# CONSENT FOR CANCER RESEARCH

**Project Title:** Case 1317; CA209-382 A Randomized Phase 2 Open Label Study of Nivolumab plus standard dose of Bevacizumab versus Nivolumab plus low dose Bevacizumab in Recurrent Glioblastoma (GBM).

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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).

One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask you study doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924

**What is the usual approach to my brain cancer?**

You are being asked to take part in this study because you have a type of brain cancer called glioblastoma multiforme which has grown or has recurred. You have already been treated with surgery, radiation, and chemotherapy. People who are not in a study are usually treated with more chemotherapy and additional surgery if appropriate. Bevacizumab is also an available and Food and Drug Administration (FDA)-approved treatment for patients with recurrent glioblastoma who have not previously received it, although it does not cure and its effect on survival is unknown. Sometimes, combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

**What are my other choices if I do not take part in this study?**
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms

**Why is this study being done?**

The purpose of this study is to test the effectiveness (how well the drug works), safety and tolerability of an investigational drug called nivolumab (also known as BMS-936558) in glioblastoma (a malignant tumor, or GBM), when added to bevacizumab.

Nivolumab is an investigational (experimental) drug. Nivolumab is an antibody (a kind of human protein) that is being tested to see if it will allow the body's immune system to work against glioblastoma tumors. Opdivo (Nivolumab) is currently FDA approved in the United States for melanoma (a type of skin cancer), non-small cell lung cancer, renal cell cancer (a type of kidney cancer), Hodgkin's lymphoma but is not approved in glioblastoma. Nivolumab may help your immune system detect and attack cancer cells.
Nivolumab is experimental because it is not approved by the Food and Drug Administration (FDA).
Bevacizumab is a drug which works on the blood vessel that supply the tumor and potentially can starve the tumor by cutting off the blood supply to these tumors. Bevacizumab is commercially available and FDA approved for patients with recurrent glioblastoma. In this study bevacizumab is also investigational because one study group (Arm B) will receive a reduced dose of bevacizumab.

90 total patients are expected to participate in this study (45 patients in each arm). Even though you may meet all the criteria for participation, it is possible that you will not be enrolled in this study.

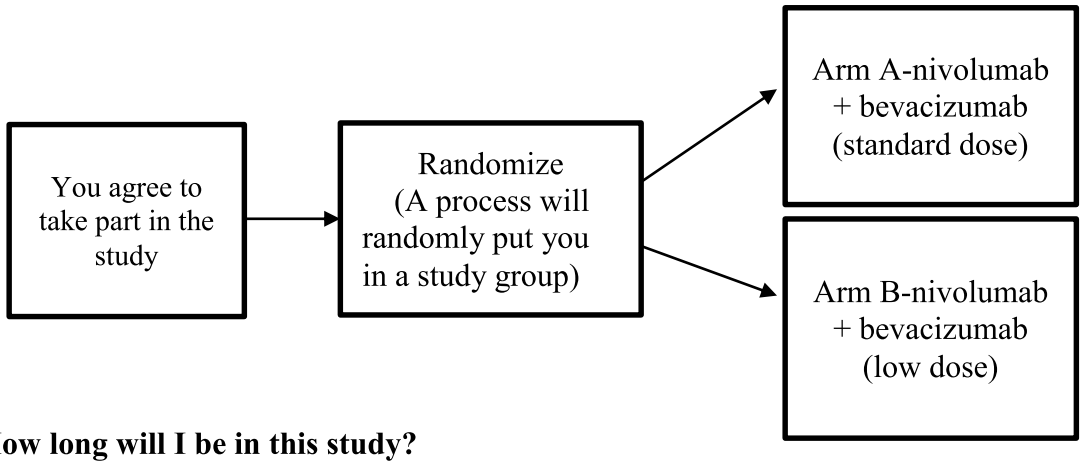
Cleveland Clinic will enroll 50-60 patients.

**What are the study groups?**
This study has two study groups.

- Arm A will receive the study drug nivolumab 240mg and bevacizumab 10 mg (standard dose) every 2 weeks
- Arm B will receive the study drug nivolumab 240 mg and bevacizumab 3 mg (low dose) every 2 weeks

A process will be used to assign you, by chance, to one of the study groups. Neither you nor your doctor can choose which group you are in. This is done by chance because no one knows if one study group is better or worse than the other.

**Example:** To find out what will happen to you during this study read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.




