Principal Investigator:	Harriet Kluger, MD	**IRB #:**	1512016953
Funding Source:	Yale Cancer Center, Merck and Co., Inc	**Sponsor ICF Template Version:**	19.0
		Sponsor ICF Template Date:	19-APR_2024

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL: SMILOW CANCER HOSPITAL

200 FR. 4 (2014-11)

Study Title: A Phase 2 Trial of Pembrolizumab plus Bevacizumab in Patients with Metastatic Melanoma or Non-Small Cell Lung Cancer with Untreated Brain Metastases.

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Funding Source: Yale Cancer Center and Merck and Co., Inc. and the NIH

Invitation to Participate and Description of Project

You are invited to take part in a research study. The research study is designed to look at whether or not the combination of pembrolizumab and bevacizumab has beneficial effects and is safe for use in subjects with metastatic melanoma or non-small cell lung cancer who also have untreated brain metastases. You have been invited to take part because you have been diagnosed with metastatic melanoma or non-small cell lung cancer and you have untreated brain metastases.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: the purpose and nature of the research study, the procedures that will be performed, the risks of the study drug(s) and procedures, possible benefits, possible alternative treatments, your rights as a participant and other information about the research study. You should take whatever time you need to discuss the research study with your physician and family. The decision to participate or not is yours. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign and date where indicated on this form.

If you choose to participate, you will be told of any significant new findings that develop during the course of your participation in this study that may affect your willingness to continue to participate.

The research study is being sponsored by Yale University. Yale is responsible for the conduct of the study. Merck and Co., Inc. (hereafter referred to as Merck) is the maker of pembrolizumab. Merck is providing funding and study drug for this research study.

APPROVED BY THE YALE UNIVERSITY IRB 5/9/2024

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Dr. Harriet Kluger is the principal investigator of this study at Yale Cancer Center. The study doctors will not receive payment for any specific results from this study.

Purpose

The purpose of this study is to explore whether or not pembrolizumab combined with bevacizumab has beneficial effects and is safe for use in subjects diagnosed with metastatic melanoma or non-small cell lung cancer (NSCLC) who also have untreated brain metastases. We will also study the effects of this combination on tumors outside of the brain (when present) and on survival.

The study drugs used that will be used in this research study, pembrolizumab and bevacizumab are approved for use by the United States Food and Drug Administration (FDA).
Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers, but may not be approved to treat your type of cancer. Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. Bevacizumab is widely used in the treatment of cancer and is FDA approved for use in advanced cancers of the colon, lung, breast, kidney and brain (glioblastoma).

For the purposes of this study, the combination of pembrolizumab and bevacizumab is considered investigational. This means that the combination has not been approved for commercial use by the FDA in your type of cancer.

This will be a multi-institution trial, with a total approximate accrual of 53 subjects. It is expected that 40 subjects will have melanoma and 13 subjects will have NSCLC. It is expected that approximately 36 subjects will be enrolled at Yale Cancer Center.

Study Procedures

You will be entered into one of 2 study groups (arms) based upon your diagnosis: Arm A is for melanoma subjects and Arm B is for NSCLC subjects. NSCLC subjects must be PD-L1 positive in order to be considered for participation in this clinical trial. PD-L1 is a protein and T-cell receptor which is thought to play a role in the ability of tumor cells to evade a person's immune system.

You may undergo some of the procedures listed below during Screening, Study drug treatment, and or Follow-up because you are in the research study and they are required by the sponsor as part of being in this study. The standard of care is the procedures that are done and the tests that are done for patients who have your condition, whether they are in a study or not. Other procedures are done because you are in a research study and they are required by the sponsor for your participation in this study.

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- Procedures that are being performed for standard of care purposes include a medical history assessment, full physical exam (including weight), vital signs, performance status evaluation routine blood tests, urine sample, pregnancy test, CT & MRI scans, etc.
- Procedures that are being performed solely for research purposes include, blood sample for research purposes, tumor tissue collection, biobanking, review of medication and study drug administration.

