Protocol Title: A Phase II Trial of Abemaciclib with or without Atezolizumab in Metastatic Castration Resistant Prostate Cancer

Sponsor Protocol Number: 20-701

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Main Consent

INTRODUCTION AND KEY INFORMATION

All research is voluntary. It is your choice whether you take part in this research or not. If you decide to participate, please sign and date at the end of this form. We will give you a copy and you can refer to this consent form at any time.

The following is a short summary of this research study to help you decide whether you would like to be a part of this study. More detailed information is provided later in this form.

For purposes of this research, you will be referred to as a "participant."

1. Why am I being invited to take part in a research study?

You are invited to take part in in this research study because you have prostate cancer that has spread to other parts of your body and is no longer responding to standard hormonal drugs (i.e. "metastatic castration-resistant prostate cancer"), and your doctor does not believe you are more appropriate for treatment with a chemotherapy drug known as a taxane (docetaxel or cabazitaxel).

2. Why is this research being done?

This trial is testing whether a molecularly targeted chemotherapy drug called abemaciclib and an immunotherapy drug called atezolizumab are effective in shrinking or preventing the growth of metastatic prostate cancer. In addition, the trial tested the safety of the combination of the two drugs, but the combination is no longer being studied.

3. Who is supporting this research?

Eli Lilly and Company is supporting this research study by providing funding for research and the study drug abemaciclib. Genentech, Inc. is supporting the study by providing the study drug atezolizumab.

4. What does this research study involve and how long will it last?

The names of the study drugs involved in this study are:

- Abemaciclib
- Atezolizumab

This study will test the safety and effectiveness of the investigational study treatments of abemaciclib and atezolizumab in patients with metastatic prostate cancer. In other words – does it work against your type of cancer, and do the benefits outweigh the risks and side effects. The effectiveness is determined by seeing how many subjects who receive the study drug(s) respond to the treatment (that is, experience a decrease in levels of the tumor marker PSA measured in the blood, or shrinkage of tumors on imaging studies) and in how many subjects the cancer does not get worse on imaging studies by 6 months of therapy. Your health-related information along with samples of your blood and tissue will be collected for this research study.

The research study procedures include screening for eligibility and study treatment including evaluations and follow up visits.

You will receive study treatment for as long as you do not have serious side effects and your disease does not get worse. You will be followed after completion of study treatment for up to 24 months.

It is expected that about 56 people will take part in this research study.

Information about you and your health is personal and private. Generally, it cannot be obtained without your written permission. By signing this form, you are providing that permission and your information may be obtained and used in accordance with this informed consent and as required or allowed by law. This means that researchers may obtain information regarding your past medical history, as well as specimens and samples from previous health care providers such as hospitals and labs.

5. What are the risks to participating in this study?

There are risks to taking part in any research study. We want to make sure you know about a few key risks right now. There may also be rare, serious and potentially life-threatening side effects. More detailed information is provided in the "What are the risks or discomforts of the research study?" section.

There is a risk that you could have side effects from abemaciclib or atezolizumab. These side effects may be worse and may be different than you would get with other approaches for your cancer.

Some of the most common side effects of abemaciclib and atezolizumab that the study doctors know about are:

- Diarrhea, nausea, vomiting, decreased appetite, stomach area pain
- Fatigue
- Fevers, infections
- Low white blood cell count, which may increase the risk of serious infections
- Low number of red blood cells, which may cause fatigue
- Low number of platelets in the blood, which may increase risk of bleeding or bruising
- Hair loss
- Headache

6. Will being in this study benefit me in any way?

We do not know if taking part in this study will benefit you. This study may help researchers learn information that could help people in the future.

7. What are my options?

Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment for metastatic castration-resistant prostate cancer. While your doctor feels that you are not more appropriate for a type of chemotherapy drug called a "taxane", some participants in this study may also be candidates for FDA-approved therapies including an immune therapy called sipuleucel-T, a radiation therapy called Radium-223, a chemotherapy drug called mitoxantrone, or a different hormonal drug (abiraterone or enzalutamide) than they have previously received. Participants with specific gene mutations detected in their blood or in their cancer may be candidates for FDA-approved drugs called PARP inhibitors (olaparib or rucaparib) or an immune therapy drug called pembrolizumab.

- Decide not to participate in this research study
- Participate in another research study if one is available.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions at any time.

A. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of an investigational drug regimen to learn whether the combination works in treating a specific disease. "Investigational" means that the drugs being studied have not been approved by the U.S. Food and Drug Administration (FDA) for use in prostate cancer. Abemaciclib has been approved for use in breast cancer, and atezolizumab has been approved for use in lung cancer, bladder cancer, breast cancer, liver cancer and melanoma.

