PRINCIPAL INVESTIGATOR: David S. Schrump, MD, MBA

STUDY TITLE: Phase I/II Evaluation of Oral Decitabine/Tetrahydrouridine as Epigenetic Priming for Pembrolizumab Immune Checkpoint Blockade in Inoperable Locally Advanced or Metastatic Non-Small Cell Lung Cancers, Esophageal Carcinomas, or Pleural Mesotheliomas

STUDY SITE: NIH Clinical Center, National Cancer Institute (NCI)

Cohort: Affected Patients

Consent Version: 08/23/2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

David S. Schrump, MD, MBA, by phone at 240-760-6239 or email at schrumpd@mail.nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers. Taking part in research at the NIH is your choice.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find the highest safe dose of the combination of investigational agents decitabine-tetrahydrouridine (DAC-THU) in combination with pembrolizumab in patients with non-small cell lung cancer (NSCLC), esophageal carcinoma (EsC) or malignant pleural mesothelioma (MPM). Once we determine the highest safe dose, it will be tested on additional subjects to help us determine whether DAC-THU in combination with pembrolizumab infusion

can cause tumors in lungs, the esophagus (throat) and the lining (membranes) of the lungs and the inner side of the ribs to shrink.

Decitabine (DAC) is an investigational (experimental) drug that works by depleting DNA methyltransferase 1 (DNMT1). DNMT1 is an enzyme, or protein that causes chemical changes, often increased in cancer. Blocking DNMT1 has been shown to reduce tumor formation. Decitabine is experimental in this study because it is not approved by the Food and Drug Administration (FDA) for patients with NSCLC, EsC or MPM. Decitabine is approved by the FDA for treating patients with a blood disease called myelodysplastic syndrome (MDS, a condition where the bone marrow does not make blood cells normally).

Tetrahydrouridine (THU) is an investigational (experimental) drug that works by blocking an enzyme that breaks down decitabine. So, THU will increase the time cells in your body are exposed to decitabine. THU is experimental because it is also not approved by the FDA, although it has been extensively used in clinical trials, including several cancer trials.

Pembrolizumab is an FDA approved agent that works by blocking a signal that would have prevented activated T cells (a type of white blood cells) from attacking the cancer, thus allowing the immune system to clear the cancer. Pembrolizumab acts by blocking a protein of the T cell that limits its activity, thus allowing the immune system to attack the tumor.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

The purpose of this study is to assess whether treatment with tetrahydrouridine-decitabine (THU-DAC) in combination with pembrolizumab is safe and effective in patients with non-small cell lung cancer (NSCLC), esophageal carcinoma (EsC) or malignant pleural mesothelioma (MPM) that cannot be removed by surgery.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 85 participants will take part in the study.

DESCRIPTION OF RESEARCH STUDY

Subjects will initially be enrolled on the study in groups of 3 or 6. The first group will take DAC-THU at the starting pre-planned dose level and a fixed dose of pembrolizumab. If none or only one of the subject experiences intolerable side effects, the next group will be enrolled at the next highest dose level. This will continue until more than one person in a group has intolerable side effects or until the highest pre-planned dose has been reached. The maximum safe dose is set at the highest dose level where no more than 1 of 6 participants experienced an intolerable side effect. Once the maximum safe dose is determined, an additional 4 subjects will be enrolled at that dose to further evaluate the effect of DAC-THU and pembrolizumab on the disease. Subsequently up to 47 additional patients with high levels of PD-L1 versus low levels of PD-L1 will be enrolled and treated at the maximum safe dose of DAC-THU in combination with pembrolizumab.

On the days you take DAC-THU, THU should be taken first (within 2 hours before or after a meal), followed an hour later by DAC.

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study

Before you begin this study, we will review your medical records and imaging studies to determine if you are eligible for this study. We will ask you questions over the telephone, other NIH approved remote platforms or in person about your medical history. You will need to have certain studies done in order to determine whether you meet the criteria to participate in this study. Any tests or procedures done specifically to evaluate if you are eligible for this study will be explained to you by your study doctor under a separate protocol.