Screening Period

If you agree to participate and sign and date this form, you will need to undergo a series of tests and procedures to determine if you are eligible to participate in the research study. You will come to the study site for screening tests and it is possible that more than one screening visit may be needed. The following tests or procedures will be performed during the visit(s) regardless of your kind of cancer (melanoma or NSCLC) unless otherwise indicated:

- Physical Examination
- Review of your medical history including medications you are taking and other medical conditions you have in addition to cancer
- Measurement of height, weight and vital signs (including blood pressure, heart rate, temperature, breathing rate and oxygen measurement)
- Performance status evaluation
- Routine blood tests for safety:
    - Complete blood count
    - Blood chemistry
    - Liver function tests
    - Thyroid stimulating hormone (TSH)
    - Free T3 and Free T4
- Urinalysis
- Blood sample for research purposes; if you are found to not be eligible, but you still wish to provide a one-time blood sample, this sample may be banked for other future research studies. This sample is required for all subjects who are eligible to participate in this study and will be taken prior to your first dose of study drug. The blood samples will be tested to see what types of proteins the blood cells express, a technique called immunophenotyping. The samples will be stored, or banked, in a laboratory at Yale University until they are used by the researchers.
- Pregnancy test (blood or urine) for women of child bearing potential only. If the results are positive, you will not be eligible to participate in this research study. Women of child bearing potential must agree to use an effective method of birth control or agree to remain abstinent during the course of the study.
- Computerized tomography (CT) scan of the chest and abdomen. CT scan of the pelvis will be done if clinically indicated.
- Brain Magnetic Resonance Imaging (MRI) to assess Central Nervous System (CNS) tumor involvement. Your MRI will be reviewed by investigators at Yale University.

- In order to participate in this research study, you must agree to provide tumor tissue from any prior surgical resections or biopsies, and any tumor that is removed or biopsied once on study.
- Blood sample for research purposes. A sample of your blood is required for all participants who are eligible to participate in this study and will be taken prior to your first dose of study drug. If you are found to not be eligible, but you still wish to provide a one-time blood sample, this sample may be banked for other future research studies. The blood samples will be tested to see what types of proteins the blood cells express, a technique called immunophenotyping. The samples will be stored, or banked, in a laboratory at Yale University until they are used by the researchers.
- Review of Smoking Status

Treatment Period

Prior to receiving the study drugs, subjects will have local therapy to a brain lesion by surgical resection or LITT (laser interstitial thermocoagulation therapy), when clinically needed. Surgical resection uses surgery to remove abnormal tissue in your brain. LITT is a surgical procedure that will require you to have general anesthesia (be put under). A small incision will be made in your scalp and a small (2.5 mm) hole will be drilled in your skull. A laser catheter (tube) will be inserted into your tumor and used to obtain a biopsy from the tumor and also to heat the tumor so that the tumor cells will no longer be alive. This thermocoagulation process typically lasts 2-3 minutes. LITT is FDA approved for use in the treatment of brain tumors. The tissue removed during surgical resection or LITT will be studied for PD-L1 expression and other biomarkers that may help researchers determine what types of tumors may or may not respond to pembrolizumab and bevacizumab. Melanoma tumors are not required to express PD-L1 in order for melanoma subjects to participate in this research study.

You will be required to provide a specimen from a tumor, if available, for research. Your study doctor will discuss with you which tumor specimen can be used and whether a new biopsy is necessary.

If at any time on study you have a surgical procedure or biopsy, you will be required to provide a portion of the tumor specimen for research.

For this research study, a cycle is three weeks (21 days). You will continue to receive the study drugs, pembrolizumab and bevacizumab, in three-week cycles until disease progression, unacceptable toxicity, withdrawal from the study or removal by the study team, termination of the study or if you develop an illness or complication that does not allow you to safely continue on study. Subjects will receive 200mg of pembrolizumab every 3 weeks intravenously (IV) (through your vein). Bevacizumab, at a dose of 7.5 mg/kg, will be administered intravenously on Day 1 of cycles 1, 2, 3, and 4 (or other cycles if bevacizumab is held during these cycles. Day 1 of the study will be defined as the first day a subject receives pembrolizumab.

If at any time during the study you experience symptoms related to your brain metastases, the study doctor may locally treat your lesions.

The following is a list of evaluations that you will undergo during the treatment period of the study:

Day 1 of each Cycle (every 3 weeks):

- Physical examination
- Review of your medical history
- Review the medications you have taken and are currently taking including treatment received for your cancer. If you are not already taking anti-convulsants, you will be started on medications to avoid seizures.
- Performance status evaluation
- Review of any side effects you may have had or may be having
- Measurement of weight and vital signs (including blood pressure, heart rate, temperature, breathing rate and oxygen measurement)
- Urinalysis (Cycles 1, 2, 3 and 4 only)
- Pregnancy test (blood or urine) for women of child bearing potential only
- Routine blood tests for safety:
    - Complete blood count
    - Blood chemistry
    - Liver function tests
- Tumor response assessment by CT scan of the chest, abdomen and pelvis (Cycle 3 and 5 and every 9 weeks thereafter)
- Brain MRI (Cycle 3 and 5 and every 9 weeks thereafter)
- Administration of pembrolizumab
- Administration of bevacizumab (Cycles 1, 2, 3 and 4 only; or other cycles if bevacizumab is held during these cycles)
- Blood samples for research purposes (Cycles 3 and 5)

