Principal Investigator:	Harriet Kluger, MD	HIC #:	1401013290
Funding Source:	Yale Cancer Center and Merck and Co., Inc.	Protocol Version:	8
		Protocol Date:	23-Oct-2017

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

200 FR. 4

Study Title: A Phase 2 Study of MK-3475 in Patients with Metastatic Melanoma and Non-Small Cell Lung Cancer with Untreated Brain Metastases

Principal Investigator: Harriet Kluger, MD
Study Doctor's Phone Number: 203-737-2572
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Study Doctor's Mailing Address: PO BOX 20856, New Haven, CT 06520
Funding Source: Yale Cancer Center and Merck and Co., Inc.

Invitation to Participate and Description of Project

You are invited to take part in a research study. The research study is designed to explore whether or not an investigational drug, pembrolizumab (also known as MK-3475 or KEYTRUDA®), 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 funded by Merck and Co., Inc. Merck and Co., Inc. is providing research support and study drug for this research study. The Department of Defense is funding a portion of the analyses to be done on tumor tissue and blood samples from non-small cell lung

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cancer subjects enrolled on this study. Dr. Harriet Kluger is the principal investigator of this study at Yale Cancer Center.

Purpose

The purpose of this study is to explore whether or not the investigational drug, pembrolizumab, has beneficial effects and is safe for use in subjects diagnosed with metastatic melanoma who have at least two untreated brain metastases or non-small cell lung cancer (NSCLC) who also have at least one untreated brain metastasis.

Pembrolizumab is also known as KEYTRUDA® (approved in USA and several other countries) and is available by prescription to treat malignant melanoma (a type of skin cancer), head and neck squamous cell carcinoma and non-small cell lung cancer that has spread to other parts of your body.

Pembrolizumab/KEYTRUDA® is being studied by the Sponsor to see if it is effective in treating more than 30 types of cancer, as a single therapy or in combination with other therapies, to see what side effects are associated with its use.
Pembrolizumab is an antibody with parts from mice and humans being developed for treatment of human cancers. Pembrolizumab is a highly selective antibody that is designed to target a protein on the surface of some white blood cells called PD-L1. After pembrolizumab binds to its target on the white blood cells, they may then begin attacking your tumor. In a different study, some subjects who had previously treated non-small cell lung cancer had a decrease in the size of their tumor after treatment with pembrolizumab.

This study will only be done at the Yale Cancer Center. It is expected that approximately 74 subjects will be enrolled at Yale Cancer Center. It is expected that 20 subjects will have melanoma and 54 subjects will have NSCLC.

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. Arm B has 2 cohorts: Cohort 1 for PD-L1 positive NSCLC subjects and Cohort 2 for PD-L1 negative NSCLC subjects or those NSCLC subjects with a PD-L1 status that cannot be determined. 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. If you have NSCLC, you may have already participated in PD-L1 testing during the pre-screening process if your tissue was able to be successfully tested and your PD-L1 status has been evaluated.

Tests and procedures that would be performed for your regular cancer care whether you are on this study or not, are called "standard of care." All of the tests and procedures listed below that will be performed at your study visits, should you choose to participate in this study, are standard of care unless noted with an asterisk (*).

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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 be required to provide a portion of tumor specimens to be stored for research. 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):

- Physical Examination
- Review of your medical history. If you are being considered for Cohort 2 of Arm B, you must have received a prior platinum-based chemotherapy regimen.
- 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
- 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. 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, abdomen and pelvis
- Brain Magnetic Resonance Imaging (MRI) to assess Central Nervous System (CNS) tumor involvement. **For Melanoma Subjects Only:** In order to participate in this research study, you must have at least one brain lesion that requires local therapy by surgical resection or Laser Interstitial Thermocoagulation Therapy (LITT). Archival or previously removed brain tumor tissue may be used, if available.

Your study doctor will review the results of these tests to determine whether you qualify for the study. If you qualify and agree to participate, you will be assigned to study treatment described in the next section.

Treatment Period

For Melanoma Subjects Only: Prior to starting study drug, pembrolizumab, subjects with melanoma will have local therapy to a brain lesion by surgical resection or LITT. 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. Melanoma tumors are not required to express PD-L1 in order for melanoma subjects to participate in this research study.

For all Subjects: You will be required to provide a specimen from a tumor outside of your brain* for research, unless it is clinically not possible to obtain one, such as in subjects who do not have tumors outside of the brain. 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 two weeks (14 days). You will continue to receive the study drug, pembrolizumab, in two-week cycles for a maximum of two years or 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 enrolled in both arms will receive pembrolizumab at 10 mg/kg every 2 weeks intravenously (through your vein).

