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Title: Pembrolizumab in HNSCC With Residual Disease After Radiation

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Principal Investigator:	Barbara Burtness, MD	**HIC #:**	1602017275
Funding Source:	Yale Cancer Center, Yale University / Merck and Co, Inc.	**Sponsor Protocol Number:**	1602017275
Sponsor ICF Template Version:	12.0	**Sponsor ICF Template Date:**	08/07/2019

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT

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

Study Title: A Phase II study of Pembrolizumab for patients with head and neck squamous cell carcinoma with residual disease following definitive chemoradiation

Principal Investigator: Barbara Burtness, MD
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Funding Source: Yale Cancer Center, Yale University and Merck and Co, Inc.

Invitation to Participate and Description of Project

You are invited to take part in a research study. This research study is designed to see if the study drug, pembrolizumab also known as KEYTRUDA, is effective for squamous cell carcinoma (SCC) of the head and neck in subjects who still have evidence of the disease after chemoradiation. You have been invited to take part because you were diagnosed with SCC of the head and neck and have undergone chemoradiation, but still have signs of the disease.

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. A research team member will review and discuss this form 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 alternatives, 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. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign and date this form. If you do not sign this consent form, you cannot take part in this study. The decision to participate or not is yours. If you are participating in any other study, you cannot, take part in this study.

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

The research study is sponsored by Yale University. Yale University is providing funding for the study and is responsible for the conduct of the study. Merck and Co. Inc. is, the maker and the provider of the study drug pembrolizumab, and is also providing funding for the study. Yale University is called the Sponsor. Barbara Burtness, MD is the principal investigator of this study at Yale University. The study doctors will not receive payment for any specific results from this study.

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Purpose

The purpose of this study is to test the effectiveness of pembrolizumab for SCC of the head and neck for subjects with persistent disease after chemoradiation.

Pembrolizumab has been approved by the United States Food and Drug Administration (FDA) for use in Squamous Cell Carcinoma of the head and neck for subjects whose cancer has spread or come back following treatment with certain chemotherapy drugs. Pembrolizumab is available by prescription to treat several other different cancers but is not approved to treat your type of cancer. The use of pembrolizumab is investigational in this study.

It is expected that 24 subjects will participate in this study at 3 sites in the United States. It is expected that approximately 16 subjects will be enrolled in the research study and treated with pembrolizumab at Yale University.

Study Procedures

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 (*).

Screening Period

If you agree to participate and sign this form, you will need to undergo a series of tests and procedures to determine if you are eligible to participate in this the research study. You will come to the study site for screening tests. It is possible that more than one screening visit may be needed to ensure the study is safe for you to participate in.

During the screening visit the following procedures will be completed:

- *You will be asked to read and sign the consent form.
- The doctor will review your medical history and demographic information with you.
- You will be asked about any medication you are currently taking.
- You will have an evaluation an ear, nose, and throat specialist to see if you could receive surgery for your cancer.
- The doctor will do a full physical exam.
- Your vital signs will be taken including your height and weight.
- You will be asked questions about how you are feeling and how well you are able to perform your daily tasks.
- If you are a woman of child bearing age you will be given a pregnancy test.
- A small amount of blood will be taken from the vein in your arm for routine lab testing.
- A urine sample will be collected for routine lab testing.
- You may have a CT scan to measure the size of your tumor.
- *Blood will be collected for research.
- *Tumor tissue from a previous biopsy will be requested for research purposes.

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- *If you have had a biopsy performed within the past 6 weeks as part of your regular cancer care that has shown that your disease remains following previous radiation therapy, we will request tissue from that biopsy for the purposes of this study. If there is not enough tissue remaining from the prior biopsy, an additional research biopsy will be required.
- *If a biopsy has not yet been performed as part of your regular cancer care, a biopsy will be taken to determine if your cancer remains. A small amount of additional tissue will be taken to be used for research purposes.
- It is important that you tell the medical staff about any other medication you are taking, or thinking of taking, before and during the study, including vitamins, nutritional supplements, herbal or other folk remedies. It is possible that your study medication could affect your other medication and there are certain medications that you will not be allowed to take with the study medication including other anti-cancer therapies and certain vaccines.