**How long will I be in this study?**

If you are enrolled and randomized (assigned to a treatment arm), the exact length of time that you participate in this study will depend on how you do on treatment. After completing all study treatments or after you are withdrawn from treatment, you will be asked to continue with follow-up visits to monitor for side effects or potential benefits you may be experiencing from study treatment.

Your total participation in this study from the time you have signed the informed consent to your last visit, including follow-up visits, may be more than three years (depending on what effect the treatment has on your cancer, and how well you tolerate the treatment).

**What extra tests and procedures will I have if I take part in this study?**

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, if you choose to take part in the study, then you will need the following extra tests. They are not part of the usual approach for you type of cancer.

Before you begin the study:

- EKG
- Collection of stored pieces of cancer tissue, if available, from your initial surgery at the diagnosis of glioblastoma, to look at certain features of the tumor. The tissue will be requested from the facility where you had your initial surgery to remove the tumor.
- Urinalysis
- Pregnancy test (women of child bearing potential)
- Hepatitis B and C testing
- Research blood samples

Neither you nor your health care plan/insurance carrier will be billed for the collection or processing of the research blood samples that will be used for this study

During the study the following will be additional research procedures:

- Urinalysis
- Pregnancy Test
- EKG

**Study Procedures**

After you meet the eligibility criteria, you will be randomized (assigned by chance to receive either:

Arm A nivolumab plus standard bevacizumab
OR
Arm B nivolumab plus low dose bevacizumab

There are three periods to the study: Screening, Treatment and Follow up

Screening

At the Screening visit you will be asked to read and sign this informed consent before any study-related procedures that are not standard of care are performed. It is your right as a subject to have the study fully explained to you and you can ask that your study doctor explain or go over any parts of this informed consent that you do not understand.

The following tests and procedures will be performed by the study staff to determine if you qualify to participate in this study:

- Review of your medical history
- Review of medications you are currently taking and have taken in the past including herbal supplements, over the counter medications, and steroid medications
- A physical examination including measurement of your height, weight and vital signs (temperature, blood pressure, respirations and heart rate) and your neurologic status.
- An electrocardiogram (ECG) to test the function of you heart
- You will be asked about the symptoms you are having from your disease (performance status)
- Collection of your blood (approximately 4 teaspoons or 20 mLs) for laboratory tests which measure your blood chemistry, including kidney and liver function, count your red and white blood cells and platelets, measure your thyroid function, and check for hepatitis B or C infection. You must not be HIV positive and your hepatitis B and C tests must be negative for you to participate in the study.
- A urine test (with dipstick) to check for any abnormalities
- If you have had brain cancer surgery in the past, either at Cleveland Clinic or elsewhere, your study doctor will request the original samples from the medical facility where it was done. In order to participate in this study, you must also provide your permission to obtain these original samples and allow your study doctor to send them to an additional laboratory for research testing.
    - Your tumor samples will also be tested to determine whether your cancer tumors have certain features which may help scientists better understand glioblastoma and also may help scientists understand why your specific type of glioblastoma either responded or did not respond to the study drug. Scientists will look for certain types of genes and proteins which may be present on the surface of or within your tumor cells and may also look to see if certain types of white blood cells called lymphocytes are present within your tumor. Genomic (DNA/RNA) testing will be used to identify specific genetic variants related to cancer risk, prognosis and treatments.
- Contrast enhanced magnetic resonance imaging (MRI) of your brain. These images will allow your doctor to monitor your disease before, during and after you receive study drug and to see if the tumors change in size. Depending on your disease status at the time you

enroll into the study, the MRI images from your original GBM diagnosis may be used as part of this study.
- A urine or blood pregnancy test for women of childbearing potential will be performed. Results of the pregnancy test must be negative for you to participate in this study.

If, based on the results of the screening visit tests and procedures, you qualify to participate in the study, you will return to the study doctor's office for the Baseline Visit.

Treatment

If you qualify to participate in the study based on the results of the screening visit tests, and procedures, you will return to the study doctor's office/clinic.

If you are assigned to treatment Arm A, nivolumab plus bevacizumab (standard dose) will be given to you as an intravenous infusion on Day 1 and then every 2 weeks. You will then be given nivolumab and bevacizumab every 2 weeks for the remainder of the treatment period.