Tissue samples from a previous surgery or biopsy will be collected to confirm your diagnosis and your level of PD-L1 (the protein targeted by pembrolizumab). If you do not have tissue available, a tumor biopsy will be performed. A tumor biopsy is the removal of a small piece of tumor using a needle or scope procedure. Research testing may also be performed on these samples. If a tumor biopsy is not required to confirm your diagnosis, mandatory biopsy will be performed for research purposes before you begin treatment.

You may receive conscious sedation before undergoing a biopsy, if needed, and you will be informed of the additional risks prior to undergoing the procedure. Conscious sedation is usually given to help someone relax and minimize discomfort. It can be given as a pill, a shot, an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) or even inhaled. You may have to wait up to an hour to start feel the effects depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. You will be monitored throughout the procedure.

A pregnancy test will also be performed if you are a female who is capable of having children.

You will not be allowed to participate if we find that you are not eligible.

During the study

If these tests show that you are eligible and you agree to participate in the study, you will come to the clinic for procedures described in the schedule of study visits and assessments listed below:

Treatment Period

On treatment dosing days, you will take your required number of THU oral capsules two hours before or two hours after a meal, and then take the oral DAC capsules 60 minutes later. You will need to take DAC-THU on two consecutive days (most likely this will be on Tuesday and Wednesday) for 2 consecutive weeks out of every 3 weeks. This 3-week period is called a cycle.

In the first week of every cycle when you begin taking DAC-THU, you will also have pembrolizumab administered in the vein for 30 minutes. Pembrolizumab may be administered during each week that you take DAC-THU, on Wednesday, Thursday, or Friday. Your study doctor will let you know when you will be given pembrolizumab. If you are taking any medications that reduce acid in your stomach (for example: Prilosec, Prevacid, Dexilant, Protonix etc.), you will not be able to take them on the days you take DAC-THU as they may interfere with the body's absorption of DAC-THU.

A member of your study team will provide you with a diary to keep track of the days you take your study medication. Please bring this diary with you to all scheduled appointments.

You will receive a total of 3 cycles (9 weeks) of therapy, which is called a course. If you tolerate therapy without significant side effects and your disease does not worsen in the end of the course, you may be allowed to take an additional course of therapy.

Before Starting Treatment

- Physical exam.
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- Routine blood (~2 tablespoons) and urine tests.
- Blood tests (~2 tablespoons) to classify your immune cells and to monitor your immune function.
- Blood (~1 teaspoon) or urine pregnancy test if you are a woman who can have children.
- Tests of your lung function.
- Research blood collection to determine how your immune system is responding to your cancer, and how many cancer cells are in your blood (~5 – 6 tablespoons).
- Tumor biopsy (mandatory) if one was not done at screening, which may include a CT scan to safely perform the tumor biopsy.
- We will ask you about any medications that you are taking and side effects you may be having.

Cycle 1 only

- Research blood will be collected to determine how your body processes the drug, how your immune system is responding to your cancer, and how many cancer cells are in your blood.
    - ~5 tablespoons will be collected on Day 1.
    - ~5 tablespoons will be collected at the end of the cycle.
    - Blood collected periodically (every 30-60 minutes) for up to 8 hours on Days 1 and 2 (~3 tablespoons in total).

During each cycle

- Routine blood tests (~2 tablespoons) performed twice weekly during the first course of therapy and then at least weekly during the rest of your therapy. (These routine blood tests may be done by your local physician.)
- We will ask you about any medications that you are taking and side effects you may be having.

At the end of each course (every 3 cycles)

- Physical examination.
- Vital signs including: blood pressure, pulse, respiratory rate and temperature.
- ~5 tablespoons of research blood will be collected for measuring the number of a certain type of immune cell and to determine how your immune system is responding to your

cancer. ~5 tablespoons of research blood will also be collected at the beginning of each course prior to your treatment, to be able to perform before and after research of your immune response to treatment.