Treatment Period

If you are eligible to start the study after screening you will come to the clinic to receive an IV infusion of *pembrolizumab once every 3 weeks. Each infusion will consist of 200 mg of medication lasting 30 minutes. While participating in the study you receive up to 4 cycles of study drug. Below is a list of procedures you will undergo while receiving study drug in this study.

- You must inform your doctor of any changes in your health or symptoms you experience even if you think they are not related to the study drug.
- You will be asked about any medication you are currently taking.
- You will be given the study medication as outlined above.
- A physical exam and vital signs will be done.
- You will be asked questions about how you are feeling and how well you are able to perform your daily tasks.
- A small amount of blood will be taken from the vein in your arm for routine lab testing.
- A urine sample will be collected for routine lab testing. This will be done during the second and fourth cycle
- You will have a CT scan to measure the size of your tumor. This will occur during the fourth cycle. A CT scan may be done during the second cycle if your doctor thinks you need one
- * Blood will be collected for research at the end of the fourth cycle.
- *A biopsy of your cancer will be taken for research purposes at the end of the fourth cycle.
- You will have an evaluation by an ear, nose, and throat specialist to see if you could receive surgery for your cancer.
- Whenever you have questions, please contact your study doctor.

Treatment Continuation

There is a possibility that you could be eligible to continue receiving pembrolizumab after your initial for 4 cycles of study drug. If you continue receiving pembrolizumab you will continue to come to the clinic to receive your IV medication every 3 weeks for up to 1 year. The infusion will be the same you received during the first 4 cycles of study drug. Below is a list of procedures you will undergo while continuing pembrolizumab.

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- You must inform your doctor of any changes in your health or symptoms you experience even if you think they are not related to your therapy with the study drug.
- You will be asked about any medication you are currently taking.
- You will be given the study medication as outlined above.
- A physical exam and vital signs will be done.
- You will be asked questions about how you are feeling and how well you are able to perform your daily tasks.
- A small amount of blood will be taken from the vein in your arm for routine lab testing.
- A urine sample will be collected for routine lab testing. This will be done on even numbered cycles only.
- You will have a CT scan to measure the size of your tumor every 8 weeks.
- Whenever you have questions, please contact your study doctor.

End of Treatment

You will be able to continue taking the study drug until any of the following occur:

- Your disease gets worse (disease progression)
- You have side effects that are not tolerable
- Your study doctor decides it is in your best interest to come off the study
- You decide you no longer want to be in the study.

If any of these reasons for stopping the study drug occur, you will be asked to come in for an end of treatment visit to ensure you can safely come off the study medications. During this visit you will have the following procedures.

- You must inform your doctor of any changes in your health or symptoms you experience even if you think they are not related to the study drug.
- You will be asked about any medications you are currently taking
- A physical exam and vital signs will be done
- You will be asked questions about how you are feeling and how well you are able to perform your daily tasks.
- A small amount of blood will be taken from the vein in your arm for routine lab testing.
- * Blood will be collected for research. If you have had blood collected for research within the past 3 weeks, you will not need to have this repeated.
- * A biopsy of your cancer may be taken for research purposes, only if you have not already had this performed at end of cycle 4.
- You will have an evaluation by an ear, nose, and throat specialist to see if you could receive surgery for your cancer, only if you have not already had this performed at end of cycle 4.
- You will have a CT scan to measure the size of your tumor only if you stop the study drug because your disease got worse (progressed) before the cycle 4 scan.

Follow-up Period

After you have permanently stopped taking the study drug and have completed your end of treatment visit we will ask you to complete a follow-up visit. The follow-up will take place approximately 30 days after your end of treatment visit. The following procedures may be completed:

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- You must inform your doctor of any changes in your health or symptoms you experience even if you think they are not related to the study drug.
- We will ask you about any new cancer drugs you are taking.
- Your doctor may choose to perform additional test as needed.

If you permanently stop taking the study drug for any reason other than disease progression, you will be asked to come in to the clinic every 8 weeks for additional follow-up visits. These visits will continue until your disease worsens or you begin any new cancer therapy. The following procedures will be completed at these visits:

- We will ask you about any new cancer drugs you are taking
- A physical exam and vital signs will be done
- You will be asked questions about how you are feeling and how well you are able to perform your daily tasks
- You will have a CT scan to measure the size of your tumor every 9 weeks.

