Official Title:	**A Phase I Trial of Atezolizumab and Varlilumab in Combination with Radiation in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC).**
NCT number:	**04081688**
Document Type:	**Informed Consent Form: Main**
Date of the Document:	**04/06/2022**

[redacted]

CONSENT TO TAKE PART IN A RESEARCH STUDY

TITLE OF STUDY: A Phase I Trial of Atezolizumab and Varlilumab in Combination with Radiation in Patients with Metastatic Non-small cell lung cancer (NSCLC)

Principal Investigator: [redacted]

STUDY SUMMARY: This consent form is part of an informed consent process for a research study and it will provide information that will help you decide whether you want to take part in this study. It is your choice to take part or not. The purpose of the research is to: test the good and bad effects of the study drug called varlilumab when given in combination with immunotherapy with atezolizumab and radiation for the treatment of lung cancer. If you take part in the research, you will be asked to receive the study drug, varlilumab in combination with atezolizumab every three weeks. You will also receive radiation to one of your tumor lesions. Your time in the study will be as long as your tumor is responding to the study treatment (up to one year). Possible harms or burdens of taking part in the study may be side effects from the study treatment and additional visits for the research testing. Possible benefits of taking part may be an improvement in your health as well as collection of new information about the study drug as a treatment for lung cancer. Your alternative to taking part in the research study is not to take part in it.

The information in this consent form will provide more details about the research study and what will be asked of you if you choose to take part in it. If you have any questions now or during the study, if you choose to take part, you should feel free to ask them and should expect to be given answers you completely understand. After all of your questions have been answered and you wish to take part in the research study, you will be asked to sign this consent form. You are not giving up any of your legal rights by agreeing to take part in this research or by signing this consent form.

Who is conducting this research study?

[redacted] is the Principal Investigator of this research study. A Principal Investigator has the overall responsibility for the conduct of the research. However, there are often other individuals who are part of the research team. [redacted]

The Principal investigator or another member of the study team will also be asked to sign this informed consent. You will be given a copy of the signed consent form to keep.

The [redacted] is the sponsor of this research study. [redacted]

Why is this study being done?

Your immune system sends out special cells called T cells to fight infections [redacted]

throughout your body. Some cancer cells can hide from these T cells by taking control of a pathway called PD-1/PD-L1. This lets the cancer cells avoid an attack from T cells. Immunotherapy drugs such as Atezolizumab (Tecentriq) block the PD-1/PD-L1 pathway. By blocking PD-1 or PD-L1, these drugs restore the body's immune response against cancer cells and allow the immune system to recognize and kill cancer cells. PD-L1 targeting drugs such as atezolizumab are now Food and Drug Administration (FDA) approved for the treatment of advanced or stage IV non-small cell lung cancer (NSCLC).

Although immunotherapy drugs such as atezolizumab lead to improved survival and are better tolerated, they work only in some patients. Research is now focused on ways to increase the number of patients who respond to these drugs. These research approaches include testing combination of PD-1/PD-L1 drugs with other treatments such as chemotherapy and radiation. Varlilumab is a new immunotherapy that also suppresses pathways (CD27) used by cancer cells to escape attack by immune system.

This study is being done to test the good and bad effects of the study drug called varlilumab when given in combination with atezolizumab (anti-PD-L1) and radiation. Giving you this medication in combination with immunotherapy with atezolizumab and radiation may increase the amount of time your disease is not active or does not spread to another part of your body. The use of varlilumab in this study is investigational. "Investigational" means that this medication has not yet been approved by the FDA to treat the type of cancer you have. Your voluntary participation in this research study may help to find out whether this drug is effective at lengthening the time until your cancer starts to grow.

Who may take part in this study and who may not?
You may take part in this study if you are 18 years of age or greater with advanced non-small cell lung cancer. Additionally, you may take part in this study if:

- You have received therapy with chemotherapy as well as PD-1/PD-L1 targeted immunotherapy previously to treat your lung cancer
- You agree to have a biopsy before starting treatment on the trial and a second biopsy after cycle 2
- You have a tumor lesion in the lung that can be treated with radiation
- You have read and signed this Informed Consent Form

You may not take part in this study if:

- You are unable to keep your doctor's appointments
- You are pregnant or breast feeding
- You have an active infection
- You have an autoimmune disease or are on high-dose steroids

The study doctor and/or research team will also ask you other questions about your medical history in order to make sure you qualify to be in this study.

Why have I been asked to take part in this study?
You are being asked to take part in this study because you have non-small cell lung cancer (NSCLC). You have already been treated with a PD-1/PD-L1 targeting immunotherapy such as pembrolizumab, nivolumab, durvalumab or atezolizumab. Your disease is now growing or did not respond to the immunotherapy treatment. People who are not in a study a[redacted]

with chemotherapy drugs such as paclitaxel, docetaxel, pemetrexed or gemcitabine.

How long will the study take and how many subjects will take part?
Study treatment with varlilumab will continue for as long as your tumor is responding (up to one year) and you are not experiencing severe side effects. At the end of one year of treatment, you may continue to receive therapy with atezolizumab if your cancer has not gotten worse. After you have stopped receiving treatment on study, we will continue to follow up with you for one year. The study drugs will be given in units of time called cycles. One cycle equals 21 days (3 weeks).

