Official Title:	Pilot Study of Weekly Brentuximab Vedotin or Brentuximab Vedotin Plus Nivolumab Every 3 Weeks in Patients with CD30+ Malignancies Refractory to Every ≥ 3 Week Brentuximab Vedotin
NCT Number:	NCT01703949
Document Type:	Informed Consent Form
Date of Document:	April 25th, 2023

UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
FRED HUTCHINSON CANCER CENTER

Consent to take part in a research study:

A Pilot Study of Weekly Brentuximab Vedotin or Brentuximab Vedotin Plus Nivolumab Every 3 Weeks in Patients with CD30+ Malignancies Refractory to Every ≥ 3 Week Brentuximab Vedotin

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University of Washington Medical Center paging operator.
Please ask the operator to page the hematology-oncology fellow on call.

We would like you to join this research study.
You have previously received brentuximab vedotin (Adcetris™) for treatment of your cancer. We would like to ask you to join this research study if your cancer did not respond or got worse during your treatment with brentuximab vedotin or within 6 months of your last dose of brentuximab vedotin. We plan to enroll 20 people on this study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in this study. You are free to say yes or no, or to drop out after joining. There is no penalty or loss of benefits if you say no. Whatever you decide, your regular medical care will not change.

Why are we doing this study?
We are studying Brentuximab vedotin (Adcetris™). Brentuximab vedotin is a drug that is approved by the U.S. Food and Drug Administration (FDA) for treatment in patients with certain lymphomas. However, some patients have cancer which either stays the same after treatment with brentuximab vedotin or gets worse.

Nivolumab is an FDA approved treatment of relapsed/refractory classical Hodgkin lymphoma patients.

In this study, we want to learn what effects, good or bad, brentuximab vedotin with or without nivolumab has on people with Hodgkin lymphoma. If you join this study, we would give you brentuximab vedotin with nivolumab and watch carefully for any side effects.

The approved planned dose and schedule of brentuximab vedotin is 1.8 milligrams (mg) per kilogram (kg) given through a vein on day 1 of an every 21 day cycle.

The approved planned dose and schedule of nivolumab is 3 milligrams (mg) per kilogram (kg) given through a vein on day 1 of every 21 day cycle.

We plan to give up to 4 cycles of this dosing regimen.

A previous study has determined the recommended dosage for this experimental schedule. Brentuximab vedotin is still being studied in clinical trials like this one to learn more about what its side effects are and whether or not it is effective in the disease or condition being studied. This includes studying whether or not it is going to help patients who have received brentuximab vedotin before.

What research tests, procedures, and treatments are part of this study?
If you decide to join this study, we will do these tests and procedures:

Screening/Baseline

- **Medical history.** You will be asked questions about your medical history. This includes ongoing conditions you have and drugs you are taking.
- **Physical exam.** Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities.
- **Electrocardiogram.** This is a painless test that measures the electrical activity and health of the heart.
- **Routine laboratory tests.** Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken, and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood may additionally be taken to perform tests which will give more information about your cancer, if clinically appropriate.
- **Optional research draw.** About 2 teaspoons of blood will be taken for research tests.
- **Optional research tissue.** When available, some tissue from your biopsy performed at the time of your diagnosis will be requested. The results will not be reported in your medical record.
- **Pregnancy test.** If you are a female who could become pregnant, you will have a pregnancy test. Either a blood or urine sample will be taken for this test.
- **Bone marrow testing.** Bone marrow aspiration and biopsy should be done to see if your cancer has spread to the bone marrow. For the bone marrow aspirate, a sample of bone marrow cells is taken by a needle inserted into a bone in your body. For biopsy, a small piece of bone is removed. These tests are done under local anesthesia.
- **Computed tomography (CT) scans.** CT is a medical x-ray imaging method. It provides 3-dimensional pictures of the body and organs by sections. CT scans of the chest, abdomen, and pelvis will be done. If it is clinically appropriate, a CT scan of the neck will be done.
- **Positron emission tomography (PET) scan.** If your doctor thinks this is clinically appropriate, PET will be done. PET is another imaging technique. It produces a 3-dimensional picture of processes going on at the cellular level in the body.