- Imaging of your tumor – this will include CT scan, PET scan, and a brain MRI or brain CT scan.
- Tumor biopsy for research if safely accessible per PI discretion (only at the end of the 1st course). A CT scan may be required to safely perform the tumor biopsy.
- Routine blood (less than 3 tablespoons) and urine tests.
- We will ask you about any medications that you are taking and side effects you may be having.

When you are finished taking the drugs (treatment)

If your disease worsens or you no longer tolerate , your treatment will be discontinued. If your disease progresses while you are on this study, we will ask to examine you to check your health status, and will perform a full physical examination including the collection of blood samples for safety and diagnostic tests.

BIRTH CONTROL

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child.

If you are a woman who can become pregnant, you will need to practice at least 2 forms of effective birth control (refer to below) before starting study treatment, during study treatment, and for about 2 months (i.e., 60 days) after you finish study treatment.

If you engage in sexual activity, the following must be used:

At least one (1) form of highly effective birth control may include:

- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation

The second (2nd) form of effective birth control will include one of the following:

- condom (men only)
- diaphragm (women only)
- the use of (a second) one of the first forms of highly effective birth control above

If are a male you must use condoms when engaging in any sexual contact with a woman who can become pregnant in addition to the woman's use of at least 1 other form of effective birth control – even if you have had a successful vasectomy.

If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

RISKS OR DISCOMFORTS OF PARTICIPATION

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

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
- You may be asked sensitive or private questions which you normally do not discuss.

The DAC-THU with pembrolizumab used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drugs.

Here are important points about side effects:

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

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different, so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

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

What side effects or risks can I expect from being in this study?

Decitabine (DAC)

POSSIBLE
• Decreased number of a type of white blood cell which may lead to infections
• Increased number of platelets
• Decrease sperm count and/or fertility (testicular toxicity); the effect appears to be reversible in animal studies
• Caused fetal loss or birth defects (teratogenicity) – refer to the section entitled **Reproductive Toxicity** below.

Tetrahydrouridine (THU)

COMMON In 100 people receiving tetrahydrouridine, more than 20 and up to 100 may have:
• None
OCCASIONAL In 100 people receiving tetrahydrouridine, from 4 to 20 may have:
• None
• None
RARE, AND SERIOUS In 100 people receiving tetrahydrouridine, 3 or fewer may have:
• None

Pembrolizumab

Pembrolizumab works by helping your immune system to fight your cancer.

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

VERY COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, more than 20 and up to 100 may have:
• Itching of the skin • Loose or watery stools • Cough

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, from 5 to 20 may have:
• Joint pain • Rash

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, from 5 to 20 may have:
• Fever • Back pain • Pain in your belly • Loss of skin color • Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools. (hypothyroidism) • Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach. (hyponatremia)

UNCOMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, from 1 to 5 may have:
• Inflammation of the lungs, so you may feel short of breath and cough. (pneumonitis) • Too much thyroid hormone so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, and/or have loose and watery stools. (hyperthyroidism) • Infusion reaction, where you may feel dizzy or faint, feel 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 have pain at the site of infusion. • Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus. (colitis) • Inflammation of the skin, so you may have peeling of the skin, itchiness, 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. (Severe skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis)

RARE, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, less than 1 person may have:
• 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. (Guillain-Barré syndrome)

RARE, SOME MAY BE SERIOUS

In 100 people receiving pembrolizumab, less than 1 person may have:

- Inflammation of the muscles so you may feel weak or have pain in your muscles. (myositis)
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), 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. (pancreatitis)
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches. (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, pain in the right side of your belly, yellow eyes and skin, and dark urine. (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), 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. (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan. (adrenal insufficiency)
- 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, swelling and low back pain. (nephritis)
- Inflammation of the middle layer of your heart wall 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. (myocarditis)
- 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. (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing. (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs. (sarcoidosis)

RARE, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, less than 1 person may have:
• Inflammation of the brain 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. (encephalitis) • Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation. (myelitis) • Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue. • Low levels of parathyroid hormone (a hormone made by 4 tiny glands in the neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling or burning in the fingertips, toes or lips. (hypoparathyroidism)

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. (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome).
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- The combination of pembrolizumab with study drugs can cause prolonged low white cell blood counts which may lead to hospitalization,

If you have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), you may experience graft versus host disease (GVHD), which

may include diarrhea, skin rashes, and liver damage, **after receiving pembrolizumab**. Sometimes this condition can lead to death.