About 15 patients will take part in this study and all patients will be enrolled at the [redacted].

What will I be asked to do if I take part in this study?

Before you begin study treatment:
You will have some exams, tests and procedures to find out if you can take part in this study. Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, your doctor will do some extra testing as part of the study. The testing that you will need to have if you take part in this study is discussed below. If some of these have been done recently they may not need to be repeated, this will be up to the study doctor.

- Your age and race/ethnicity will be recorded.
- You will be asked about your medical history and any medications you are currently taking, both prescription and over the counter.
- You will have a complete physical examination, with your physician or physician's assistant, including measurement of your vital signs (breathing rate, blood pressure, temperature, and heart rate), height, and weight.
- Evaluation of your ability to carry out daily activities.
- The following blood samples will be collected within 28 days of registration:
  - About 2 teaspoons (10 mL) for routine testing, such as, a complete blood count, kidney and liver function tests to ensure that it is safe to administer any of the drugs included in this study
  - About 1 teaspoon (5 mL) for thyroid function testing
- A urine sample will be collected within 28 days of registration.
- If you are a woman who could become pregnant (even if you had your tubes tied), your doctor will perform a blood or urine pregnancy test. If you are pregnant, you cannot participate in this study.
- Imaging tests typically performed for cancer patients, including imaging of chest, abdomen and brain. Scans may include:
  - Computed tomography (CT), a scan that uses x-rays to look at one part of your body. It may be done with or without contrast. Contrast means that dye is injected into your vein to increase the differences between normal and abnormal tissue.
  - Magnetic resonance imaging (MRI), imaging that uses a strong magnetic field to look at one part of your body.
- **Biopsy of tumor tissue:** You will need to have a fresh tumor biopsy. This sample is required because the research on the sample is an important part of the study. The research biopsy is done in a similar way to biopsies are done for diagnosis. This tissue will be tested for certain proteins and biomarkers that may be related [redacted]

the study drug. The test may also help to understand the nature of your disease. The tumor sample will be processed and stored at the [redacted]. These laboratory tests are new and under development. Any remaining slides after the testing is completed will be saved for future research if you agree. The cost of the biopsy will be covered by the study.

If you do not meet the eligibility requirements, you cannot take part in this study. The study doctor will inform you of other options that are available to you.

STUDY TREATMENT

If the tests, exams, procedures show that you can be in the study, you will be registered. All study participants will receive varlilumab, radiation therapy and atezolizumab.

- Varlilumab: You will receive varlilumab every 21 days on day 1 of each cycle. Varlilumab will be given intravenously (IV) through a vein over 90 minutes.
- Atezolizumab: You will receive atezolizumab every 21 days on day 2 of each cycle. Atezolizumab will be given intravenously (IV) through a vein over 30 minutes.
- Radiation Therapy: You will receive radiation therapy for 5 days between the first and second cycles. The radiation will be to one of the lung tumor lesions. Each treatment may take up to 15-30 minutes depending on the technique used. Before you begin radiation therapy, you will have imaging of the chest in order to design your radiation treatment. Doctors will use information gathered from these scans to plan the best way to deliver radiation to your tumor.

<u>While on study treatment:</u>

During the treatment period, you will need the following examinations, tests, and procedures described below. Some of these exams, tests, and procedures are part of your regular medical care.

You will have the following done on Day 1 of every 21 day cycle:

- You will be asked to report any symptoms and health problems you have and any new medications you have started.
- You will have a complete physical examination, with your physician or physician's assistant, including measurement of your vital signs (breathing rate, blood pressure, temperature, and heart rate), height, and weight.
- Evaluation of your ability to carry out daily activities.
- You will have blood tests:
  - About 2 teaspoons for routine testing, such as, a complete blood count, kidney, and liver function tests.
  - About 1 teaspoon for thyroid function tests every 3 weeks
  - Approximately 4 teaspoon for research (collected only on day 1 of cycle 1 and 2)
- Tumor Assessments: You will have a CT scan of the chest and/or abdomen every 9 weeks while receiving study treatment to check how your cancer is responding to the treatment.
- **Tumor Biopsy:** You will be asked to have an additional tumor biopsy after Cycle 2 of treatment. The research biopsy is done in a similar way to biopsies done for diagnosis. This sample is required because the research on the sample is an important part of the study. This tissue will be tested for certain proteins and biomarkers (indicators of normal biological or disease processes) that may be involved in immune system activation or to understand the nature of your disease. The tumor sa[redacted]

processed and stored at the [redacted] These laboratory tests are new and under development. Any remaining slides after the testing is completed will be saved for future research if you agree. The cost of the biopsy will be covered by the study.

Your doctor will stop study treatment if any of the following occur:

- Your tumor grows larger or you develop new tumors (disease progression)
- You develop unacceptable side effects
- You become pregnant or are unwilling to use appropriate birth control techniques
- The study doctor determines that it is not in your best interest to continue the study treatment
- New information becomes available
- The study is stopped by the [redacted] Review Board (IRB) or FDA
- You choose to stop study treatment

<u>After you have completed study treatment:</u>
After all study treatment has stopped, your doctor will ask you to return to the clinic for an end of treatment visit, which will be approximately 30 days after your last dose of study drug. The following assessments will be done at these visits:

- You will be asked to report any symptoms and health problems you have and any new medications you have started.
- You will have a complete physical examination, with your physician or physician's assistant, including measurement of your vital signs (breathing rate, blood pressure, temperature, and heart rate), height, and weight.
- Evaluation of your ability to carry out daily activities.