Day 1 of Cycle 8 (and every 9 weeks thereafter):

The procedures listed above will be performed (unless otherwise specified) in addition to the following:

- Blood sample(s):
    - Thyroid stimulating hormone (TSH)
    - Free T3 and Free T4
- Blood samples for research purposes
- Brain MRI
- Tumor response assessment by CT scan of the chest, abdomen and pelvis

End of Treatment

The following procedures will be performed within 28 days of your last dose of study drug:

- Physical examination
- Review the medications you have taken and are currently taking including treatment received for your cancer
- Performance status evaluation
- Review of any side effects you may have had or may be having

- Measurement of weight and vital signs (including blood pressure, heart rate, temperature, breathing rate and oxygen measurement)
- Routine blood tests for safety:
  - Complete blood count
  - Blood Chemistry
  - Liver function tests
- Urinalysis
- Blood sample for research purposes

Study Treatment Beyond Disease Progression
With most anti-cancer drugs, an increase in the size or number of tumors detected with CT or MRI scans or a physical exam is a signal that your disease has progressed and that you should consider switching to another therapy. However, an early increase in the size or number of tumors may not always be a sign of disease progression. Because of this possibility, you will have the option of continuing to receive study drug even after a scan in the course of your treatment shows an increase in the size or number of your tumors. A later scan will help to determine whether the increase was caused by real progression of your disease. Additional tests may help determine the cause for the increase in the size or number of your tumors and may be required to allow you to continue in the study.

You may have other potentially beneficial approved treatments available to you. These treatments may include those that may shrink tumors, delay progression of cancer, provide symptom relief, or prolong your life. The option to continue pembrolizumab and bevacizumab treatment in spite of an apparent increase in tumor size should be carefully discussed with your study doctor. There are risks of continuing to receive pembrolizumab and bevacizumab treatment beyond an apparent increase in tumor size because of the possibility that it represents true progression of your disease. In that case, you may be exposed to an ongoing risk of side effects caused by the study drugs and delay the initiation of other treatment options that may have demonstrated benefit in clinical trials. In addition, your cancer may progress to the point that you are no longer able to receive other potentially effective therapies. If you show true progression of your disease, you will be discontinued from the study and the study doctor will ask you to visit the office for follow up exams.

If the size or number of your tumors show apparent progression, you will be asked to sign a separate consent form to continue receiving the study drugs.

Follow-up Period
You will continue to have tumor assessments by CT scan of the chest, abdomen and pelvis and a Brain MRI every 9 weeks until disease progression, withdrawal of consent, start of a new anti-cancer therapy, or death.

Long Term Follow-Up
You will be contacted by the study team every 3 months for survival follow-up information.

Optional Specimens for Future Storage/Genetic Testing

You are invited to allow some of your samples (called specimens) and related information to be stored (banked) for future research. This may help researchers in the future learn more about how to prevent, find and treat melanoma or NSCLC. Your specimens will be stored for an unlimited time, and may be used to make a cell line that will live indefinitely.

Future research may look at your genes, which are the units of inheritance that are passed down from generation to generation. Genes are responsible for many things about you such as eye color, hair color, blood type and hundreds of other traits. Future genetic analysis may possibly include finding out the details of how your DNA is put together, such as whole exome or genome sequencing, or genome wide association studies (that is, looking at genes other than those associated with a specific disease). The materials at some point may be injected into animals in some of the research. We expect that there will be widespread sharing of these specimens and associated information.

When your specimens and information are stored, we are careful to try to protect your identity from discovery by others. Your samples and information will receive a unique code. Other researchers will only receive coded samples and information, and will not be able to link the code to you. Strict security safeguards are in place to reduce the chance of misuse or unplanned release of information.

Using your specimens for research will probably not help you. We do hope the research results will help people in the future.

There is a risk that your information could be misused. The chance of this happening is very small. We have protections in place to lower this risk. There can also be a risk in uncovering genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Very rarely, health or genetic information could be misused by employers, health insurance companies, and others. A federal law called the Genetic Information Nondiscrimination Act (GINA) generally, makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information.

Your specimens and information will only be used for research and will not be sold. There is a possibility that this research may lead to development of products that will be commercialized. If this happens, there is no plan to share any financial gain with you or your family.

Research results will not be returned to you or your doctor. If research results are published, your name and other personal information will not be given.

The choice to take part is up to you. You may choose not to let us store and use your samples, and your care will not be affected by this decision. If you decide that your samples can be kept, you may change your mind at any time. To withdraw your samples from the study, you can call a member of the research team or you may write to the Principal Investigator using the contact

information on page one of this form at any time and tell them you do not want your samples used any longer.