Within 3 days prior to each cycle

- **Physical exam.** Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities.
- **Routine laboratory tests.** Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment.
- **Optional research draw.** About 2 teaspoons of blood will be taken for research tests. The results will not be reported in your medical record.

Day 1 of each 21 day cycle (up to 4 cycles of treatment):

- **Infusion.**

- Brentuximab vedotin will be given by intravenous (into a vein) infusion. This infusion will take about 30 minutes.
- Nivolumab will be given by intravenous (into a vein) infusion. This infusion will take about 30-60 minutes.

After cycle 2

- **Computed tomography (CT) scans.** CT is a medical x-ray imaging method. It provides 3-dimensional pictures of the body and organs by sections. CT scans of the chest, abdomen, and pelvis will be done. If it is clinically appropriate, a CT scan of the neck will be done. These will be done to see how your cancer is responding, so your doctor can determine if you should continue on treatment.

End of treatment

- **Physical exam.** Physical exams will assess your overall health status and include measuring your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight will also be recorded. You will also be asked how easily you perform daily activities.
- **Routine laboratory tests.** Blood samples will be taken for routine tests. About 2 - 3 teaspoons of blood will be taken. A little over a teaspoon of blood may additionally be taken to perform tests which will give more information about your cancer, if clinically appropriate.
- **Bone marrow testing.** Bone marrow aspiration and biopsy should be done if you had cancer in your bone marrow prior to treatment. For the bone marrow aspirate, a sample of bone marrow cells is taken by a needle inserted into a bone in your body. For biopsy, a small piece of bone is removed. These tests are done under local anesthesia.
- **Computed tomography (CT) scans.** CT is a medical x-ray imaging method. It provides 3-dimensional pictures of the body and organs by sections. CT scans of the chest, abdomen, and pelvis will be done. If it is clinically appropriate, a CT scan of the neck will be done.
- **Positron emission tomography (PET) scan.** If your doctor thinks this is clinically appropriate, PET scans will be done. PET is another imaging technique. It produces a 3-dimensional picture of processes going on at the cellular level in the body.

After you have finished treatment with brentuximab vedotin and nivolumab, you will enter the follow-up part of the study.

Long term follow up

Long-term follow-up means keeping track of your medical condition. In order to do this, we will obtain information from the following.

- Physical exam. Physical exams will assess your overall health status. This will be done per clinical standard of care, but a typical follow up schedule will be every 3 months for 1 year after treatment, then every 6 months for 4 years afterward.

How long will I be in this study?

The total time expected on this study may be up to approximately five and a half years.

The total time includes up to four cycles of actual treatment with brentuximab vedotin and nivolumab which will be approximately three months if all therapy is given on time. After that, we would like you to visit the office/clinic for follow-up exams per clinical standard care. As described above, we may follow your health status for up to 5 years.

The study doctor or your doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You are unable or unwilling to follow study procedures.
- The whole study is stopped.
- You may also withdraw from the study at any time, for any reason. This is your right and there will be no penalty for withdrawing from the study.

If you are thinking about dropping out of this study, please tell the study doctor. The doctor can tell you about the effects of stopping brentuximab vedotin and/or nivolumab. You and the doctor can talk about what follow-up care and testing would help you the most.

If you leave the study, your test results and information which have already been collected cannot be removed from the study records.

If you withdraw yourself from the treatment part of the study, the doctor may ask you if you will continue in the long term data follow-up part of the study.

What are the side effects (risks)?
In this part of the consent form, we tell you the side effects we expect from the tests and treatments in this study. There may be side effects we do not know about yet. If we learn about other side effects, we will tell you.

We carefully watch everyone in the study for side effects. If you want more information about side effects and risks, please ask your doctor or research staff.

This form lists possible side effects of brentuximab vedotin and nivolumab given every 3 weeks. Since we are giving brentuximab vedotin in combination with nivolumab, there may be other side effects we do not know about.

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 brentuximab vedotin and/or nivolumab. In some cases, side effects can last a long time or never go away. There also is a risk of death.

You should talk to your doctor about any side effects that you have while you are in this study. Your doctor will advise you on the appropriate management of side effects, which may include delaying brentuximab vedotin and/or nivolumab or taking medicine to control side effects.

Brentuximab Vedotin Side Effects

The following side effects have been associated with brentuximab vedotin treatment in some patients:

Very common

A lot of people who take this drug may have these side effects. In 100 people, 10 or more people may have these side effects.