<u>Follow-Up</u>
If you have any ongoing side effects at the time you complete the study or your doctor discontinues you from the study, the study doctor will continue to follow your condition until the side effect resolves or becomes stable.

If your disease worsens or you withdraw from the study treatment but not from study follow-up, the study staff will contact you approximately every 12 weeks after your last visit to check on your health status (for a period of up to one year). If they are not able to reach you, they may use a public information source (like county records) to obtain information about your survival status only, which will be reported as part of the data for the study.

What are the risks and/or discomforts I might experience if I take part in this study?
You may have side effects from the drugs or procedures used in this study, and they will vary from person to person. Study doctors will carefully watch everyone taking part in the study for any side effects. However, the study doctors and the study funders do not know all the side effects that may happen, and unknown side effects that could occur. The study doctors may give you medicine to help lessen the side effects. In some cases, side effects can be serious, long lasting, and/or may never go away. There also is a rare risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.
If you experience any severe side effect, you should:

- Seek professional medical help immediately
- Call your study doctor
- If necessary, go to the nearest emergency room

Potential Risks Related to Biopsy
The possible risk associated with removal of a piece of your cancer (a biopsy) depends on the part of the body where the biopsy will be performed. You may experience pain from the biopsy site, and you may have bruising, soreness or scarring at the biopsy site. Rarely, a patient who has had a biopsy may experience infection and/or internal bleeding and depending on the location of the biopsy, "punctured lung" and/or "collapsed lung" (an abnormal collection of air or gas in the space that separates the lung from the chest) may occur. Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Possible Side Effects of Varlilumab (CDX-1127)
To date, varlilumab has been administered to approximately 370 patients with various types of cancers, and most side effects have been mild-to-moderate in intensity. Safety data is available from 343 patients who were administered varlilumab alone and the remaining who received varlilumab in combination with another agent(s). Side effects attributed to varlilumab have included:

Common (Out of 100 people who receive varlilumab, 20 or more people may have):
- Fatigue (27%)
- Rash (24%)

Common, some may be serious (Out of 100 people who receive varlilumab, at least 10 but less than 20 people may have):
- Nausea (13%)
- Itching (16%)
- Diarrhea (11%)

Less common, Some may be serious (Out of 100 people who receive varlilumab, at least 5 but less than 10 people may have):
- infusion reaction with symptoms including chills, nausea, rash, hot flashes (8%)
- decreased appetite (7%)
- vomiting (7%)
- headache (7%)
- fever (6%)

A decrease in the lymphocyte count, a type of white blood cell, has commonly been observed following administration of varlilumab and has not been associated with symptoms. Varlilumab has been given in combination with other drugs that activate the immune system called checkpoint inhibitors, specifically Opdivo (nivolumab), Tecentriq (atezolizumab), and Yervoy (ipilimumab). Immune-related side effects are expected with checkpoint inhibitors and have been observed among the 202 patients who have received varlilumab in combination with these drugs. Serious drug related immune-related side effects requiring hospitalization, such as inflammation of the digestive tract (colitis), inflammation of the liver (hepatitis), and inflammation of the lung (pneumonitis) have rarely occurred when varlilumab has been given in combination with checkpoint inhibitors. One patient who developed pneumonitis while being treated with varlilumab and nivolumab died from this side effect. However, t[redacted]

these side effects has not been greater than would be expected for the checkpoint inhibitors alone.

Additional rare events requiring hospitalization or otherwise considered serious:

- bronchospasm
- low salt (sodium) in blood
- inflammation of the kidney

Additional side effects thought possible:

In laboratory tests, varlilumab has demonstrated the capacity to activate immune cells that are capable of destroying tumor cells. However, varlilumab may also activate immune cells and cause damage to normal tissue. Varlilumab induced activation of normal immune cells may cause symptoms during or shortly after finishing the varlilumab infusion. Signs and symptoms of such an infusion reaction may include low blood pressure, fever, shortness of breath, vomiting, abdominal pain, rash and other symptoms that may be mild to moderate or that could be severe and lead to life threatening complications such as renal failure, mental status changes and even death. Because varlilumab is a protein, it is also possible that you could have an allergic reaction to varlilumab with similar signs and symptoms as just described. Therefore, you will be monitored in the clinic for 60 minutes after receiving the drug (the usual time frame in which these types of extreme reactions may develop), as well as throughout the study period. Other types of immune activating antibodies have been tested in people and have had side effects ranging from mild to life threatening.