You will be asked to indicate your choice at the end of this form.

Potential Risks, Side Effects, Discomforts and Inconveniences

While in this study, you may have side effects. Anticipated side effects are listed here. In addition to the risks listed below, there may be risks that are currently unknown. If significant new risks develop during the course of study that might affect your willingness to participate, information will be reported to you as soon as possible. Possible side effects that you may experience during this study will be fully explained to you by the study staff. Please ask as many questions as you want so that you can understand the possible side effects of your specific treatment before you decide whether you want to be in this study. Please ask the study doctor or the study staff to explain any information or words that are not clear to you.

Risks Associated with Pembrolizumab
Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers but may not be approved to treat your type of cancer.

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e., causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Very Common, Some May Be Serious (For Example, Causing Hospitalization, Life-Threatening or Where Noted, May Cause Death)

Out of 100 people who receive pembrolizumab, 20 or more people may have the following:

- Itching of the skin
- Loose or watery stools
- Cough

Common, Some May Be Serious (For Example, Causing Hospitalization, Life-Threatening, or Where Noted, May Cause Death)

Out of 100 people who receive pembrolizumab, at least 5 but less than 20 people may have the following:

- Joint pain
- Fever

- Back pain
- Rash
- Pain in your belly
- Loss of skin color
- Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools
- Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

Uncommon, Some May Be Serious (For Example, Causing Hospitalization, Life-Threatening, or Where Noted, May Cause Death)

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to death
- Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion.
- Inflammation of the bowels/gut that can cause pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus
- Inflammation of the skin so you may have peeling of the skin, itching, and/or skin redness. The skin inflammation (for example peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection. These severe conditions can sometimes lead to death (epidermal necrolysis)

Rare, Some May Be Serious (For Example, Causing Hospitalization, Life-Threatening, or Where Noted, May Cause Death)

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness
- Inflammation of the muscles so you may feel weak or pain in the muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe upper abdominal pain that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver which may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly,

yellow eyes and skin, and dark urine

- Inflammation of the pituitary gland in the brain (a gland in the head), which may you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, and experience swelling and/or low back pain
- Inflammation of the middle layer of your heart wall (myocarditis) that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (called sarcoidosis)
- Inflammation of the brain (called encephalitis) with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate frequently, urinary incontinence, difficulty urinating, and constipation (myelitis).
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling or burning in your fingertips, toes or lips (hypoparathyroidism)
- Inflammation of the stomach (gastritis). You may have pain in your belly, feel full, or sick to your stomach. You may also experience nausea, vomiting or loss of appetite.
- Low number of red blood cells (cells that carry oxygen) due to destruction of red blood cells (hemolytic anemia). You may feel weak, tired, lightheaded, short of breath, or have

a fast heartbeat. You may also experience difficulty with physical exercise, pale or yellow skin, dark urine, or fever.
- Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food (exocrine pancreatic insufficiency). You may have bloating, gas, discomfort in your belly, diarrhea, abnormal stool that is oily, or weight loss.

In addition to the above, if you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If you have had a solid organ transplant (for example, if you have received a kidney or heart transplant), you may experience rejection of the transplanted organ. Your doctor will monitor you and should tell you what signs and symptoms you should report depending on the type of organ transplant that you have had.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effects:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time (optic neuritis).

Risks Associated with Bevacizumab:
The addition of bevacizumab to anticancer therapies has led to an increased frequency of the side effects listed below.

Very common (occurring in greater than or equal to 10% of subjects):

- High blood pressure (hypertension)
- Numbness or loss of feeling in the fingers or toes (peripheral sensory neuropathy)
- Low numbers of white blood cells (neutropenia, leucopenia) potentially associated with fever (febrile neutropenia)
- Low numbers of platelets (thrombocytopenia),
- Shortness of breath (dyspnea)
- Diarrhea
- Bleeding from the rectum (rectal hemorrhage)
- Nausea and vomiting
- Pain, including headache and joint pain (arthralgia)
- Constipation
- Mucosal inflammation or inflammation of the mouth (stomatitis)
- Protein in the urine
- Mucocutaneous bleeding, which includes nosebleeds (epistaxis)Lack of energy and weakness (asthenia, fatigue)
- Loss of appetite (anorexia)
- Fever (pyrexia)
- Runny nose (rhinitis)
- Dry skin, flaking and inflammation of the skin (exfoliative dermatitis)
- Change in skin color (skin discoloration)
- Change in the sense of taste (dysgeusia)Eye disorder, watery eyes (lacrimation increased)
- Abdominal pain
- Weight loss
- Low levels of magnesium in the blood (Hypomagnesemia) which could cause weakness and muscle cramping. Rarely heart rhythm abnormalities may occur
- Decreased levels of sodium in the blood (Hyponatremia), which can cause confusion, seizures, fatigue and low levels of consciousness
- Alteration in speech (dysarthria)
- Fertility problems in women (ovarian failure)
- Nail-related changes
- Delay in wound healing, failure of a wound to heal, or spontaneous opening of a wound
- Cough