- Stomach pain (abdominal pain)
- Hair loss (alopecia)
- Not enough red blood cells (anemia), which could make you feel tired or need a blood transfusion
- Pain in your joints (arthralgia)
- Back pain
- Bone pain
- Constipation
- Cough
- Not feeling hungry (decreased appetite)
- Diarrhea
- Feeling dizzy (dizziness)
- Feeling out of breath (dyspnea)
- Tiredness (fatigue)
- Very low white blood cells with a fever (febrile neutropenia). This makes it easier to get an infection and can be life-threatening
- Headache
- Low levels of potassium in your blood (hypokalemia). You may feel weak or tired. You could have muscle cramps, an abnormal heartbeat, or a hard time pooping.
- Not being able to sleep (insomnia)
- Muscle pain (myalgia)
- Nausea
- Low levels of a type of white blood cell called neutrophils that help your immune system (neutropenia). You could have a higher chance of getting an infection.
- Numbness or tingling in the hands and feet, which can spread to the arms and legs (peripheral neuropathy). You might have problems with muscle weakness, balance, coordination, or feeling in your fingers or toes.
- Itching (pruritis)
- Fever (pyrexia)
- Swelling and sores in the mouth (stomatitis)
- Vomiting
- Weight loss

Common

Some people who take this drug may have these side effects. In 100 people, between 1 and 9 people may have these side effects.

- Bloating or swelling in your belly (abdominal distension)
- Belly pain (abdominal pain)

- Sudden and serious reaction to the injection of a drug (acute infusion related reaction). You could have a rash or itchy skin, swelling in your face or throat, wheezing, chills, or fever. You could feel faint or out of breath.
- High levels of liver enzymes (ALT/AST elevation). This may mean that there are problems with your liver. If this becomes serious, it can cause death.
- Painful swelling in your lungs (bronchitis). You could have a cough, a hard time breathing, or chest pain. You could cough up a thick liquid called mucus. You could feel tired, have a fever, or have chills. If this happens, get emergency medical help right away.
- Patchy redness on your skin (erythema)
- Your skin could get red and feel hot (flushing)
- Shingles (herpes zoster), which is a painful, blistering rash caused by a viral infection
- High blood sugar levels (hyperglycemia), which can cause serious health problems including diabetes. You could feel very thirsty, need to pee often, have blurry vision, feel tired, or have a headache.
- Seasonal flu (influenza). You could have fever, body aches, chills, sweats, headache, runny nose, or a sore throat. In some people, this infection can lead to death.
- Muscles feeling weak (muscular weakness). You may have a hard time doing normal daily activities.
- Swelling and redness in your throat and nose (nasopharyngitis). You may have throat pain, cough, or a runny nose, like the common cold.
- Infection in your mouth (oral candidiasis), sometimes called “thrush”
- Throat pain (oropharyngeal pain)
- Infection in your lungs (pneumonia). You could have a cough, fever, chills, pain in your chest, or trouble breathing. If this happens, get emergency medical help right away.
- Swelling of the lungs (pneumonitis). You could have trouble breathing, cough, feel tired, or feel less hungry. If this happens, get emergency medical help right away.
- Rash
- Blood infection (sepsis), which is serious and can cause death. You may have a fever, fast heartbeat, and fast breathing. If this happens, get emergency medical help right away.
- Sinus problems (sinusitis). You may have a stuffy nose, headache, or fever. You may feel pressure behind your eyes or pain at the base of your skull.
- Low levels of a type of blood cell called platelets (thrombocytopenia). This could make you have problems with your blood clotting, bruise easily, feel tired, or bleed longer than usual when you get cut.
- Infection that could cause you to pee more often or have pain when you pee (urinary tract infection).
- Hives (urticaria)
- Chills
- Upset stomach (dyspepsia)
- Pain in your arms or legs (pain in extremity)
- Infection in the nose, sinuses or throat (upper respiratory tract infection). You may have fever, pain, or a hard time breathing (upper respiratory tract infection)

Uncommon

A few people who take this drug may have these side effects. In 1000 people, between 1 and 9

people may have these side effects.