Based on studies of other antibodies that activate the immune system in different ways, the following side effects might also be possible:

- hair loss, loss of pigmentation (color) in the skin (vitiligo)
- Severe inflammation of the gastrointestinal tract (including severe diarrhea, passage of blood, abdominal pain, damage to the lining of the intestine, perforation of the intestine). These events may be serious or life threatening, and may require additional treatments such as treatment with corticosteroids, blood transfusions, intravenous artificial nutrition, and hospitalization. In some cases, sigmoidoscopy, colonoscopy (minimally invasive tests where your doctor inserts a scope in your rectum to look inside your colon or part of it) or surgery may be required.
- Changes in number of the various types of cells in the blood, such as neutrophils (which fight infection) and platelets (which make blood clot),
- Changes in functioning in the organs of the endocrine system: pituitary inflammation/failure (causing weight loss, fatigue, weakness, depression, loss of energy, nausea, vomiting, loss of appetite, and confusion; usually treatable but can rarely be fatal), over or under-activation of the thyroid (hypothyroidism or hyperthyroidism), adrenal insufficiency (if not treated, adrenal insufficiency may result in severe abdominal pains, diarrhea, vomiting, muscle weakness and fatigue, depression, extremely low blood pressure, weight loss, kidney failure, changes in mood and personality, and shock) and decreased function of the testes or ovaries (causing loss of sexual function/drive, muscle loss, sleep disturbance, mood/mental disorders, loss of bone mass, loss of hair, infertility and other symptoms)
- Inflammation of the eye (causing visual disturbances or pain)

Based on experience with other immune activating antibodies, it is expected that if [redacted]

above were to occur, they would likely be quickly controlled with appropriate therapy. However, it is possible that side effects could potential rapidly worsen and become life-threatening and even cause death. Any delay in treating these side effects may prolong their duration, and make them more difficult to treat. **You should always report any new symptoms during your regular study visits, and immediately contact the study doctor if you develop any worrisome symptoms including the following:**

Diarrhea:

- An increase by 2 or more bowel movements a day above your normal pattern, especially if they wake you up at night or the urge to move your bowels comes on suddenly. Even if you are not feeling particularly unwell, DO NOT DELAY IN CONTACTING THE STUDY PHYSICIAN OR NURSE.
- ANY blood in the bowel movements, even if there is no diarrhea.
- ANY marked change in bowel habits, either new constipation or diarrhea.

Abdominal (Stomach) pain or tenderness:

- Even if there is no diarrhea, and particularly if the pain is associated with a fever or requires the use of pain medications. Note: narcotic pain relievers used for abdominal (stomach) pain can suppress diarrhea or symptoms of other adverse events – please check with the study physician or nurse before using for abdominal (stomach) pain.

For patients with tumors positive for CD27 (found in some cancers of the blood), it is possible that varlilumab could rapidly kill the tumor cells and cause something called tumor lysis syndrome. This is unlikely to happen with varlilumab but if it were to occur it could cause changes in laboratory tests without any associated symptoms, or in severe cases, damage to the kidney or other organs.

As varlilumab acts on CD27, it is possible that varlilumab could cause leukemia or lymphoma malignancies that express CD27 to grow and therefore worsen the clinical situation. Another possibility is that varlilumab may kill normal CD27 positive immune cells that could result in an increased risk for developing infections. It is unlikely that these two risks will actually occur because they have not been observed in testing with varlilumab, including in animal studies.

If you were to require prolonged treatment with medications that suppress immunity, such as steroids, to manage a serious side effect associated with varlilumab and/or atezolizumab, your body's ability to fight off certain infections (i.e., opportunistic infections) may be lowered. These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Possible Side Effects of Lung Radiation

Common, Some may be serious (5% of people who receive radiation, may have):

- Swelling and redness, tanning, thickening, numbness, or peeling of the skin in the area of radiation
- Difficulty and/or pain with swallowing
- Hair loss in the treatment area, may be permanent
- Shortness of breath
- Cough with or without increased phlegm production
- Tiredness
- Pain in chest wall

Less Common, Some may be serious (5% or less of people who receive may have):

- Inflammation of the lung that may cause difficulty breathing and can be life-threatening
- Narrowing of the throat which may cause vomiting, difficulty swallowing
- Scarring in the lung
- Lung collapse
- Fluid around lungs
- Bleeding from the lungs which may cause coughing up blood
- Fever
- Narrowing of the esophagus

Possible Side Effects of Atezolizumab (MPDL3280A)

Common, Some may be serious (20% of people who receive atezolizumab may have):

- Tiredness
- Infection

Less Common, some may be serious (At least 4% but less than 20% of 100 people who receive atezolizumab may have):

- Anemia which may require blood transfusion
- Diarrhea, nausea, vomiting
- Difficulty swallowing
- Fever
- Flu-like symptoms including body aches
- Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Loss of appetite
- Pain in back
- Cough, shortness of breath, stuffy nose
- Itching, acne, rash
- Low level of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior, decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting
- Pain in belly
- Pain or swelling of the joints
- Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

Uncommon, some may be serious (less than 4% of people who receive atezolizumab may have):

- Bruising, bleeding

Atezolizumab (MPDL3280A) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: shortness of breath, swelling of the ankles and body.
- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, have eye pain, see floaters or have headaches
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Severe 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
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe upper abdominal pain that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs

Varlilumab combined with Atezolizumab

Varlilumab combined with atezolizumab has been studied in another clinical trial. A total of 18 patients with advanced cancer received the combination therapy. The most frequent treatment related side effects were fatigue (39%), itching (28%), anemia (17%), diarrhea (17%) and nausea (17%). However, there also may be new side effects of the combination that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects that you experience with this combination treatment.