Common (occurring in 1%–10% of subjects):

- Infection, presence of bacteria in the blood (sepsis), collection of pus in tissue or organs (abscess), and skin and soft tissue infection (cellulitis)
- Infection in urine (urinary tract infection)
- Tear or hole in the gut (perforation of the gastrointestinal tract)

- Abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected (fistula) including bowel and vagina (recto-vaginal fistulae)
- Low numbers of red blood cells (anemia)
- Bleeding, (hemorrhage) including bleeding associated with the tumor
- Clogging of a blood vessel in the lung (pulmonary embolism)
- Blocking of the arteries by a blood clot (arterial thromboembolism), including stroke (cerebral vascular accident) or heart attack
- Heart failure, (congestive cardiac failure) especially in subjects who have received a certain type of chemotherapy in the past, such as mitoxantrone or other
- chemotherapy drugs called anthracyclines (e.g. doxorubicin)
- Blood clots in the veins (deep vein thrombosis)
- Blockage in the intestine (ileus, intestinal obstruction)
- Body water loss (dehydration)
- Pain, tenderness, or blistering on the fingers or feet (hand-foot syndrome, palmar-plantar erythrodysesthesia syndrome)
- Low levels of oxygen in the blood (hypoxia)
- Fainting (syncope)
- Allergic reaction, including allergic reaction to the drug during the infusion
- Gastrointestinal disorder
- Voice changes and hoarseness (dysphonia)
- Muscular pain and muscular weakness (myalgia)
- Pain, including rectal pain (proctalgia), back pain, and pelvic pain
- Rapid beating of the heart (supraventricular tachycardia)
- Sleepiness, feeling tired (somnolence, lethargy)

Less common (occurring in 0.1%–1% of subjects):

- Abnormal connection between the windpipe (trachea) and the esophagus (the tube that connects the mouth to the stomach) (tracheal-esophageal fistula)
- Abnormal connection between the tubes within the gallbladder and surrounding organs (biliary fistula)

Rare but serious (occurring in 0.01%–0.1% of subjects):

- Medical condition that presents with symptoms of impaired brain function (headaches, vision changes, confusion, or seizures), and often, high blood pressure (posterior reversible leukoencephalopathy syndrome [PRES]
- Serious infections of the skin or deeper layers under the skin, especially with participants who have had holes in the gut wall or problems with wound healing (necrotizing fasciitis)

Very rare but serious (occurring in less than 0.01% of subjects):

- Medical condition that presents with symptoms that suggest changes in the normal brain function (headaches, vision changes, confusion, or seizures), and often, high blood pressure (Hypertensive encephalopathy)

Unknown Frequency:

- Abnormalities in the fetuses (unborn babies) of pregnant women treated with bevacizumab alone or in combination with chemotherapy that is known to be harmful to fetuses
- Open sore or hole in the gut lining of the stomach or small intestine (gastrointestinal ulcers)
- Hole in the nasal passage (nasal septum perforation)
- Hole in the gallbladder (gallbladder perforation)
- Abnormally high blood pressure in the blood vessels of the lungs that makes the right side of the heart work harder than normal (pulmonary hypertension)
- Hypersensitivity infusion reaction – including shortness of breath (dyspnea), difficulty breathing, flushing, rash, redness of the skin (erythema), low blood pressure (hypotension) or high blood pressure (hypertension), oxygen reduction (desaturation), chest pain, shivering (rigors), and nausea and vomiting
- Inflammation of eye caused by infection (Infectious endophthalmitis), may lead to blindness
- Eye (Intraocular) inflammation (which may lead to blindness) including inflammation of the tissue of the eye (sterile endophthalmitis), inflammation of the iris of the eye (uveitis),and inflammation of the cells in the vitreous cavity (vitritis)
- Separation of the retina from its connection at the back of the eye (Retinal detachment), Retinal pigment epithelial tear
- Increased pressure in the eye (Intraocular pressure increased)
- Bleeding into the eye (Intraocular hemorrhage –vitreous hemorrhage or retinal hemorrhage)
- Bleeding in the tissue lining the eye (Conjunctival hemorrhage)
- Weakened blood vessel that bursts or bleed into brain (Hemorrhagic stroke)

Other Relevant and Important Information and Risks Associated with Bevacizumab
Bevacizumab may also cause changes in laboratory tests, such as changes in kidney function tests (increased blood creatinine), decreased blood potassium (hypokalemia) and sodium (electrolyte), increased blood sugar, or altered coagulation (how your blood clots) values.