- Pain in the belly caused by swelling of the large intestine (enterocolitis)
- Bleeding in your throat or gut (gastrointestinal hemorrhage). You could vomit blood, have dark sticky poop, or see red blood in your poop. You could have problems breathing, belly or chest pain, or feel lightheaded or faint.
- Damage to your liver that makes it stop working (hepatotoxicity). This is serious and could cause death. You may have yellow eyes or skin, feel tired, sick to your stomach, or vomit. You could have belly pain, bleeding that doesn't stop, sudden weight gain, or swollen hands or feet. If this happens, get emergency medical help right away.
- Loss of the ability of your gut to move and digest food, which could block your intestines (ileus)
- Increased risk of infection.
- A hole in your gut (intestinal perforation), which can be serious and cause death. You may have belly pain and vomit blood. You may feel tired, weak, or out of breath. If this happens, get emergency medical help right away.
- Damage in your gut (neutropenic colitis). You could have a higher chance of getting an infection in your gut. This could happen suddenly. You could feel sick to your stomach, throw up, have pain in your belly, chills, a high fever, and watery poop.
- Problems with your lungs caused by a drug or radiation (pulmonary toxicity). You could have trouble breathing on your own, feel tired, or have a dry cough.
- Serious painful rash that spreads to most of your skin (Stevens-Johnson syndrome/toxic epidermal necrolysis). This can cause death. Symptoms of this rash include widespread skin pain, blisters, hives, swollen tongue, red or purple rash that spreads, or skin peeling
- Lots of cancer cells dying and breaking apart, which causes serious problems (tumor lysis syndrome or TLS). This usually happens 2-3 days after starting chemotherapy. If you start feeling sick and get worse over time, check with your doctor

Rare

Very few people who take this drug may have these side effects. In 10,000 people, between 1 and 9 people may have these side effects.

- Belly pain caused by a sudden and serious problem with your pancreas (acute pancreatitis). You may have pain in your upper belly or back, fever, fast heartbeat, nausea, or vomiting

Very Rare

A very small number of people who take this drug may have these side effects. In 10,000 people, less than 1 person may have these side effects.

- Your body could have an immune response to the drug (drug-specific antibody)
- Block in your throat or gut that can cause serious problems and may need surgery (gastrointestinal obstruction). You may have throat or belly pain, feel like throwing up, be unable to poop, or feel very bloated. If this happens, get emergency medical help right away.
- A hole in your throat or gut (gastrointestinal perforation), which can be serious and cause death. You may have chest or belly pain and vomit blood. You may feel tired, weak, or out of breath. If this happens, get emergency medical help right away.
- Problems with the lining of your throat or gut, which can lead to sores (gastrointestinal ulcer). You could have pain in your chest or belly, feel sick to your stomach, or throw up.

- You could get sick from something that doesn't usually cause problems, like a virus or germ (opportunistic infection). This may happen because your immune system isn't as strong as usual.
- Brain damage caused by the John Cunningham virus (progressive multifocal leukoencephalopathy, PML). If you have a weakened immune system, you could get PML. You could become confused, clumsy, have weakness on one side of your body, or have problems with talking or seeing. This is a serious condition that can cause death or serious disability

Patients Over 60 Years Old
Patients over 60 years old who got brentuximab vedotin for Hodgkin's lymphoma had similar side effects as younger patients. Most patients older than 60 had pain, weakness, or unusual sensations in their hands and feet (peripheral neuropathy). More older patients had serious cases of peripheral neuropathy than younger patients. This could be because of age. Or it could be because more patients over 60 had diseases that are connected with neuropathy, like high blood sugar (diabetes) and low levels of thyroid hormones (hypothyroidism). Patients who already had some neuropathy symptoms before treatment didn't seem more likely to get serious cases of peripheral neuropathy.

Pregnancy and Breastfeeding
Note: Recommended contraception duration for men and women receiving brentuximab vedotin monotherapy is 6 months from the last dose.
Brentuximab vedotin causes miscarriages and birth defects in animals. If you are pregnant, you should not get brentuximab vedotin because it may hurt your unborn child. Brentuximab vedotin also affects the testes (sperm-producing organs) in animals. Men being treated with brentuximab vedotin should not get their partner pregnant.

It is not known whether brentuximab vedotin or its breakdown products end up in breast milk. If it does end up in breast milk, it could hurt a nursing baby.