REPRODUCTIVE RISKS

Both males and females will be included in this study. If you are pregnant, you cannot participate in this study. You should not become pregnant or father a baby while participating in this study because the drugs in this study can be associated with unknown risks that could affect you or an unborn baby.

All subjects and their spouses or partners must use an effective birth control method. Some examples of birth control are the following: have had a prior history of surgically-induced sterility (i.e., tubes tied, vasectomy), avoiding any activity that could cause you to become pregnant (no sexual intercourse), or using birth control pills, IUD, condom, or double-barrier contraception diaphragm with spermicidal jelly, transdermal (through your skin) or injectable contraceptives.

Whether you are a man or woman, you must practice birth control during the study and for at least three months after you receive the last dose of the study drug. Before entering the study, you and the study doctor must agree on the birth control method you will use during the entire study. A counselor and more information about preventing pregnancy will be made available to you if you have any questions.

FEMALES

If you are capable of becoming pregnant, a pregnancy test (using a urine and/or blood sample) will be done and the results must be negative before you are permitted to enroll in this study. A repeat pregnancy test must be done if you miss any periods or your periods becomes irregular.

If you are currently breast-feeding a child and agree to participate in this study, you must stop breast feeding before receiving the first dose of study drug. You must agree to discontinue breast-feeding for the entire time you are participating in the study to prevent any potential health risk or injury to the child.

If you become pregnant while in this study or within 12 weeks after your last dose of the study drug, you must tell the study doctor as soon as possible. The study doctor will advise you of the possible risks to your unborn child and options available to you. Because of the possible risks to an unborn child, the study drug will be stopped. You may be asked to receive medical follow-up services for yourself during the pregnancy and for the baby after birth. You may be asked to provide more information about the pregnancy and its outcome.

MALES

Male subjects must be surgically sterile or agree to use an acceptable method of contraception. You should make certain that you use adequate birth control measures to protect your spouse/female sexual partner(s), who may be capable of becoming pregnant.

You should also make certain that you inform your spouse/female sexual partner(s), who are capable of becoming pregnant, about the risk of harm to an unborn child posed by this drug so that they can take their own contraceptive measures. Male participants should immediately inform the study doctor if your partner becomes pregnant during the study, within 12 weeks after your last dose of the study drug.

You should not take any over-the-counter medicines, herbal products, vitamins or food supplements while taking part in this study, unless you tell the study doctor and g[redacted] from the study doctor to go on taking these medicines. You will follow the [redacted]

study doctor about the use of any of these products. You should also tell the study doctor about all medicines that other doctors may have prescribed for you to take.

Are there any benefits to me if I choose to take part in this study?
Taking part in this study may or may not make improve your health better or allow you to live longer. The information from this study will help doctors learn more about varlilumab as a treatment for NSCLC. This information could help other people who have a similar medical condition in the future.

What are my alternatives if I do not want to take part in this study?
You do not have to take part in this research study. If you decide not to take part in this study, you have other choices. Instead of being in this study, you can:

- Choose to have the usual approach described above
- Take part in another study
- Receive no therapy specific to your cancer
- Get 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, but instead tries 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. You are under no obligation to take part in this research study. If you decide that you do not wish to take part in this study, you are free to leave the study at any time.

How will I know if new information is learned that may affect whether I am willing to stay in the study?
During the course of the study, you will be updated about any new information that may affect whether you are willing to continue taking part in the study. If new information is learned that may affect you after the study or your follow-up is completed, you will be contacted.

Will I receive the results of the research?
In general, we will not give you any individual results from the study. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

Will there be any cost to me to take part in this study?
You and/or your insurance company will be billed for the costs of your treatment that are considered standard of care (for example, doctor/ Advanced Practice Nurse (APN) visits, nursing care to administer the treatments, routine lab tests, restaging scans, etc.) as you would have received these services even if you were not participating in this study. You will be responsible for any co-payments due for office visits, co-insurances and deductibles due on any tests and/or procedures that are required and considered standard care.

The study will provide the drug varlilumab at no charge to you while you take part in this study. Atezolizumab is a standard FDA-approved therapy for treatment of NSCLC and this will be billed to your insurance provider. If you have any questions about insurance coverage, including any out of pocket expenses you might incur, or which laboratory or facilities you [redacted] lowed to [redacted]

IRB ID: [redacted]
Approval Date:
Expiration Date:

have tests at, a financial counselor will be made available to you upon request.

Optional and/or research related items such as tumor biopsies and tumor tissue collection will be paid for by the [redacted].

Will I be paid to take part in this study?
You will not be paid for your participation in this research study.

How will information about me be kept private or confidential?
All efforts will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. Your personal information may be given out if required by law. Information about your cancer and treatment will be collected from your medical record for the study. The information will be with a study identification number and stored in a secured electronic file. The electronic file is password protected and accessible only to authorized study personnel. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

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

What will happen to my information or biospecimens collected for this research after the study is over?
After information that could identify you has been removed, de-identified information or biospecimens collected for this research may be used by or distributed to investigators for other research without obtaining additional informed consent from you.