If you are assigned to treatment Arm B, nivolumab plus bevacizumab (low dose) will be given to you as an intravenous infusion on Day 1 and every 2 weeks. You will then be given nivolumab and bevacizumab every 2 weeks for the remainder of the treatment period.

During the Treatment Period, you will be asked questions about your condition including:
- How your cancer is affecting your daily activities.
- What medications you took or are currently taking including herbal supplements and over-the-counter medicines.
- What side effects you experienced. During your clinic visits, you should report the development of any new or worsening medical problems (since your last visit) to the study doctor or other study personnel taking care of you.

The following procedures/samples will be performed and/or collected at Day 1 Week 1 and then every 2 weeks:
- A brief physical examination, including body weight and examination of performance status.
- A neurological exam
- Vital sign measurements (blood pressure, heart rate, temperature and breathing rate) will be assessed. If you develop a reaction during the infusion, you will continue to have your vital signs measured until the study doctor determines it is no longer necessary.
- A urine test (with dipstick) to check for any abnormalities
- An electrocardiogram (ECG) to test the function of your heart. This test may be done if requested by your physician.

- Pregnancy test will be done Day 1 Week 1 and then every 4 weeks
- Collection of your blood (approximately 4 teaspoons or 20 mLs) for laboratory tests which measure your blood chemistry, including kidney and liver function, count your red and white blood cells and platelets will be drawn prior to each study drug dose through Week 21 and then every 4 weeks

  Additional blood samples will be drawn for research purposes at week 4, week 8 and at every MRI visit thereafter
- A contrast enhanced MRI of your brain will be completed every 6-8 weeks (± 1 week) thereafter, until your disease has worsened or you stop receiving study treatment (whichever occurs later). An MRI of your brain will show photographic images or pictures of your brain, which will allow your doctor to monitor the progress of your disease. Your doctor may decide to do an MRI more frequently if it is medically indicated.
- At about the same visit as the MRI, you doctor will assess your neurologic function by using a set of standard questions called the neurologic assessment in neuro-oncology (NANO)

You may be discontinued from receiving study treatment based on your disease assessments or if you are having side effects that make you unable to tolerate study therapy. Based on discussions between you and your study doctor, you may discontinue for other reasons including your decision to stop being treated.

Follow up

When you stop or complete study treatments you will begin the last part of the study, the follow-up period. During this period your study doctor will continue to assess your health condition. It is important to know, for example, if you have recovered, developed an illness or suffered an important adverse event.

Initial Follow-up Phase (Follow up visits 1 and 2)

After stopping the study treatment, the first two follow up visits will be at your doctor's office. The first one will be about a month after you stop treatment and the second will be about 2 1/2 months after the first follow-up visit. It is important to know, for example, if you have recovered, developed an illness or suffered an important adverse event the procedures/samples performed and/or collected while you were taking study drug may be repeated at one or more of these follow up visits.

- A Physical exam, including body weight and examination of performance status
- Vital sign measurements (blood pressure, heart rate, temperature, and breathing rate
- You will be asked about any medications you are taking and how you are feeling.
- Pregnancy test

Additional Follow up (after follow-up visit 2)

The remaining follow up visits may be conducted over the telephone or at your doctor's office. These visits will occur approximately every 3 months and potentially more frequently. You will be asked the same questions regarding your medical condition that you answered while taking study drug. During this period your study doctor will continue to assess your health condition. It may be necessary to go to your study doctor's office for additional MRI scans as was done while you were receiving treatment.

During the additional follow up visits you will be asked to complete health related questionnaires (either via phone or a clinic visit).

**Research on Tumor Samples and Future Research:**

We would like to store samples of tissue or blood that we collect during the procedures done as part of the study. These stored samples will be used for other research and might include genetic studies for other cancers, or other diseases that are common to your age group. If genetic testing is done, the samples will be labeled so your name and your identity will remain unknown. The results of any genetic or other testing will not be given to you or your doctor, as your identity will not be known. It is not possible for us to know now what tests will be discovered in the future. We cannot give you a list of all the possible ways the samples will be used. We are asking that you give your permission for us to take, store and do research on these samples without contacting you again in the future. None of this research is a direct help to you, but could help us learn other ways to prevent cancer or other diseases and might be helpful to others in the future. You will receive no payment for these samples or from any tests or products that are developed in the future from the use of the samples. If you give permission for the samples now and change your mind later, you will need to write to the doctor listed on the first page of this form and let him/her know that you changed your mind. If we have not already used the sample, it will be destroyed and not used. If you have any questions, please ask your doctor.

