this drug combination as a treatment for cancer. This information could help future cancer patients

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled.

Your other choices may include:
- Getting treatment or care without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care.

You may talk to his or her doctor about these and other options.

9. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):
- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- Sanofi-Aventis, the study's funding organization and their agents or study monitors;
- Your insurance company (if charges are billed to insurance).

If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic, or physician's office records. Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information.

There is a small risk of health insurance discrimination based on genetic testing; however, per the Genetic Information Nondiscrimination Act of 2008 (GINA), group and individual health insurers may not use your genetic information to set insurance eligibility, premiums, or contribution amounts, nor can they request or require that you take a genetic test. In addition, employers with 15 or more employees may not use your genetic information to make decisions regarding hiring, firing, job assessments, or promotsions, nor can they request, require, or purchase your genetic information. In Ohio, there is a similar state law that also provides some protection for private health insurance plans. GINA does not protect you against genetic discrimination by companies that sell life, disability, or long-term care insurance.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. 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 the website at any time.

You may also be asked to sign a separate Health Insurance Portability and Accountability Act (HIPAA) research authorization form if the study involves the use of your protected health information.

10. What are the costs of taking part in this study?

You will not be charged for the study treatments or additional tests required for this study that are not required for the care and management of your cancer. The study drug Aflibercept is being provided to you at no cost.

The following procedures/tests are considered to be research and will not be billed to you or your insurance company:

- Archived Tissue Sample at screening
- Serum/Plasma PD Research at screening and day 1 of weeks 3,9 and 13
- FDG-PET scan at screening and at week 8
- DCE-MRI at screening and at week 8
- Glucose blood test at screening and every other week while receiving treatment
- ECG at screening
- Tumor Biopsy (if performed) at screening and week 8

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. 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. You will be billed for any deductibles co-insurance and or co-payments required by your insurance company or third-party payer.

11. Will I be paid for taking part in this study?

You will not be paid for participating in this clinical trial.

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

OHIO STATE UNIVERSITY LIABILITY

If you are injured as a result of your participation in this study, you may obtain immediate care at The Ohio State University Medical Center. The cost of this treatment will be charged to you or your insurance company. Your health insurance company may or may not pay for treatment of injuries as a result of your participation in this study. The Ohio State University has no funding set aside for the payment of health care expenses resulting from injury for this study.

SPONSOR LIABILITY

If the injury was caused by a defect in the study drug Aflibercept, then sanofi-aventis, the provider of the study drug, will pay the reasonable costs for necessary medical treatment that are not covered by your medical insurance provided you have followed the directions of the study doctor. This commitment for free medical treatment does not include treatment for any other complications or illness that you may experience during this study, which do not result from your participation in the study.

By signing this consent form, you will not be waiving any of the legal rights which you otherwise would have as a subject in a research study.

13. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

14. Who can answer my questions about the study?

For questions, concerns, or complaints about the study you may contact **Dr. John Hays at 614-685-6700.**

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. John Hays at 614-685-6700.**

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this form.

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
	AM/PM
Relationship to the subject	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	**Signature of person obtaining consent**
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	**Signature of witness**
	AM/PM
	Date and time
Printed name of witness	**Signature of witness**
	AM/PM
	Date and time