What will happen if I am injured during this study?
Subjects in this study may be exposed to certain risks of personal injury in addition to those associated with standard forms of treatment. In addition, it is possible that during the course of this study, new adverse effects that result in personal injury may be discovered.

If you get ill or are injured as the direct result of being in this study inform your study doctor as soon as possible. The Institution will make appropriate referrals for treatment. The Study Sponsor shall reimburse all the reasonable and necessary costs of diagnosis and treatment of any Study subject injury, including hospitalization, if it:

(a) Is not a medical condition that you had before you started the study;
(b) Is not the result of the natural progression of your disease or condition;
(c) Is not caused by your failure to follow the study plan; and
(d) Is not proved to be directly caused by the Institution's negligence or misconduct.

There are no other plans for the University to provide other forms of compensation (such as lost wages) to you for research related illnesses or injuries. However, by signing this form, you are not giving up any legal rights to seek further compensation.

The University will make appropriate referrals for medical and/or dental treatment for patients who sustain personal injuries or illnesses as a direct consequence of the treatment. The patient's health insurance carrier or other third-party payer will be billed for the cost of this treatment; provided that the University shall not submit to federally funded programs, [redacted]

Medicaid or CHAMPUS, for reimbursement first if submission to such programs is prohibited by law. No financial compensation will be provided by the University and no other type of assistance is available from the University.

What will happen if I do not wish to take part in the study or if I later decide not to stay in the study?
It is your choice whether to take part in the research. You may choose to take part, not to take part or you may change your mind and withdraw from the study at any time.

If you do not want to enter the study or decide to stop taking part, your relationship with the study staff will not change, and you may do so without penalty and without loss of benefits to which you are otherwise entitled.

You may also withdraw your consent for the use of data already collected about you, but you must do this in writing to [redacted] (address provided on page 1).

Any data that has already been sent to [redacted] of Human Research Services at the [redacted] cannot be withdrawn because there may not be any identifiers to link the data with you. We are required by the Food and Drug Administration however, to continue to report anything that relates to the safety of these drugs.

At any time, the study doctor can take you out of this study if it would not be in your best interest to stay in it. Your study doctor can stop treatment even if you are willing to stay in the study.

If you decide to withdraw from the study for any reason, you may be asked to return for at least one additional visit for safety reasons.

Also, you should understand that the Sponsor, in consultation with the study doctor, can withdraw you from the study at any time if you do not follow the instructions related to the study, if you need a different treatment, or if you have a study-related injury.

Who can I call if I have questions?
If you have questions about taking part in this study or if you feel you may have suffered a research related injury, you can call the study doctor:

[redacted]

If you have questions about your rights as a research subject, you can call the IRB Director at [redacted]

[redacted] Authorization) TO USE OR SHARE HEALTH INFORMATION THAT IDENTIFIES YOU FOR A RESEARCH STUDY

The next few paragraphs tell you about how investigators want to use and share identifiable health information from your medical record in this research. Your information will only be used as described here or as allowed or required by law. If you sign this consent form, you agree to let the investigators use your identifiable health information in the research and share it with others as described below. Ask questions if there is something you do not understand.

[redacted]
IRB ID:
Approval Date:
Expiration Date:

What is the purpose of the research and how will my information be used?
You are being invited to take part in this research study, which is described at the beginning of this form. The purpose of collecting and using your health information for this study is to help investigators answer the questions that are being asked in the research.

What information about me will be used?
- All information in your medical record
- Hospital discharge summaries
- Radiology records or images (MRI, CT, PET scans)
- Medical history or treatment
- Physical examinations
- Medications
- Consultations
- Laboratory/diagnostic tests or imaging
- Pathology and operative reports, specimen(s) or slide(s)
- Records related to blood and other tissue samples

Who may use, share or receive my information?
The research team may use or share your information collected or created for this study with the following people and institutions:
- [redacted]

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

Will I be able to review my research record while the research is ongoing?
No. We are not able to share information in the research records with you until the study is over. To ask for this information, please contact the Principal Investigator, the person in charge of this research study.

Do I have to give my permission?
No. You do not have to permit use of your information. But, if you do not give permission, you cannot take part in this study. (Saying no does not stop you from getting medical care or other benefits you are eligible for outside of this study.)

If I say yes now, can I change my mind and take away my permission later?
Yes. You may change your mind and not allow the continued use of your information (and to stop taking part in the study) at any time. If you take away permission, your information will no longer be used or shared in the study, but we will not be able to take back information that has already been used or shared with others. If you say yes now but change your [redacted]

IRB ID: [redacted]
Approval Date:
Expiration Date:

your information in the research, you must write to the researcher and tell him or her of your decision: [redacted] (address provided on page 1).

How long will my permission last?
There is no set date when your permission will end. Your health information may be studied for many years.