Fertility Risks
It is possible that treatment with brentuximab vedotin could lower your chances of becoming pregnant for several months after stopping treatment. When we tested a drug that is similar to brentuximab vedotin in female animals, we saw changes in the ovaries where eggs mature. We don't know if these changes will happen in people who get brentuximab vedotin.

The changes in the ovaries showed signs of reversing when treatment was stopped. You will need to use contraceptives during and after taking part in this study to prevent pregnancy. The length of time you must use contraceptives is longer than the amount of time it took for most of the changes to reverse.

Infusion-Related Reactions
Some subjects experienced an infusion-related reaction during or soon after treatment with brentuximab vedotin and/or nivolumab. Symptoms of infusion-related reactions include chills, nausea, cough, itching, and shortness of breath. Two subjects experienced a serious allergic

reaction (wheezing/difficulty breathing, hives, itching, swelling) that required immediate medical attention and treatment discontinuation.

Peripheral Neuropathy
Some subjects who received brentuximab vedotin developed abnormal nerve function in their arms or legs. This is called peripheral neuropathy. It occurs when damage is done to nerves that carry information to muscles. This causes changes in touch, vibration, pain and temperature. Symptoms reported by these patients included burning sensation, pain, weakness, numbness and tingling (feeling of pins and needles) of hands and/or feet and severe abnormal nerve function that caused difficulty walking. Please make sure to tell your study doctor if you have any of these symptoms so that your side effects can be properly evaluated.

Low Blood Cell Counts
Some patients experienced a decrease in their white blood cells (neutropenia) that was related to treatment with brentuximab vedotin. This could result in an increased risk of infection. You could have any of the following:

- Low levels of a type of white blood cell called neutrophils that help your immune system (neutropenia). You could have a higher chance of getting an infection.
- Very low white blood cells with a fever (febrile neutropenia). This makes it easier to get an infection and can be life-threatening.
- Not enough red blood cells (anemia), which could make you feel tired or need a blood transfusion.
- Low levels of a type of blood cell called platelets (thrombocytopenia). This could make you have problems with your blood clotting, bruise easily, feel tired, or bleed longer than usual when you get cut.

Infection Risk
Brentuximab vedotin may cause you to be less resistant to infections, including severe infections. It is very important that you notify your study physician if you develop a fever, sore throat, difficulty breathing, and/or painful sores (ulcers) around the mouth and/or anus. If you are unable to reach your study physician or other research team members, you should go to your nearest emergency room for treatment. If you have to go to the emergency room, be sure to mention your study physician's name and that you are participating in an anticancer treatment research study.

Other Important Side Effects
Some patients who were treated with brentuximab vedotin had the following important or potentially life-threatening side effects. These have been reported less frequently than the side effects listed above:

- Severe painful rash that spreads to most of your skin (Stevens-Johnson Syndrome/toxic epidermal necrolysis). This is a rare condition that could be life threatening and can cause death. Get emergency medical care if you have any of the following: widespread skin pain, blisters, hives, tongue swelling, a red or purple skin rash that spreads, or unexplained shedding of your skin.
- Severe low white blood cells, fever, and possible infection that resulted in death.