After your follow-up visit(s) have concluded, the study doctor will continue to contact you periodically in order to collect information regarding your status and any new cancer drugs you are taking. We would like to collect information on your health and your cancer for as long as we can. The longer we can keep in contact with you and the more information we can gather the easier it will be for us to determine if the study drug is effective for people with your condition.

If you decide to stop taking part in the study completely, you are recommended to go through study withdrawal procedures that the study doctor considers necessary. No further visits will occur, however, to help complete the research, we may be collect information on your status from publicly available registries where possible under applicable local laws.

Unscheduled Visits
If your study doctor believes that you should have additional visit(s) for your safety, (e.g., to be checked for a new symptom or for an abnormal laboratory result), you may be asked to attend a visit that is in addition to the visits scheduled by the study. If necessary, additional tests related to a safety concern may be ordered at no additional cost to you.

Potential Risks, Side Effects, Discomforts and Inconveniences

Risks associated with Pembrolizumab (also known as KEYTRUDA):
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 study drug 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.

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What is known about this study drug?
Pembrolizumab works by helping the immune system to fight your cancer. However, pembrolizumab can also cause the immune system to attack normal organs and tissues in the body and can affect the way they work, which can result in side effects that may become serious or 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.

What side effects could the study drug(s) cause?

VERY COMMON, SOME MAY BE SERIOUS (i.e. 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 (pruritis)
- Loose or watery stools (diarrhea)
- Cough

COMMON, SOME MAY BE SERIOUS (i.e. 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 (arthritis)
- Fever (pyrexia)
- Back pain
- Rash (skin eruption)
- Not enough thyroid hormone (hypothyroidism) so you may feel tired, gain weight, feel cold, have infrequent, or hard stools
- Low level of salt in the blood (hyponatremia) that may cause you to feel tired, confused, have a headache, muscle cramps, and/or feel sick to your stomach
- Pain in your belly (abdominal pain)
- Loss of skin color (vitiligo)

UNCOMMON, SOME MAY BE SERIOUS (i.e. 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:

- Too much thyroid hormone (hyperthyroidism) so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools
- Inflammation of the lungs (pneumonitis) so you may feel short of breath and cough. Sometimes this might lead to death
- Inflammation of the bowels/gut (colitis) which may cause severe 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, itchiness, and/or skin redness (Stevens-Johnson Syndrome). This could be widespread throughout your body.

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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. The severe conditions can sometimes lead to death (Toxic Epidermal Necrolysis (TENS)).

- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, or feel short of breath, experience a decrease in blood pressure at the time of receiving your infusion (IV) or just after, or pain at the site of infusion

RARE, SOME MAY BE SERIOUS (i.e. 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 liver (hepatitis) that 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, have yellow eyes and skin, and have dark urine
- Inflammation of the pituitary gland (a gland in the head) (hypophysitis), which may cause 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) (adrenal insufficiency) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and abdominal aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan.
- Inflammation of the kidney (nephritis) so you may pass less urine or have cloudy urine or bloody urine, have swelling and low back pain
- Inflammation of the muscles (myositis) so you may feel weak or pain in the muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) (pancreatitis) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat
- Inflammation of the eye (uveitis) so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- 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 nerves (peripheral neuropathy) 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

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- Inflammation of the middle layer of your heart wall (Immune-mediated 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 (thyroiditis), 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 (myasthenia gravis).
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as lymph nodes, eyes, skin, or lungs (sarcoidosis).
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behaviour, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis).

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 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 (arthritis).
- 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, and 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 (Hemophagocytic lymphohistiocytosis (HLH)).

If you have had an allogenic stem cell transplant (a procedure in which a person received blood-forming stem cells from a donor), you may experience graft vs. 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.

There is also a risk that your disease may worsen or progress while you are taking pembrolizumab. This is a risk with all investigational drugs as the effectiveness of investigational drugs is still being evaluated. If your cancer is initially determined to be resectable, meaning that it may be possible to remove your tumor(s) surgically, there is a risk that your disease may become unresectable if it worsens while on study.