AGREEMENT TO PARTICIPATE

1. Subject consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name:_____

Subject Signature:_____ Date:_____

2. Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (printed name):_____

Signature:_____ Date: _____

FOR NON-ENGLISH-SPEAKING SUBJECTS:
Signature of Reader/Translator If the Subject Does Not Read English Well:

The person who has signed the short form, _____, does not read English well. You read English well and are fluent in _____ (name of the language), a language that the subject (his/her parent(s)/legal guardian) understands well. You understand the content of this consent form and you have translated for the subject (his/her parent(s)/legal guardian) the entire content of this form. To the best of your knowledge, the subject (his/her parent(s)/legal guardian) understands the content of this form and has had an opportunity to ask questions regarding the consent form and the study, and these questions have been answered (his/her parent(s)/legal guardian).

Reader/Translator Name: _____

Reader/Translator Signature: _____Date:_____

Witness Name: _____

[redacted]
IRB ID:
Approval Date:
Expiration Date:

Addendum: Request to Store Tissue and/or Health Information for Future Research Use

We ask your permission to store some of your left-over tissue for future research and health information collected about you during the main study [redacted]: A Phase I Trial of Atezolizumab and Varlilumab in Combination with Radiation in Patients with Metastatic Non-small cell lung cancer (NSCLC) for future research. Following are details about our request. Please know that you may still participate in the main study even if you say no to this request to store tissue for future research.
This research involves collection, storage, and analysis of tissue samples. Some of these samples are required for you to take part in this study because the research done on the samples is an important part of the study. You will not get health benefits from any of these studies, but they are an important part of the research. The researchers leading these studies hope the results will help other people with cancer in the future. The researchers will not add the results of the studies to your medical records and you or your study doctor will not know the results.

OPTIONAL STORAGE OF LEFT-OVER SAMPLES FOR FUTURE RESEARCH
Your leftover tissue samples and will be stored in the Cancer Institute of New Jersey Tissue Repository Service (TRS), which is owned and operated by [redacted]. The repository is at [redacted]

The purpose of the repository is to store leftover tissue samples to be used for future research to be conducted by the Principal Investigator and the research staff at [redacted]. The goal of the research is to better understand and develop better means to prevent, diagnose and treat disease. All of the subjects in this study will be asked to allow leftover tissue to be stored and used for future use in the repository. The more samples and health information available in storage, the more useful the repository will be for medical research.

*We use the term "tissue" to refer to specimens such as blood, urine, existing already taken tumor tissue from a previous surgery before entering this study, or tissue taken from a surgery as part of this research study.

We ask your permission to store left over tissue samples collected from you during the two required biopsies for future research. We also ask your permission to collect and store blood for future research. Blood for banking will be collected on (1) day 1 of cycle 1 and, (2) day 1 of cycle 3. Following are details about our request. Please know that you may still participate in the main study even if you say no to this request to store tissue for future research.

Some of the future research may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment. This research follows the Genetic Information Nondiscrimination Act (GINA), a federal law that generally mak[redacted]

health insurance companies, group health plans, and most employers to request the genetic information we get from this research and discriminate against you based on your genetic information.

How and where will your tissue and health information be stored and by whom?

Information obtained from this research with material obtained from your blood or tissue sample(s) will be kept confidential so that neither the investigator nor the Sponsor can link your individual research results with your identity.

Your sample(s), and materials derived from your sample(s), will be given a code number, and only information related to your age, sex, race, health condition and other relevant clinical information collected in the main study will be linked with the sample's code number. Your name, date of birth, address, or other personal identifying information, will not be linked with the sample(s) you give.

How will tissue samples be collected ?

Only the leftover tumor tissue that was collected during the two required tumor biopsies as part of this research study would be stored and used for future research. Blood will also be collected on day 1 of cycle 1 and cycle 3.

You can still be in the study whether or not you allow leftover samples to be used for future research.

1. My leftover blood and tissue may be stored in a Biobank for use in future unspecified cancer related research. Medical information related to the sample may also be collected.

☐ Yes _____ (subject's initials)

☐ No _____ (subject's initials)

OPTIONAL SAMPLE BANKING FOR FUTURE RESEARCH STUDIES:

A fresh sample of tumor tissue (biopsy) will be collected prior to starting treatment in trial and a second sample will be collected after cycle 2. Researchers will use the tissue samples to study biomarkers. Biomarkers are tests that identify, predict, or characterize your cancer. Some examples of cancer biomarkers are CEA test for colon cancer, PSA test for prostate cancer and HER-2 or BRCA 1/2 tests for breast cancer.

- Part of the tissue sample will be used to measure the amount of PD-L1 in the tumor.
- Part of the tissue sample will be used to measure how much, and where your tumor expresses immune biomarkers

These types of samples are called correlative samples. These laboratory tests are new and under development. There is a risk of possible loss of confidentiality. Your privacy is very important and the researchers will make every effort to protect it. Study staff will identify your correlative sample results by a unique code. Researchers will keep the list that links the code to your name separate from your sample and health information.

WHAT IS INVOLVED IN SAMPLE BANKING?

If you agree to take part, here is what will happen next:

1. Your study doctor will send a sample from the tissue that was collected at the time of each biopsy to the biorepository.
2. Your study doctor will send blood samples collected on day 1 of cycle 1 and cycle 3 to the biorepository.
3. The [redacted] biorepository will store your sample and some related health information may be stored in the biorepository, along with samples and information from other people who take part in this sample collection. The biorepository will store the samples until they are used up by the study researchers.
4. Neither the biorepository or the study researchers who use the samples will notify you or your study doctor when research is conducted or give reports or other information about any research that is done using your banked samples.