- Brain damage caused by a virus (progressive multifocal leukoencephalopathy, PML). If you have a weakened immune system, you could get PML. You could become confused, clumsy, have weakness on one side of your body, or have problems with speech or vision. This is a serious condition that can cause death or serious disability. If you have any of these symptoms, get medical help **right away**.
- Tumor lysis syndrome (TLS) can be a life-threatening complication. TLS usually occurs within a few days after the start of the cancer treatment. It may result in metabolic complications caused by the rapid breakdown of a large number of dying cancer cells. Potential complications may include nausea, vomiting, metabolic abnormalities, edema (swelling), shortness of breath, heart rhythm disturbances, and acute kidney failure.
- Progressive multifocal leukoencephalopathy (PML) is a rare, serious brain infection caused by a certain virus. People with a weakened immune system can get PML. PML can result in death or severe disability. Tell your study doctor immediately if you have any of the following symptoms or if anyone close to you notices these symptoms: confusion or problems thinking, loss of balance or problems walking, difficulty speaking,
- Acute Pancreatitis is a condition in which inflammation of the pancreas causes pain in the upper abdomen. If severe, it could require hospitalization and may even be life-threatening. Seek emergency medical care if you develop sudden abdominal pain that may radiate to your back or get worse after you eat.
- Damage to the liver that can cause an increase in liver enzymes in the blood, and, if severe, be life-threatening.
- Damage to the lungs which may affect your ability to breathe and get enough oxygen into your bloodstream, and if severe, can be life-threatening.
- Severe belly pain caused by a sudden and serious problem with your pancreas (acute pancreatitis). If this happens get emergency medical help **right away**.
- High levels of liver enzymes (ALT/AST elevation). This may mean that there are problems with your liver. If this becomes serious, it can cause death.
- Gastrointestinal toxicity, which may result in conditions like ileus (paralysis or obstruction of the intestines), colitis (inflammation or infection of the intestines), and perforation of the intestines (hole in the intestines, which could possibly leak contents into the abdomen).
- Some symptoms of Stevens-Johnson syndrome may be similar to another condition called Toxic Epidermal Necrolysis, which may also be caused by Brentuximab Vedotin. Symptoms of Toxic Epidermal Necrolysis are a painful red area that spreads quickly, blisters on the skin and mucous membranes, peeling of the skin, discomfort, and/or fever. This condition could be life-threatening. Seek immediate medical attention.
- Problems with your digestion:
    - Loss of the ability of your gut to move and digest food, which could block your intestines (ileus)
    - Pain in the belly caused by swelling of the large intestine (colitis)
    - A tear or a hole in your stomach or gut that can cause belly pain and make you throw up blood (gastrointestinal perforation). You may feel tired, weak, and out of breath. This may require surgery and can be serious or cause death.

Nivolumab Side Effects

The most common side effects of Nivolumab are (≥5% of patients):

- Fatigue
- Skin reactions: including rash, itching, hives, redness and dry skin
- Diarrhea
- Nausea
- Decreased appetite
- Low red blood cells
- Fever
- Joint pain or stiffness

Less common side effects of Nivolumab are (2-4% of patients):

- Bowel inflammation
- Liver function blood test abnormalities
- Loss of color (pigment) from areas of skin
- Dry mouth
- Vomiting
- Weight loss
- Thyroid gland abnormalities
- Blood chemistry abnormalities, including low blood phosphate, magnesium and potassium levels
- High blood uric acid level
- Lung inflammation (*pneumonitis* – see details below)
- Cough
- Dizziness
- Headache
- Chills
- Muscle soreness, weakness, stiffness, spasms or paralysis
- Pain in arms or legs
- Tingling, burning or numbness in hands and feet
- Shortness of breath
- Abnormal taste
- Flushing
- High or low blood pressure
- Allergic reaction during or between study drug infusions
- Increased sensitivity of skin to sunlight
- Constipation
- Difficulty swallowing
- Heartburn
- Low blood platelets (may increase risk of bleeding)

Rare but potentially serious side effects of Nivolumab are (<2% of patients):

- Low blood oxygen level
- Acute lung injury or failure
- Collection of fluid around the lungs
- Inflammation of the appendix

- Increase in inflammatory blood proteins (i.e. lipase)
- Adrenal gland abnormalities
- Pituitary gland abnormalities
- Changes in vision (including decreased or blurry vision), inflammation of the eye or bleeding into the eye
- Liver inflammation
- Acute kidney injury or failure
- Abnormal blood cell production
- Inflammation of the mouth and lining of the digestive tract
- Swelling of the face, arms or legs
- Inflammation of the pancreas
- Back pain
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Chest discomfort
- Heart palpitations
- Collection of fluid around the heart
- Increased blood sugar
- Dehydration
- Infections: including sepsis, lung infections and skin infections
- Decreased movement of the intestines
- Disorientation
- Swelling of the optic disc
- Inflammation of the optic nerve
- Inflammation or loss of the lining of the brain and spinal cord
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes and internal organ involvement (including liver, kidney and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]