Some side effects are more common in elderly subjects than in younger subjects. These side effects include blood clots in the arteries, which can lead to a stroke or a heart attack. In addition, elderly subjects have a higher risk of a reduction in the number of white cells in the blood (neutropenia, leucopenia) or platelets (thrombocytopenia), diarrhea, nausea, headache,
and fatigue.

Patients with a medical history of diabetes (diabetes mellitus) or a history of arterial thromboembolism have an increased risk of developing arterial thromboembolism.

Other Risks
Brain Biopsy:
A brain biopsy will be obtained while you undergo any surgical procedure (resection or LITT) that is necessary to treat the brain tumor. Although uncommon, infection or bleeding at the surgical site or brain could occur as well as the possibility of temporary or permanent neurological

problems. These risks depend on the location of the tumor in the brain and will be reviewed with you in detail by your study doctors before the procedure.

Blood Collection and Intravenous (IV) Catheter Placement:
The risks of taking blood may include pain, redness, swelling and/or bruising where the needle enters your body, light-headedness and fainting. On rare occasions, local blood clot formation or infection with redness and irritation of the vein has occurred. The blood pressure cuff may cause discomfort or bruising to the upper arm. Approximately 10 mL of blood will be taken during your participation in this research study pre-treatment, after 6 weeks of therapy, 12 weeks of therapy and every 9 weeks thereafter for research purposes only.

Tumor Biopsy:
As with any procedure, there are risks and discomforts. You may feel some amount of pain or discomfort during a biopsy, including slight, stinging pain when a local anesthetic is injected by needle to numb the area, pressure and dull pain where the biopsy needle is inserted, discomfort from lying still for an extended time, and soreness, inflammation, bleeding, swelling, and/or infection at the biopsy site. With a tumor biopsy, there is a rare possibility of tumor cells spreading into the nearby area. If a general anesthetic is used, you will not feel pain during the procedure because you will be asleep. Your physician will explain the details of the procedure and the risks to you, depending on how the biopsy will be obtained.

Brain MRI scan:
You may not have an MRI done if you have metal in your body, for example, some hip replacements, hearing aids, pacemakers, bullets, or jewelry that cannot be removed. You should inform the technologist or study doctor if you have any metal in your body. During the MRI exam, you may feel some heat and hear tapping noises but have no reason to worry. Some people may have a 'closed in' feeling while inside the machine. The injection may make you sick to your stomach or have pain, warmth, swelling, bruising, a small blood clot or infection at the injection site. Rarely, you may get a rash or other signs of allergy from the injection or get a rare disease where some of your body parts get scarred. If you have a history of kidney problems, you must inform the technologist or physician as you may not be able to receive an injection during the MRI exam. Please talk to your physician if you have any concerns or questions.

Risks associated with gadolinium contrast:
You may have a small IV catheter placed before the MRI scan so that gadolinium contrast can be injected into a vein as this may help to better determine if your cancer has spread. With gadolinium contrast severe reactions are rare. The FDA approves the contrast agent Gadolinium for use with human participants. You need to know that there are certain risks associated with the use of that contrast. Some healthy subjects (fewer than 3%) may experience mild nausea, headache or dizziness after the injection. These side effects usually resolve without need for treatment. There is also a risk of allergic reaction (less than 1%). An allergic reaction can cause hives and itching or difficulty breathing. In individuals with kidney dysfunction, the gadolinium can cause a serious condition called nephrogenic systemic fibrosis. Because of this, prior to your MRI scan you will have to undergo blood work to make sure that your kidney function is normal.

Detailed information on the contrast agent Gadolinium can be provided to you at your request.

You should inform your study doctor: (1) if you are pregnant or breast feeding, (2) if you have a history of allergic reactions to MRI or CT contrast agents, (3) if you have a history of kidney disease, seizure, asthma, or allergic respiratory disorders, and (4) if you have anemia or disease that affects red blood cells.

Reproductive Risks:
Female
It is not known if the study drugs may affect an unborn or nursing baby or has an adverse effect on sperm. Females who are pregnant, trying to become pregnant or breast-feeding, may not be in the study. The study doctor will perform a blood and/or urine pregnancy test before the start of and during the study, for females who are able to have a baby.