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

Day 1 of each Cycle (every 2 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*
- Measurement of height, 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
- Administer the study drug, pembrolizumab*

Cycle 3, Day 1 only (after 4 weeks of study drug):
In addition to the above-listed procedures that are to be done on Day 1 of each cycle, you will also have:

- Brain MRI*

Day 1 of every 4th cycle (every 8 weeks):
In addition to the above-listed procedures that are to be done on Day 1 of each cycle, you will also have:

- Blood sample(s):
  - Thyroid stimulating hormone (TSH)
  - Free T3 and Free T4 – this will be done only if your TSH value is abnormal
- Blood samples for research purposes*
- Tumor response assessment by CT scan of the chest, abdomen and pelvis
- Brain MRI

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

- Physical examination
- Review of your medical history
- 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*
- Measurement of height, 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
- Blood sample for research purposes*

Follow-up Period
You will continue to have tumor assessments by CT scan of the chest, abdomen and pelvis and a Brain MRI every 8 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.

Potential Risks, Side Effects, Discomforts and Inconveniences

While in this study, you may have side effects. Most of these side effects are listed here. However, there may be other side effects unknown at this time. You need to know and understand about side effects that could occur in this study before you agree to be a study participant. In addition to the risks listed below, there may be risks that are currently unknown.

What is known about this study drug?

Pembrolizumab (also known as KEYTRUDA® or MK-3475) is being studied by Merck to see if it has any effect in treating cancer. Pembrolizumab has been given to men and women with cancer to see what side effects would occur.

Overall, as of 03-Mar-2018, approximately 25,519 patients have been treated with pembrolizumab in clinical studies.

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 life-threatening), may lead to death. 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

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

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
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. 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 (i.e. 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.

RARE
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 and possible temporary paralysis
- 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 (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.
- 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

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.

Additional serious side effects in in <1.0% of subjects receiving pembrolizumab include the following:

- Dizziness or fainting (low blood pressure), flushing, rash, fever

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 this side effect:

- 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

There has been one reported case of diabetes mellitus (DM) at Yale associated with pembrolizumab (MK-3475), which required treatment with insulin. At this time it is unknown if this is a permanent condition. Symptoms typically experienced with diabetes are frequent urination, increased thirst, and increased hunger. You should inform your study doctor if you have any of these symptoms.

Pneumonitis, also known as inflammation of the lungs, has been observed in 94 (3.4%) of the 2,799 subjects with melanoma or non-small cell lung cancer (NSCLC) treated with pembrolizumab in four global clinical studies. Sixty-three (63) of these subjects received additional steroid treatment to help with their recovery. Thirty-six (36) of these cases were considered severe and resulted in 4 deaths due to pneumonitis.

If you have a history of pneumonitis that did not require additional steroid treatment, your study doctor will discuss additional risks that you may be exposed to.

Possible side effects in patients with brain metastases: Patients with untreated brain metastases have not received pembrolizumab (MK-3475) in the past. However, as with other immune therapies, pembrolizumab (MK-3475) might cause swelling around lesions in the brain, which could result in symptoms such as seizures, weakness, confusion or other neurological symptoms. It is important to report any neurological symptom to your treating physician. These symptoms might have to be controlled with steroids and/or anti-seizure medications.

Other Risks

Brain Biopsy (Melanoma Subjects Only):

We will obtain a brain biopsy while you undergo a 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 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 have occurred. The blood pressure cuff may cause discomfort or bruising to the upper arm. Approximately 40 mL of blood will be taken during your participation in this research study for research purposes.

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 physician 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:
It is not known if pembrolizumab may affect an unborn or nursing baby or if it has an adverse effect on sperm. Therefore, females who are pregnant, trying to become pregnant or breast-feeding, may not be in the study. The study doctor will perform a urine and/or blood pregnancy test before the start of the study, for females who are able to have a baby. Women of child bearing potential must agree to use one effective method of birth control while participating in this research study.

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 drug or procedure is stopped, but in some cases side effects can be

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serious, long lasting or permanent.

For more information about risks and side effects, ask the researcher or contact their office at 203-737-2572. 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 and do not guarantee that you will receive any benefits. We hope the information learned from this research study may benefit other patients with melanoma or NSCLC who have brain metastases in the future.

Economic Considerations

You will not be paid for taking part in this study. Tests and procedures that would be performed for your regular cancer care whether you are on this study or not are called "standard of care." There will be no charge to you or your insurance provider for the study drug, pembrolizumab.