Your Responsibilities
If you participate in this study, you will be expected to:

- Keep all study appointments and follow all instructions given to you by your study doctor and study staff
- Describe how you feel and discuss possible side effects.
- Tell the study doctor about all medications you are taking including prescriptions, herbal supplements and over-the-counter medications.
- Discuss any medication (prescription or over the counter) that you wish to start taking with your study doctor before you start taking it.
- Tell the study doctor about any changes in your health
- Certain medications cannot be taken while you are participating in this trial. Your study doctor will explain what these medications are. If you need treatment with any medications that are not allowed during your participation in this trial, you must inform the study doctor or the study staff. You will not be denied medications required to treat an illness you may have, but you may be required to stop taking the study medication. This is for your safety, since some medications may not work well with the study treatment, and you might have physical problems.
- Tell your study doctor about <u>any</u> additional medical treatments that you plan to receive during the study (such as elective surgery or radiation).
- Tell your study doctor or study staff if you change your address, telephone number, or other contact information

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

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

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- The study drug(s)/study approach may not be better, and could possibly be worse, than the usual approach for your cancer.
- Personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

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

Here are important points about side effects:
- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:
- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

In addition to side effects outlined above, you may also experience the possible side effects of bevacizumab listed below.

**Risks of Nivolumab**

Very common side effects of nivolumab that may affect more than 1 in 10 people:
- Fatigue
- Rash
- Diarrhea
- Itching

Common side effects of nivolumab which may affect more than 1 in 100 but less than 1 in 10 people include:
- Abdominal pain
- Allergic reaction/hypersensitivity
- Decreased appetite
- Dizziness or vertigo (feeling off balance which can lead to dizziness)
- Fever
- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
- ALT increased: lab test result associated with abnormal liver function

- Bilirubin (liver function blood test) increased
- Amylase increased: lab test result associated with pancreas inflammation
- AST increased: lab test result associated with abnormal liver functions
- Chills
- Constipation
- Cough
- Creatinine increased: lab test result associated with decreased kidney function
- Dry mouth
- Dry skin
- Headache
- Lipase increased: lab test result associated with pancreas inflammation
- Increase blood sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis-see details below)
- Musculoskeletal pain
- Nausea
- Redness (of the skin)
- Shortness of breath
- Sodium levels in blood low
- Swelling including face, arms and legs
- Thyroid gland function decreased
- Thyroid gland function increased
- Thyroid stimulating hormone increased (lab test associated with abnormal thyroid function)
- Tingling, burning, numbness or weakness, possible in arms,legs,hands and feet
- Vomiting

Uncommon side effects of nivolumab which may affect more than 1 in 1,000 but less than 1 in 100 people

- Adrenal gland function decreased
- Bronchitis
- Dehydration
- Diabetes
- Double vision
- Dry eye

- Erythema multiforme (allergic skin reaction)
- Hair loss
- Heart rate increased
- Heart rhythm abnormal
- High blood pressure
- Hives
- Inflammation of the eye
- Inflammation of the heart
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland
- Joint pain or stiffness
- Liver inflammation
- Low blood pressure
- Pemphigoid: blistering of the skin or mouth caused by immune system attacking health tissues
- Pituitary gland function decreased (you could experience fatigue, low blood pressure, weight loss, weakness, depression, nausea or vomiting)
- Lung infiltrates associated with infection or inflammation
- Muscle inflammation
- Psoriasis: characterized by patches of abnormal, scaly skin
- Renal (kidney)failure or kidney injury
- Respiratory failure
- Upper respiratory tract infection
- Vision blurred

Rare but potentially serious side effects of nivolumab which may affect up to 1 in 10,000 people but less than 1 in 1,000 people include:

- Anaphylactic reaction (severe allergic reaction)
- Cranial nerve disorder, refers to an impairment of one of the twelve cranial nerves that emerge from the underside of the brain, pass through openings in the skull, and lead to parts of the head, neck, and trunk. These disorders can cause pain, tingling, numbness, weakness, or paralysis of the face including the eyes.
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acids
- Drug induced liver injury