Other Risks

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Blood Collection:
The risks of taking blood may include pain, redness, discoloration, swelling, bruising, and/or a small amount of bleeding 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 total volume of blood to be collected from you in one visit is about 40ml (approximately 2.7 tablespoons). To make the blood samples easier to take a small tube called a cannula may be placed into your vein and the samples may be drawn from the cannula. You may experience discomfort because of the insertion of a cannula.

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.

Reproductive Risks:

It is not known if the study drug(s) may affect an unborn or nursing baby. If you are pregnant, trying to become pregnant or breast-feeding, you may not be in the study. The study doctor will perform a blood or urine pregnancy test before the start of and during the study, if you 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
- 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 at any time during this study you think you might be pregnant, or later learn that you were pregnant while receiving the study drug or during the period of 3 months after stopping the study drug, you must contact the study doctor immediately for further instructions about your participation in this study and follow-up. If at any time you report a pregnancy the study team will collection information about the results of the pregnancy and/or birth and will schedule any follow-up visits that may be necessary.

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This health information will become part of the clinical study records and will be shared with the study sponsor so that the sponsor may determine if there are any effects of the study medication upon unborn children.

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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 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 study drug pembrolizumab. 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 the study you must notify the study doctor right away. If your partner is already pregnant when you begin the study you must use a condom (male) during the study and for a period of 120 days after your last dose of pembrolizumab. You must also agree to not donate sperm during the study and for a period of 120 days after your last dose of study drug.

If you or your partner become pregnant during the study, you may be asked permission to follow the outcome of the pregnancy and report the condition of your baby to the Sponsor. This would involve being contacted by study staff at least monthly to check on how you and your baby are doing until your pregnancy is over. The health information that your partner provides will become part of the research study records and will be shared with the study sponsor. This information may help determine if there are any effects of the study drug on unborn children.

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 serious, long lasting or permanent.

For more information about risks and side effects, ask the researcher or contact their office at 203-200-4622.

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 others with head and neck cancer in the future.

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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 pembrolizumab or for tests or procedures that are not considered standard of care. All of the tests and procedures listed in this consent form that will be performed at your study visits are standard of care unless noted with an asterisk (*). There will be no charge to you or your insurance provider for the pembrolizumab. The administration of the study drug, pembrolizumab, will be charged to you or your insurance provider. All other tests and procedures will be charged to you or your insurance provider in the usual way. This may include other tests and procedures not listed in this consent if your doctor feels it is necessary for your care, such as additional laboratory tests.

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. Barbara Burtness' office for assistance at 203-200-4622.

You or your insurance provider will be charged for continuing medical care and/or hospitalization that are not a part of the research study.

Investigator Conflict of Interest

The principal investigator on this study, Dr. Barbara Burtness, has received financial compensation from the study sponsor, Merck Sharp & Dohme, for consulting services. If you have questions about this interest, you may ask to speak with Dr. Burtness.

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 which includes taking approved treatments without participating in this research study, including:
- Upfront surgical resection
- Taking part in another study.
- Receiving no treatment at this time (known as observation)
- 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.

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

For purposes of this study, Yale University, Yale-New Haven Hospital, and, Dr. Barbara Burtness 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. Barbara Burtness 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 study doctor may need this information to watch, review and report on the safety of the study treatment(s).

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, CT scans, response assessments, pregnancy tests, blood samples for research purposes only, survival follow-up information, records about any study drug(s) that you received and family history of cancer.

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, social security number, and medical record number**.** This information will be de-identified prior to providing it to Merck and Co., meaning we will replace your identifying information with a code that does not directly identify you as well as your initials. The study doctor will keep a link between your code and identity 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. 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:

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- The U.S. Department of Health and Human Services (DHHS) agencies and other government agencies in the United States and in foreign countries that watch over the study
- Representatives from the Sponsor, Yale University, the Yale Center for Clinical Investigation, and the Yale 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, Barbara Burtness, MD, and the Yale University 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., and/or their representatives, including QualTek.
- 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
- Other clinical centers participating in this study, including Ohio State University and the University of Texas Southwestern Medical Center
- Representatives from Yale Human Research Protection Program and Yale Research Quality Assurance Representatives may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential.
- The people you have named as emergency contacts (if any) in case you do not show up for your appointments with the study doctor and the study team has not been able to reach you.