If you are able to have a baby, you must avoid having sex (abstinence) or use reliable birth control methods during the study and for a period of 120 days after your last dose of pembrolizumab. The following birth control methods are allowed during the study as per local regulations or guidelines:

Two (2) of the following barrier methods in combination:
- Diaphragm
- Condom (by the partner)
- Copper Intrauterine device (IUD)
- Contraceptive sponge
- Spermicide

OR One (1) of the above barrier methods in combination with:
- Hormonal contraceptives (including oral, subcutaneous, intrauterine, or intramuscular) that are registered and marketed containing estrogen and/or a progestational agent

If you become pregnant during the study, or within 120 after the study, you must notify the study doctor right away. The study drug will be stopped, and you will be taken out of the study.

Male
There may be risks if you are male and your partner is pregnant or trying to become pregnant. If you are male and your partner is able to have a baby, you and your partner must practice abstinence or use a reliable birth control method during the study and for a period of 120 days after the last dose of study drug. The following birth control methods are allowed during the study:

Two (2) of the following barrier methods in combination:
- Diaphragm
- Condom
- Copper Intrauterine device (IUD)
- Contraceptive sponge
- Spermicide

OR One (1) of the above barrier methods in combination with:

- Hormonal contraceptives (including oral, subcutaneous, intrauterine, or intramuscular) that are registered and marketed containing estrogen and/or a progestational agent

If your partner becomes pregnant during or within 120 days after the study, you must notify the study doctor immediately.

You must also agree to not donate sperm during the study and for a period 120 days after your last dose of study drug.

There may also be side effects, other than listed above that we cannot predict. Other drugs will be given to make side effects that occur less serious and less uncomfortable. Many side effects go away shortly after the study drug or procedure is stopped, but in some cases side effects can be serious, long lasting or permanent.

For more information about risks and side effects, ask the researcher or contact their office at 203-200-6622. If you are a non-small cell lung cancer subject, you may also call Dr. Sarah Goldberg at 203-737-5649.

Benefits

If you agree to take part in this research study, we cannot guarantee that you will receive any benefits. We hope the information learned from this research study may benefit other patients who have metastatic melanoma or non-small cell lung cancer with untreated brain metastases in the future.

Economic Considerations/Cost

If you take part in this study, the sponsor pays the study doctor to conduct the study and covers the cost of the study drug and the study-related tests and procedures (they are NOT part of your routine medical care). However, there may be additional costs to you. These can include costs of transportation and your time to come to the study visits. You or your health insurance must pay for services, supplies, procedures, and care that are part of your routine medical care. You will be responsible for any co-payments required by your insurance.

If you need assistance in answering financial questions related to your insurance, contact your study team who can connect you with a representative in the YCCI Clinical Research Billing and QA office at 1-877-874-2560.

For more information on clinical trials, you can visit the National Cancer Institute's (NCI) web site at http://www.cancer.gov/aboutnci/organization/clinical-center-fact-sheet.

To learn more information about paying for clinical trials and insurance, you can visit the NCI web site at:

• http://www.cancer.gov/clinicaltrials/learningabout/payingfor
• http://www.cancer.gov/clinicaltrials/learningabout/payingfor/insurance-coverage

Another way to get information is to call the NCI at 1-800-4-CANCER (1-800-422-6237) and talk to an Information Specialist, Monday-Friday 8am-8pm EST. You can request free information to be sent to you, such as the Cancer Clinical Trials FactSheet."

Investigator Interest

The Principal Investigator on this study has received financial compensation from the manufacturer of the study drug Pembrolizumab for providing services on an advisory board and lecturing.

Treatment Alternatives

You do not have to participate in this study. Your other choices may include:

- Getting treatment or care for your cancer without being in a study. This includes taking pembrolizumab or bevacizumab alone without participating in this research study.
- Taking part in another study.
- Receiving no treatment at this time.
- Getting comfort care, also called palliative care; this type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. Comfort care does not treat the cancer directly but instead is meant to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices and their risks and benefits before you decide if you will take part in this study.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Cancer Institute which is funding this project. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of such as child abuse and neglect, or harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document such as including your research data in your medical record and sharing your de identified data and specimens with other researchers

Confidentiality and Authorization to collect, use and disclose Protected Health Information

For purposes of this study, Yale University, Yale-New Haven Hospital, and Dr. Harriet Kluger as the Principal Investigator will use medical information collected or created as part of the study, such as medical records and test results, which identifies you by name or in another way. Your consent to participate in the study means you agree that Yale University, Yale-New Haven Hospital, and Dr. Kluger may obtain your medical information that they request for study purposes from your physicians and your other health care providers from the past or during your participation in the study.