The following tests and procedures are considered part of the standard of care for patient with your disease. The costs associated with these tests and procedures will be charged to you or your insurance provider in the same manner as if you were not part of this research study. Therefore, you or your insurance provider will need to assume responsibility for these costs. You will be billed for all costs or co-payments that are not paid by your insurance provider:

- Physical examination
- Medical history
- Measurement of height, weight and vital signs
- Performance status evaluation
- Routine blood tests for safety
- Pregnancy test (blood or urine)
- Computerized tomography (CT) scan of the chest, abdomen and pelvis
- Brain MRI (excluding at Cycle 8, Day 1)
- Surgical resection or Laser Interstitial Thermocoagulation Therapy (LITT) of the brain

The sponsor will pay for any study related procedures that are not considered standard care for patients with your disease. These include:

- Blood samples for research purposes
- Tissue samples for research purposes
- Brain MRI at Cycle 3, Day 1 only (after 4 weeks of study drug)
- Study drug, pembrolizumab

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Taking part in this research study may lead to added costs for you or your insurance provider. You are encouraged to speak with your insurance provider prior to entering the research study to find out your individual coverage. If you have difficulty determining your individual insurance coverage, you may call Dr. Kluger's office for assistance at the contact information provided on page one of this form.
You or your insurance provider will be charged for continuing medical care and/or hospitalization that are not a part of the research study.

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 whole brain irradiation, stereotactic radiosurgery, chemotherapy and taking other drugs that are FDA-approved for melanoma or lung cancer but have not been fully studied in patients with brain metastases. These drugs include chemotherapy and targeted therapies for melanoma or lung cancer and immune therapy for melanoma. Please discuss alternative therapies with your treating physician. Pembrolizumab (MK-3475) is FDA approved for patients with unresectable or metastatic melanoma and disease progression following Ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Nivolumab (Opdivo), an immunotherapy drug, is approved by the FDA for use in patients with a type of advanced lung cancer called squamous non-small cell lung cancer that has grown after they received platinum-based chemotherapy regardless of PD-L1 status. Nivolumab (Opdivo) is also approved by the FDA to treat advanced melanoma skin cancer that can't be surgically removed and isn't responding to other drugs. Pembrolizumab (MK-3475) is FDA approved for patients with advanced, metastatic non-small cell lung cancer whose disease has progressed after other treatments and with tumors that express a protein called PD-L1.
- 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 before you decide if you will take part in this study.

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 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. Harriet

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, diagnostic tests such as MRI scans, response assessments such as CT scans, pregnancy tests, PD-L1 status (NSCLC subjects only), blood samples for research purposes, and records about any study drug 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. 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 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.

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.)

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 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), 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, Dr. Harriet Kluger, and the Yale study team
- 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 and Co., Inc. and/ or their representatives
- The Department of Defense, which is funding some of the studies on tumor and blood samples and may have access to research records
- 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 and 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.

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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

Yale School of Medicine 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 should contact the study doctor immediately at the number(s) listed on page one of this form. 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 waive 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. Your health care outside the study and the payment for your health care will not be affected if you do not agree to participate. 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. Future research study appointments will be cancelled. You may request that the researchers destroy your research blood sample(s) by contacting your study doctor. As long as it is possible to identify your samples (i.e., your samples have not been anonymized or the study site has not destroyed the first key), then the researchers will destroy the sample. However, data obtained from your samples prior to receiving your request for destruction will not be deleted. If you request destruction of your sample(s), you will not lose any benefits, medical treatment or legal rights to which you are otherwise entitled.

Withdrawing from the study does not mean that your research sample(s) will automatically be destroyed. If you want your research samples to be destroyed after you withdraw from the study, you will have to make a request for them to be destroyed.

At any time, you may request that the Yale researchers destroy your sample by contacting your study doctor. As long as it is possible to identify your samples (i.e., your samples have not been anonymized or the study site has not destroyed the first key), then the researchers will destroy the sample. However, data obtained from your samples prior to receiving your request for destruction will not be deleted. If you request destruction of your sample(s), you will not lose any benefits, medical treatment or legal rights to which you are otherwise entitled.

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).

If you choose not to participate or if you withdraw it will not harm your current or future relationship with your own doctors or with Yale-New Haven Hospital.

If you fail to give your consent by signing 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 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, Dr. Harriet Kluger, 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 insure the integrity of the study and/or study oversight.

Questions

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.

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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.

Patient (print name)	Signature	Date
Person obtaining consent (print name)	Signature	Date
Person obtaining consent (print name) – only if applicable, otherwise blank	Signature	Date
Interpreter/ Witness (print name) – only if applicable, otherwise blank	Signature	Date

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. Harriet Kluger at 203-737-2572. 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 Investigation Committee at (203) 785-4688.

APPROVED BY THE YALE UNIVERSITY IRB 2/24/2020