- Disease caused by the body's immune system attacking healthy organs
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessels
- Inflammation of the brain, potentially life-threatening or fatal
- Inflammation of the heart
- Inflammation of the lining of the brain and spinal cord
- Lung infiltrates associated with infection or inflammation
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Polymyalgia rheumatica
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Rhabdomyolysis (muscle fiber substances released into the blood stream which could damage your kidneys) Polymyalgia Rheumatica, an inflammatory disorder causing muscle pain and stiffness
- Rosacea: acne-like skin condition resulting in redness of face
- Rupture of the intestines/hole in the intestine
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin and lymph nodes
- Stevens Johnson Syndrome: inflammation disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Symptoms associated with fever, white blood cell activation and abnormal function(including destruction of other blood cells by certain white blood cells), low blood cell counts, rash and enlargement of the spleen
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains
- Vogt Koyanagi Harada syndrome; a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision; the ear leading to hearing loss, ringing in the ears and/or the skin leading to loss of skin color

**Lung Inflammation (pneumonitis):** It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has

occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Complications, including rejection, have also been reported in patients who have received an organ or tissue transplant. Treatment with nivolumab may increase the risk of rejection of the organ or tissue transplant

**Please inform your study doctor or nurse <u>AT ONCE</u> if you experience any of the following:**

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

**<u>Risks of Bevacizumab</u>**

Likely (> than 10%, occurs in more than 10 people out of 100 people)

- High blood pressure (including dangerously high blood pressure called hypertensive crisis that can have an effect on brain function and can be life threatening
- More protein leaking into the urine than usual (which may indicate kidney damage)
- Shortness of breath
- Nose bleeds
- Sores in mouth and/or throat
- Changes in taste
- Watery eyes
- Skin and nail changes (including dryness itching, rash, discoloration, ulcers or peeling)

Less Likely (<5-15%, occurs in less than 5 to 15 people out of 100 people)

- Fast heartbeat usually originating in an area located above the ventricles
- Feeling of spinning or whirling
- Belly pain
- Inflammation (swelling and redness) of the large bowel (colon)
- Constipation
- Diarrhea
- Heartburn
- Bleeding in some organ(s) of the digestive tract
- Blockage in an organ(s)/part(s) of the digestive tract
- Partial or complete blockage of the small and/or large bowel. Ileus is a functional rather than actual blockage of the bowel.
- Irritation or sores in the lining of the mouth
- Nausea or the urge to vomit
- Vomiting
- Fatigue or tiredness
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Pain
- 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
- Infections
- Infection (collection of pus) around the rectum
- Premature opening of a wound along surgical stitches after surgery
- Increased blood level of a liver enzyme (ALT/SGPT) which may indicate a problem with liver function
- Increased blood level of a liver or bone enzyme (alkaline phosphatase) which may indicate liver damage
- Increased blood level of a liver enzyme (AST/SGOT) which may indicate a problem with liver function
- Increased blood level of a liver pigment (bilirubin) often a sign of liver problems
- Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle
- Decreased number of a type of white blood cell count (which may increase risk of infection)

- Decrease in the number of red blood cell count (may cause anemia and make you fell weak and tired)
- Weight loss
- Decrease in the total number of platelets count that might interfere with clotting (may make you more likely to bruise or bleed)
- Loss of appetite
- Joint pain
- Muscle pain
- Destruction or breakdown of jawbone
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Headache or head pain
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Fainting
- Blood in the urine
- Bleeding in the vagina
- Stuffy or runny nose, sneezing
- Cough
- Hoarseness
- Itching
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung
- Loss of function of the ovaries, which can lead to menopause. The effect of this on fertility is not know

Rare but serious (< 5%, occurs in less than 5 people out of 100 people)

- Damage of or clots in small blood vessels in the kidney that can cause complications, some of which are serious including abnormal destruction of red blood cells (hemolysis) or platelets (that help to clot blood) and kidney failure
- Collection of signs and symptoms that indicate sudden heart disease in which the heart does not get enough oxygen. Sudden symptoms such as chest pain, shortness of breath, or fainting could indicate heart disease and should be reported right away. Signs such as abnormal EKG and blood tests can confirm damage to the heart.
- Heart failure: inability of the heart to adequately pump blood to supply oxygen to the body
- Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole)
- Heart attack caused by a blockage or decreased blood supply to the heart

- Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)
- Ventricular fibrillation: irregular heartbeat that involves the lower chambers of the heart (ventricles) that results in uncoordinated contraction of the heart; life threatening and potentially fatal, needing immediate attention
- Gastrointestinal fistula: Abnormal hole between an organ of the digestive tract and another organ or tissue
- Gastrointestinal perforation: A tear or hole in the stomach or gut that can lead to serious complications and may require surgery to repair
- Sore (ulcer) somewhere in the digestive tract
- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Leakage from stomach due to breakdown of an anastomosis (surgical connection of two separate body structures)
- Bleeding in the brain
- Stroke caused by decreased blood flow to the brain
- Abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss associated with MRI imaging findings (RPLS)
- Sudden decrease of kidney function
- Abnormal hole between part of the urinary system and another organ or tissue
- Abnormal hole between the vagina and another organ or tissue
- Abnormal hole between the lower breathing tube and the body cavity that surrounds the lungs
- Bleeding from the lungs
- Hole in the wall that separates the nostrils of the nose
- Blockage or narrowing of a blood vessel (artery) that can cause damage or loss of function including a heart attack or stroke
- Abnormal hole between the breathing tube (windpipe) and the tube that goes from mouth to stomach through which food passes (esophagus). This is life-threatening and potentially fatal.
- Delay in wound healing or breakdown of a wound that had healed.
- Fertility issues for women. Bevacizumab could cause a women's ovaries to stop working and may impair her ability to have children

- Reversible Posterior Leukoencephalopthy Syndrome (RPLS) or similar leukoencephalopahthy syndrome: RPLS is a medical condition related to leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life- threatening and may have a long term effect on brain function

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, and monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is usually 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.

Magnetic Resonance Imaging (MRI)

If you take part in this research, you will have an MRI (magnetic resonance imaging and/or magnetic resonance spectroscopy). MRI uses a magnet and radio waves to make images (pictures) of the inside of the head and/or body. There have been no ill effects reported from exposure to the magnetism or radio waves used for these studies; however, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal that may cause injury to you. We will ask you about metal within your body (this includes certain dyes used in tattoos and body piercings). If there is any question about potentially hazardous metal within your body, you will not be able to participate in this research study. We will also keep the MRI room locked so that no one carrying metal objects enters the room while you are having this scan performed. In addition, the MRI scanner makes a loud buzzing noise that could affect hearing ability. You will be provided with earplugs and assistance in their use in order to protect your hearing. You will be able to communicate with the scanner technologist using an intercom and/or signaling device. The technologist will try to help you feel as comfortable as possible in the scanner. You can ask to stop the scan and be removed from the scanner at any time by using the intercom or signaling device.

There is a very slight risk of an allergic reaction if contrast material is injected. Such reactions usually are mild and easily controlled by medication. If you experience allergic symptoms, a radiologist or other physician will be available for immediate assistance.

**Gadolinium-based** contrast agents (dyes) may increase the risk of a rare but serious disease called nephrogenic systemic fibrosis in people with poor kidney function. Nephrogenic systemic fibrosis triggers thickening of the skin, organs and other tissues. There is no effective treatment for this debilitating disease.
A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

There may be additional risks or side effects which are unknown at this time.

Your condition may not get better or may become worse while you are in this study.

Certain drugs may increase the severity of these side effects if taken during the study. Ask your study doctor for a full list of prohibited medications

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

**Reproductive (pregnancy) Risks (Female and Male Subjects)**

Based on the way nivolumab works and data from animal reproductive studies, nivolumab can cause harm to an unborn child. You should not become pregnant during treatment with nivolumab. Females should use effective birth control for at least 5 months after the last dose of nivolumab. Male subjects who are sexually active with a woman of child bearing potential should also use an adequate method(s) of birth control to avoid pregnancy of their partner for up to 7 months after the last dose of nivolumab.

Based on the way bevacizumab works bevacizumab can cause harm to an unborn child. You should not become pregnant during treatment with bevacizumab. Females should use effective birth control for at least 6 months after the last dose of bevacizumab.

Bevacizumab may cause ovarian failure and loss of fertility.

Both nivolumab and bevacizumab can be present in breast milk. Women should not breast feed during treatment with nivolumab or bevacizumab.

Your study doctor is familiar with the different forms of acceptable contraception (see table below) and will be able to give advice about which method might be best for you.