The protected health information that will be collected in this study includes demographics, medical history, physical examinations, routine lab tests, review of adverse events and medications you take (past and present), vital signs, MRI scans, CT scans, pregnancy tests, blood or tissue samples for research purposes, survival follow-up information and records about any study drug(s) that you received.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases such as HIV or hepatitis. Positive results of HIV and Hepatitis will be reported to CT Department of Public Health. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the study staff will get information that identifies you and your protected health information. This may include information that might directly identify you, such as your name, date of birth, and medical record number**.** This information will be de-identified whenever possible prior to

providing it to the sponsor, meaning we will replace your identifying information with a code that does not directly identify you. The study doctor will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the Principal Investigator or selected members of the study team. Any information that can identify you will remain confidential.

The records for this trial will be stored in locked cabinets and/or offices and password protected computers. The study team will only give this coded information to others to carry out this research study or to sponsor representatives to comply with federal laws and regulations. It is anticipated that records containing the information that links you to your coded information will be maintained indefinitely, as there are no plans at this time to destroy these records at the end of the study.

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g., health insurance company, disability provider.)

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University and the Human Investigation Committee (the committee or Institutional Review Board that reviews, approves, and monitors research on human subjects), Yale Center for Clinical Investigation who are responsible for ensuring research compliance. These individuals are required to keep all information confidential
- Your providers who are participants in the Electronic Medical Record (EMR) system
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The study doctor, Harriet Kluger, MD, the Yale study team, and research team members at each participating institution
- The U.S. Food and Drug Administration (FDA). This is done so that the FDA can review information about the new drug product involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- The manufacturer of study drug, Merck & Co. Inc. and/ or their representatives
- Drug regulatory agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure

that the information relating to this research is available to all parties who may need it for research purposes.
All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at Yale School of Medicine and Yale-New Haven Hospital is required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Authorized representatives of the Food and Drug Administration (FDA**)** and the manufacturer of the study drug being tested, Merck & Co. Inc., may need to review records of individual subjects. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others.

The sponsor will see the research information we collect about you when they come to Yale to monitor the conduct of this research study. The "Sponsor" includes any persons that work for or are hired by the sponsor to conduct research activities related to this study. For this study the sponsor is Merck & Co. Inc. Yale researchers will also send the sponsor your health information during the study or at the end of the study. When Yale researchers send information about you to the sponsor, they will not send information that directly identifies you such as your name.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, you will not be allowed to look at or copy your study related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

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.

In Case of Injury

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale University and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

Voluntary Participation and Withdrawal

Participation in this study is voluntary. You are free to choose not to take part in this research study. Refusing to take part in this research study will not lead to penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

Withdrawing from the Study:
If you decide to participate in this research study, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. They will make sure that proper procedures are followed and a final visit is made for your safety. This will cancel any future research study appointments.

The researchers may withdraw you from participating in the research if necessary. You may be withdrawn by the researchers for progression of disease/poor response to treatment, development of serious side effects, or non-compliance (not following instructions from the study team).

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled.

If you choose not to give your consent by not signing and dating this document, or if you cancel your consent later, then you will not be eligible to participate in this study and will not receive any study treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

Withdrawing Your Authorization to Use and Disclose Your Health Information:
You may withdraw or take away your permission to use and disclose your health information at any time. You do this by telling the study staff or by sending written notice to the study doctor, Harriet Kluger, MD, at the address listed on page one of this form. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to ensure the integrity of the study and/or study oversight.

Questions

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the

telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

Human Research Protection Program
Institutional Review Boards
FWA00002571
25 Science Park – 3rd Fl., 150 Munson St.
New Haven CT 06520-8327

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, Dr. Kluger at (203) 200-6622.

If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Research Protection Program at (203) 785-4688 or email hrpp@yale.edu.

We have used **some technical terms** in this form. **Please feel free to ask about anything** you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

Optional Future Research

Please indicate your choice below by checking yes or no:

_____ Yes, I agree to allow my blood and tissue samples to be stored and used for future research.

_____ No, I do not agree to allow my blood and tissue samples to be stored and used for future research.

Principal Investigator:	Harriet Kluger, MD	**IRB #:**	1512016953
Funding Source:	Yale Cancer Center, Merck and Co., Inc	**Sponsor ICF Template Version:**	19.0
		Sponsor ICF Template Date:	19-APR_2024

Authorization and Permission

I have read (or someone has read to me) this form and have decided to participate in the project as described above. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and give out information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to participate in this research.

I also confirm that I have received a Trial Alert Card providing contact details of the study doctor and agree to carry this card with me at all times.

Study Participant (print name)	Signature	Date
Person obtaining consent (print name)	Signature	Date
Person obtaining consent (print name) – only if applicable, otherwise blank	Signature	Date
Witness (print name) – only if applicable, otherwise blank	Signature	Date

APPROVED BY THE YALE UNIVERSITY IRB 5/9/2024