- Myasthenia gravis, a nerve disease that may cause weakness of the eye, face, breathing and swallowing muscles.
- One death in a patient who received Nivolumab combined with Ipilimumab was considered due to myasthenia gravis and severe infection (sepsis)
- Abnormal brain function due to brain inflammation (encephalitis), potentially lifethreatening or fatal
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn, has occurred in patients who received Nivolumab treatment
- Muscle fiber released into the blood stream which could damage your kidney (Rhabdomyolysis) and chronic muscle inflammation with muscle weakness (polymyositis) has been reported in one patient. Muscle tissue under the skin (fascia) becomes swollen and thick (eosinophilic fasciitis). This can affect your hands, arms, legs and feet and they can swell quickly.
- Red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over (hemolytic anemia)
- Tumor bleeding (hemorrhage) or tumor flare
- Disease of the heart muscle (cardiomyopathy)
- Seizure
- Gait disturbance and personality change

Lung Inflammation (Pneumonitis):
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 and CT abnormalities have not developed any symptoms of pneumonitis, some patients have developed mild to severe symptoms. 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. We will perform regular tests including physical exams, measurement of oxygen levels, blood tests, chest x-rays and CT scans.

Please inform your study doctor or nurse AT ONCE 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 or 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 happen at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests. We will watch you very closely for changes in your overall lung symptoms, and you may need to go to the hospital for this. You may require specific treatment in order to control the pneumonitis. You may need to see a special doctor, called a pulmonologist, who has extra training to be an expert in how lungs work.

Long treatment with medicines that decrease inflammation may lower your body's ability to fight off certain infections (opportunistic infections). Some side effects of Nivolumab may cause us to use these types of medications. If you experience an infection because of this, you may need treatment with antibiotic or antifungal medication. It is important to know that these infections can still be fatal even when treated with antibiotics or antifungals.

Radiation

There are some risks from the CT (and possible PET scans) that you will undergo in this research study. These scans will expose you to radiation. If you live in the US, you receive about 3 millisieverts of radiation each year. It comes from space and the earth around you. This is called "background radiation." A "millisievert" (mSv) is a unit used to measure doses of radiation. The radiation dose to your whole body from each of these scans will be about as follows:

- CT scan of the head and neck (if done): 5 mSv
- CT scan of the chest: 7 mSv
- CT scan of the abdomen: 8 mSv
- CT scan of the pelvis: 6 mSv
- F-18 FDG PET scan: 19 mSv

If you have more procedures that expose you to radiation, this risk will go up. The risk to your health from this level of radiation exposure is too low to be detectable and may be nonexistent. You may have other x-rays or scans for your care. Your doctors will explain the risks of the other x-rays or scans.

Blood Draws

Blood draws may cause pain, bleeding, and/or bruising. You may faint and/or get an infection. Infection rarely happens. There may be redness and irritation at the place where the needle enters your vein.

Bone marrow aspiration and biopsy

Complications from a bone marrow aspiration and biopsy include pain, infection and bleeding.

Risks from other procedures

There is a very rare chance of developing allergic dermatitis. This is itching and redness of the skin due to the sticky pads used for EKG tests.

What are the benefits?

We do not know if this study will help patients. We are testing the administration of brentuximab vedotin in combination with nivolumab to see the effects on people who have not had a response or progressed on the standard dosing of brentuximab vedotin. Patients who get brentuximab vedotin and nivolumab in this study may get better, but their condition could stay

the same or even get worse. We hope the information from this study will help other people with cancer in the future.

You have other choices besides this study.
You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.

If you do not join this study, you have other choices for treatment. Talk to your doctor about your choices.

Your other choices may include:
- Another research treatment.
- Standard treatment.
- No treatment.
- Comfort care.

Protecting your Privacy as an Individual and the Confidentiality of Your Personal Information
Some people or organizations may need to look at your research records for quality assurance or data analysis. They include:
- Researchers involved with this study
- The study sponsors and their agents
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Center IRB. An IRB is a group that reviews the study to protect your rights as a research participant
- Fred Hutchinson Cancer Center and University of Washington.
- US National Institutes of Health, National Cancer Institute, Office for Human Research Protections, Food and Drug Administration, and other agencies as required.

These people are interested in study data, not your personal information. Personal information is information that can identify you. It may include your name, date of birth, social security number, phone number, or other information.

We will do our best to keep your personal information confidential. But we cannot guarantee total confidentiality. Your personal information may be given out if required by law. For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are rare.

We will not use your personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Information about your participation in this study such as the title of the study and the names of the researchers involved in the study will be made a part of your permanent medical record. If

you authorize others to see your medical record, they will find out about your participation in this study.