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

Reproductive Toxicity

In animal studies, **decitabine** has been shown to decrease sperm count and/or fertility (testicular toxicity); however, the effect is reversible. Decitabine has also been shown to cause fetal loss or birth defects (teratogenicity). Please refer to the section entitled, **Birth Control** above, for the contraception requirements on this study.

Research Procedure Risks

Blood Draw

Risks of blood sampling include pain and bleeding at the site where the blood is collected, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop. Rarely, there is also a risk of infection at the needle site.

Urine Collection

There are no physical risks or discomforts associated with urine collection.

Biopsy Risks

Risks associated with the biopsies include pain and bleeding at the biopsy site. Rarely, there is a risk of infection at the sampling site. If received, the most common risks of conscious sedation last up to a few hours after being given can include drowsiness, feeling slow or sluggish, low blood pressure, headache, and nausea.

Pulmonary Function Tests

These tests are safe and side effects are unlikely. During the test you will be asked to breathe deeply or rapidly, which may occasionally cause brief light headedness or slight soreness of the chest.

Scans and Contrast

CT, PET and MRI scans are common standard imaging tests used in the diagnosis of cancer. The most common discomfort is the length of time a patient must lay still during a scan. Occasionally, a patient may become uncomfortable with the closed space of the machines, particularly the MRI. If this occurs, your doctor can order a medicine to help you relax during this scan. If a contrast agent (the special dye) is given with the scan there is a small risk of having a reaction to the contrast. In that small group of patients who have a reaction, the most common symptoms are nausea, pain in the vein where the contrast was given, a metallic or bitter taste in the mouth, and a warm or flushing feeling that lasts from 1-3 minutes. Rarely do these symptoms require any treatment. In very rare cases, people have had severe reactions that affect their breathing and heart rhythm. If you have had a reaction in the past, be sure to tell you doctor or nurse about it.

An IV catheter may need to be inserted for administration of the contrast agent or anesthetic. This can cause pain at the site where the IV is placed and carries a small risk of bruising or infection, or inflammation of the skin and vein with pain and swelling.

For IV contrast: You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach.

For oral contrast: You may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from 5 CT scans, 5 PET/CT scans, 5 brain CT scans as well as 2 CT-guided biopsies over the course of the first year. The amount of radiation exposure you will receive from these procedures is equal to approximately 13.6 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans, PET/CT scans and CT-guided biopsies that you get in this study will expose you to the roughly the same amount of radiation as 45.3 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.4 out of 100 (1.4%) and of getting a fatal cancer is 0.7 out of 100 (0.7%).

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study.

  - If your tumor has high levels of a protein called PD-L1 and you have NSCLC, you could receive pembrolizumab alone since this is now an approved drug for initial therapy of NSCLC with high PD-L1 expression. Alternatively, you could choose to be treated with conventional chemotherapy with or without radiation.
  - If your tumor has low or absent expression levels of PD-L1, pembrolizumab alone is not a treatment option for you at this time. As such, in the absence of a clinical trial, you could receive conventional chemotherapy with or without radiation

- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if you become pregnant
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if he/she decides to close the study

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a COI Guide. You may ask your research team for a copy of the COI Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

Genomic Data Sharing

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity, and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

Will you receive reimbursement or direct payment by NIH as part of your participation?

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. Someone will work with you to provide more information.

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

- If some tests and procedures performed outside the NIH Clinical Center, you may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not generally be provided or paid for by the NIH Clinical Center.
- Once you have completed taking part in the study, medical care will no longer be provided by the NIH Clinical Center.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, David S. Schrump, MD, MBA, schrumpd@mail.nih.gov, 240-760-6239. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.