What are the possible risks of sample banking?

1. The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2. There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3. In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small but cannot promise that they will not occur.

<u>Economic Risks of Harm</u>

Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Therefore, your genetic information potentially could be used in ways that could cause you or your family economic distress.

There are state and federal laws that protect against genetic discrimination:
There is a federal law call the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways: (1) health insurance companies and group health plans may not request your genetic information that we get from this research; (2) health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums; and (3) employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

How will information about me in the biorepository be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When the biorepository sends your sample(s) to the researchers, it will not send information identifying you (such as your name, address, phone number or other personal identifying information). The biorepository will identify the samples by a unique code only.
2) Your study doctor will keep the list that links the unique code to your name. The list will be kept separate from your sample and health information. Any staff with access to the list must agree to keep your identity confidential.
3) Researchers who receive your sample(s) and information will not know who you are. They must also agree that they will not try to find out who you are.
4) The biorepository staff will not give information that identifies you to anyone, unless required by law.
5) If researchers publish results, they will not use your name or other personal information.

What are the possible benefits of sample banking?

You will not benefit personally from providing samples for this tissue bank because research usually takes a long time to produce meaningful results. However, your participation may help investigators understand, prevent, or treat the diseases and conditions studied in the future.

Is there other important information to consider?

Yes. There is no cost to you to allow us to store and use your tissue and information for future research. Nor will you be paid to participate in this repository. Should any products or services result from research using your samples and information, there is no plan to share any of the profits with you.

The research we are doing is only a stepping stone in understanding disease. It may take a long time for our research to produce useful health-related information. Therefore, tests done for our research using your samples and information will not be useful in directing your medical care. Information from our research will not be returned to you, your family members, your doctor, or outside parties. It is possible, however, that members of regulatory authorities, such as the U.S. Food and Drug Administration, [redacted]al Review Board, or other persons required by law may be allowed to look at this information.

Are there any costs or payments for sample banking?

There is no cost to you to allow us to store and use your tissue and information for future research. Nor will you be paid to participate in this repository. Should any products or services result from research using your samples and information, there is no plan to share any of the profits with you.

What are your rights if you agree to the storage and use of your tissue for future research?

You understand that you have the right to ask questions about any part of the future study at any time. You understand that you should not sign this form unless you have had a chance to ask questions and have been given answers to all of your questions.

Your participation in this part of the study is voluntary. You do not have to particip[redacted]te. If you do, you can change your mind at any time.

IRB ID: [redacted]
Approval Date:
Expiration Date:

Authorization to use your health information for future research purposes
Because information about you and your health is personal and private, it generally cannot be used in this future research studies without your written authorization (permission). If you sign this addendum consent below, it will provide that authorization.

Making your choice:
My blood and related information may be collected and stored in the biorepository for use in future health cancer-related research.

Yes _____ (subject's initials)

No _____ (subject's initials)

My tumor tissue samples and related information may be kept in the biorepository for use in future cancer-related research.

Yes _____ (subject's initials)

No _____ (subject's initials)

What if I change my mind about banking my samples?
If you wish to take part in the [redacted]) and tell him/her to destroy any remaining tissue samples and data of yours that are currently being stored in the repository.

However, please note that it may not be possible to destroy samples, information and data created from your samples that may have already been used in research studies prior to your request. The [redacted]

What if I have more questions about sample banking?
If you have questions about the use of your samples for research, contact the study doctor, [redacted]

Authorization to use your health information for future research purposes
Because information about you and your health is personal and private, it generally cannot be used in this future research studies without your written authorization (permission). If you sign this addendum consent form, it will provide that authorization. The details of what information we will collect and how we will use it are discussed in the main consent under the heading, "AUTHORIZATION TO USE YOUR HEALTH INFORMATION FOR RESEARCH PURPOSES" near the end of the main consent document.
Thank you for considering participation in this research.

This is the end of the section about additional studies.

AGREEMENT TO PARTICIPATE

1. Subject consent:

I have read this entire consent form, or it has been read to me, and I believe that I understand what has been discussed. All of my questions about this form and this study have been answered. I agree to take part in this study.

Subject Name:_____

Subject Signature:_____ Date:_____

2. Signature of Investigator/Individual Obtaining Consent:

To the best of my ability, I have explained and discussed all the important details about the study including all of the information contained in this consent form.

Investigator/Person Obtaining Consent (printed name):_____

Signature:_____ Date: _____

FOR NON-ENGLISH-SPEAKING SUBJECTS:
Signature of Reader/Translator If the Subject Does Not Read English Well:

The person who has signed the short form, _____, does not read English well. You read English well and are fluent in _____ (name of the language), a language that the subject (his/her parent(s)/legal guardian) understands well. You understand the content of this consent form and you have translated for the subject (his/her parent(s)/legal guardian) the entire content of this form. To the best of your knowledge, the subject (his/her parent(s)/legal guardian) understands the content of this form and has had an opportunity to ask questions regarding the consent form and the study, and these questions have been answered (his/her parent(s)/legal guardian).

Reader/Translator Name: _____

Reader/Translator Signature: _____Date: _____

Witness Name: _____