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. The study sponsor, people who work with the sponsor on the study, and government agencies and other groups that watch over research studies like this one may look at all your health information. Regulatory authorities may also require that the study doctor turn over to them copies of all your health information to make sure the study has been done the right way. They also want to make sure that your health information has been collected the right way, or for other reasons that are allowed under the law.

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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 University are 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. Federal law does not protect you against this, but the laws of your state may provide additional protection. 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., may need to review records of individual subjects. As explained above, the study sponsor may send your study data (with your initials and a code number, but not your name) outside of the United States for the reasons described in this form. Please know that the laws in other countries may not provide the same level of data protection and may not stop your study data from being disclosed to others. As a result, they may see your name, but they are bound by rules of confidentiality not to reveal your identity to others.

The sponsors will see the research information we collect about you when they come to Yale University, 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 and Co., and Yale University. Yale University, researchers will also send the sponsor your health information during the study or at the end of the study. When Yale University 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. You may also, under data protection laws, have the right to ask that any mistakes in your study-related health information be corrected. 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 School of Medicine and Yale University, 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.

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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 sign this consent and 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.

You may request that the Sponsor destroy your tissue or blood sample(s) by contacting your study site. 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 Sponsor will destroy the sample. However, if any analysis or research has already been performed on the samples, the Study Sponsor does not have to destroy the results of this analysis or research. 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. Reasons to stop study drug(s) include the following:

- Your cancer gets worse (disease progression)
- You are unable to tolerate the study drug or have significant side effects.
- Your study doctor no longer feels it is in your best interest to continue receiving the study drug
- You voluntarily withdraw your consent to continue receiving the study drug.
- You do not follow your study doctor's instructions for taking part in the study.

Reasons to stop the whole study include the following:

- You voluntarily withdraw your consent to continue in the study
- You do not follow your study doctor's instructions for taking part in the study
- You were enrolled into the study in error.

By signing this consent you agree that site staff may still check on your health and well-being, by checking your clinical notes, hospital records, contact your general practitioner or check publicly available registries.

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If you have a side effect at your final study visit or withdrawal visit then your Study Doctor may wish to contact you and ask you about this, until it has completely resolved. The Sponsor or the manufacturer of the drug, Merck, may also ask the Study Doctor for this information.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale University. We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment.

If you choose not to give your consent by not 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 study drug or procedures 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 Barbara Burtness, 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 as permitted in this document 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.

Biomarker Research
A biomarker is a biological substance from your body, the cells of your body, or the cells of your cancer that is useful for measuring or predicting the progress of disease, and potential response of your cancer to the study drug. We will perform biomarker research on your samples to see if there is a way to predict how people response to the study drug, Pembrolizumab.

Below are the biomarkers that we will collect in this study:
1. Archival (tissue that was already collected from you) will be requested from a previous biopsy. This will not require any additional procedures. This tissue sample will be used to study how your cancer cells respond to the study drug.

2. Two tumor biopsy samples will be collected from you. The first will be collected at the beginning of the study (prior to getting the study drug). If you have already had a biopsy done as part of your regular cancer care within 6 weeks prior to starting the study drug, we will use tissue

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from this biopsy if there is enough left over, so an additional biopsy will not be needed for research.

The second biopsy will be collected after you have received the study drug, either at the end of cycle 4 or when you stop taking the study drug (whichever comes first).

Additionally, if you undergo a biopsy as part of your regular cancer care at any point while you are on the study, we may request if any extra tissue is left over from that biopsy.

These biopsy samples will be used for research to help us to understand why the study drug did or did not work.

3. Blood samples will be collected from you in the beginning of the study, at the end of cycle 4 and when you stop taking the study drug. These blood samples will be used for research to help us to understand how cancer cells respond to the study drug.

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 cancer.

Your specimens that we collect for research described above (tumor biopsy, tissue, and blood) 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).

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. There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers (except those with fewer than 15 employees) to discriminate against you based on your genetic information. However, it does not

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protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

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. Your samples will be destroyed.

Please indicate your choice below by checking yes or no:

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

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

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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, including transfer to countries outside of the United States. By signing this information and consent form, I have not given up any of the legal rights that I otherwise would have as a subject in a research study. By refusing to give permission, I understand that I will not be able to participate in this research.

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
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. Barbara Burtness at 203-737-4622. 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

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