Financial disclosure statement
The makers of brentuximab vedotin, Seattle Genetics, Inc., is paying the research team and/or the University of Washington for the conduct of this study.

Dr. Gopal has a financial relationship with Seattle Genetics, Inc. Dr. Gopal has been/is a member of Millennium Pharmaceuticals' Speakers' Bureau, which has a business relationship with the sponsor, and have received/are receiving payment from Seattle Genetics for speaking engagements about cancer and Seattle Genetics drugs. Dr. Gopal receives compensation for these activities in addition to their salary from the University of Washington. This financial interest and the design of the study have been reviewed and approved by the University of Washington. A management plan to mitigate any potential conflict of interest has been developed in response to this review.

Please feel free to ask further questions about these matters.

Will you pay me to be in this study?
There is no payment for being in this study.

How much will this study cost me?
There are some extra costs for being in this study. You or your insurer will have to pay these costs. Some insurers will not pay for research. Check with your insurer before you join this study.

The costs are:

- Cost of tests that may be given more often than usual to monitor your health while you are receiving treatment.
- Cost of people and equipment to give you the brentuximab vedotin. There is no charge for the brentuximab vedotin itself.
- Cost of people and equipment to give you the nivolumab
- Cost of nivolumab
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care you may need because of this study.

You or your insurer will have to pay for the costs of treating your cancer in this study. You will **not** be billed for:

- The brentuximab vedotin itself or the dispensing of the study drug.
- If you need to have CT or PET scans done for the research study at time points which are considered non-standard of care, the study may pay for these to be done. Please check with the study team if there is any question.

What if I get sick or hurt in this study?
If you get sick or hurt in this study, tell your study doctor in person or call Dr. Gopal at (206) 606-2037.

Emergency medical treatment is available at the usual charge. If you have a research related injury or illness, a limited amount of free medical treatment may be available at approved locations. Limited funds may be available to pay for treatment at other locations. You or your insurer will be billed for any additional costs. The study staff can provide more information.

There are no funds to pay you for loss of work or other costs, lost time, or pain to you or your family. You or your insurer will be billed for treatment of problems that results from your cancer or from standard clinical care.

You will not lose your legal right to seek payment for treatment if you sign this form.

Your rights

- You do not have to join this study. You are free to say yes or no. Your regular medical care will not change.
- If you join this study, you do not have to stay in it. You may stop at any time (even before you start). There is no penalty for stopping. Your regular medical care will not change.
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we may learn new information you need to know. For example, some information may affect your health or well-being. Other information may make you change your mind about being in this study. If we learn these kinds of information, we will tell you.

For more information
If you have questions or concerns about this study, you may talk to your doctor anytime. Other people you can talk to are listed below.

If you have questions about:	Call:
This study (including complains and request for investigator information)	(206) 606-2037 Dr. Ajay K. Gopal, Principal Investigator
If you get sick or hurt in this study	(206) 606-2037 Dr. Ajay K. Gopal, Principal Investigator
Your rights as a research participant	(206) 667-5900 Institutional Review Office, Fred Hutchinson Cancer Center (206) 543-0098 Human Subjects Division, University of Washington
Your bills and health insurance	(206) 606-1377 Patient Financial Services, Fred Hutchinson Cancer Center

Emergency number (24 hours): 206-598-6190

University of Washington Medical Center paging operator. Please ask the operator to page the hematology-oncology fellow on call.

Consent

I have read this consent form (or it has been read to me). All my questions about the Study and my part in it have been answered. I freely consent to be in this research Study.

By signing this consent form, I have not given up any of my legal rights.

- ☐ **I agree to have the optional blood draws collected as part of this Study.**
- ☐ **I do NOT agree to have the optional blood draws collected as part of this Study.**
- ☐ **I agree to allow collection of my tissue from my diagnosis, if available.**
- ☐ **I do NOT agree to allow collection of my tissue from my diagnosis, if available.**

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

(Complete only if applicable) If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

_____
Witness or Interpreter / Printed Name, Signature, and Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

_____
Printed Name of Person Conducting the
Informed Consent Discussion

_____ _____
Signature of Person Conducting the Informed Consent Discussion Date

Copies to: Participant,
Medical Records,
Research File