Any birth control method used must be highly effective with a failure rate less than 1% per year, and must be discussed with your doctor if it is started during the course of the study. You must not be pregnant or breastfeeding, and you should not become pregnant or breastfeed while you are taking the study treatments. Females should not breastfeed while receiving nivolumab and up to 5 months from the last dose of nivolumab. You must use an adequate method(s) to avoid pregnancy for the duration of this study and for up to 5 months after the last dose of nivolumab. Male subjects who are sexually active with a woman of child bearing potential should also use an adequate method(s) of birth control to avoid pregnancy of their partner for up to 7 months after the last dose of nivolumab.

Women of child bearing potential are expected to use one of the highly effective methods of contraception listed below.

Male Subjects:
Male subjects must inform their female partners who are women of child bearing potential of the contraceptive requirements and are expected to adhere to using contraception with their partner. Female partners of male subjects, who are women of child bearing potential, are expected to use one of the highly effective methods of contraception listed below. In addition, male subjects are expected to use a condom as noted in the list below

| | |
|---|---|
| Highly Effective | Progestogen only hormonal contraception associated with inhibition of ovulation |
| | Hormonal methods of contraception including oral contraceptive pills (combination of estrogen and progesterone), vaginal ring, injectables, implants and intrauterine devices (IUDs) |
| | Non-hormonal IUDs such as ParaGard® |
| | Bilateral tubal ligation |
| | Vasectomized Partner |
| | Intrauterine hormone-releasing system (IUS) |
| | Complete abstinence |
| | |
| Other Methods | Condom |
| | |
| Unacceptable Methods | Vaginal sponge |
| | Progestin only pills |
| | Cervical cap with spermicide |
| | Periodic abstinence (calendar, symptothermal, post-ovulation methods) |
| | Withdrawal (coitus interruptus) |
| | Spermicide only |
| | Lactation amenorrhea method (LAM) |
| | A male and a female condom must not be used together |
| | |

Occurrence of Pregnancy or Suspected Pregnancy

There may be unknown risks to you, your unborn baby or nursing infant if you are or become pregnant during this study or are breastfeeding during this study.

It is important to contact your study doctor if:

- you have difficulty following the study doctor's contraception advice
- your normal period is late or is missed

- you think for any other reason you might be pregnant
- you start to take any medication or non-prescription supplements (including over-the-counter drugs and herbal supplements) without the study doctor's approval
- there is a change in your method(s) to avoid pregnancy

If you become pregnant during this study, suspect pregnancy or if you missed your period or it is late, or if you have a change in your usual menstrual cycle (e.g., heavier bleeding during your period or bleeding between periods), you should immediately contact your study doctor**.**

A Federal law, called the Genetic Information Nondiscrimination Act (GINA), effective May 21, 2010, generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

**What possible benefits can I expect from taking part in this study?**

We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your cancer, which may give you relief from some symptoms, improve your quality of life or prolong your survival. However, it is possible that your condition could worsen. Your participation in this study will help to obtain information about treating subjects with recurrent glioblastoma (GBM).

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

**Can I stop taking part in this study**?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

**What are my rights in this study?**

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights

**What are the costs of taking part I this study?**

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

The study agent, Nivolumab, will be provided free of charge by Bristol Myers Squibb while you are participating in this study. Neither you nor your insurance provider will be responsible for the costs of any research-only tests or procedures. The blood work for research purposes will not be charged to you. It will be paid for by the research study.

You and/or your health plan/insurance company will need to pay for bevacizumab or avastin and or 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.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

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

If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor
If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924.

**HIPPAA Authorization**

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to David Peereboom MD, and the research study 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 and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- The drug supplier (Bristol Myers Squibb, its study monitors and representatives)
- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;

- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;
- Health care providers who provide services to you in connection with this study
- Other individuals and organizations that analyze your health information in connection with this study, such as laboratories and other study sites participating in this study.
- Other individuals that assist in determining your health, vital status or contact information should you withdraw from treatment or are otherwise lost to follow-up

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

David Peereboom M.D.
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave. CA-51
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 cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic 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) 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

**Voluntary Participation**

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.

**Questions about the Research**
If you have any questions, you can ask the Principal Investigator and/or research staff
David Peereboom M.D.at 216-445-6068

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

**Where Can I Get More Information?**
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

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

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/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

**US National Institutes of Health (NIH) Clinical Trial Database:**
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

**Signature**

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

| Signature of Participant | Date | Printed Name of Participant |
|---|---|---|

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

| Signature of Person Obtaining Consent | Date |
|---|---|

Printed Name of Person Obtaining Consent