Abemaciclib is an orally administered molecularly targeted chemotherapy drug called a cyclin-dependent kinase inhibitor, which acts to block the ability of cancer cells to divide and thus prevents tumors from growing. In the laboratory setting, this drug is effective in prostate cancer models that have become resistant to standard hormonal treatments, and this drug is currently being studied for its effectiveness in prostate cancer in other clinical trials. Atezolizumab is an intravenously administered drug called an immune checkpoint inhibitor, which acts to activate the immune system to kill cancer cells. Atezolizumab is ineffective on its own in most patients with prostate cancer, but may be effective in certain subsets of patients and is being tested in combination with other drugs for prostate cancer in other clinical trials. Multiple research groups have demonstrated in laboratory model systems that abemaciclib can may make immune checkpoint inhibitors more effective. The purpose of this study is to test whether the drugs abemaciclib and atezolizumab are effective in shrinking or preventing the growth of metastatic prostate cancer. In addition, the trial tested the safety of the combination of the two drugs, but the combination is no longer being studied.

Previous studies have demonstrated that patients with prostate cancers that have mutations in genes involved in a form of repairing DNA damage in their cancer cells, called mismatch repair, can experience shrinkage of their cancer with immune checkpoint inhibitors. CDK12 is a protein involved in other forms of DNA damage repair (other than mismatch repair), and there is some evidence from prior studies that cancers with mutations in the *CDK12* gene can also shrink in response to immune checkpoint inhibitors. We are thus testing in study participants whose tumors are known to have mutations in *CDK12* whether atezolizumab is an effective treatment strategy. There are other studies that have demonstrated that cancers with mutations in the *CDK12* gene often have other genetic changes that may lead them to be sensitive to cyclin dependent kinase inhibitors, so we are also testing whether abemaciclib is effective in these patients.

Another purpose of this study is for researchers to learn if a biomarker test is helpful to decide which participants are likely to respond to abemaciclib oratezolizumab. A biomarker is a measurable substance that is known to be associated with a certain condition and can indirectly show how well a specific drug regimen is working. Tumor tissue obtained through a biopsy or surgical procedure prior to your treatment on trial ("archival tissue") and a biopsy of a metastatic tumor while you are receiving trial therapy will be used for the biomarker test. In addition, blood tests will be taken for research studies at certain intervals before, during and after your drug dosing on trial. Researchers do not know if using the biomarker test is better, the same, or worse than if treatments were chosen without using the biomarker test.

B. WHAT IS INVOLVED IN THE RESEARCH STUDY?

The study design divides study participants into two separate cohorts. The first cohort is a set of subjects whose tumors are not known to have mutations in the *CDK12* gene (the "biomarker unselected cohort") – either because tumor tissue never underwent genetic profiling, or because genetic profiling was performed but did not demonstrate a mutation in the *CDK12* gene.

If you are in the biomarker unselected cohort, you will be placed in the following group:

Arm A: Abemaciclib orally twice daily every day

The second cohort of participants in a set of subjects whose tumors are known to have mutations in the *CDK12* gene based on genetic profiling of the tumor that occurred prior to enrollment on this study. Participants in this cohort are not randomized, but are assigned to their investigational study treatment based on

how many participants in this cohort previously received study treatment as follows:

Arm C: Participants 1-5: Atezolizumab 1200 mg through a port or vein in your arm (intravenously) on Day 1 of each 21-Day cycle

Participants 6-21: Abemaciclib orally twice daily every day

Before the research starts (screening):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Clinical exam**: During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking. Your height and weight will also be measured.
- **Vital Signs**, including body temperature, blood pressure, pulse and respiratory rate
- **An assessment of your tumor** by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) and/or Bone scan
- **Routine blood tests,** including baseline tests so that we can measure any additional effect of the study drug and disease status and measure levels of the tumor marker PSA in your blood.
- **Pulmonary (lung) function tests**

If these tests show that you are eligible to participate in the research study, you may begin the study treatment. If you do not meet the eligibility criteria, you will not be able to participate in this research study.

Additional research procedures to be performed at the time of screening but not required to determine eligibility:

- **Research blood tests (approximately 2 teaspoons)** for biomarker studies
- **Your previously collected and stored tissue (archival tissue) will be obtained for tests**. No additional tissue will be collected.
- **Biobanking:** Biological specimens (blood and tissue) will be collected and shared with an outside lab or collaborator for analysis. The specimens will be anonymized but identifiable through your study ID number. The study ID can only be linked to your medical record through a key stored on a secure server accessible only by the study team. The specimens will be banked for future use.
- **Data Collection:** Data will be collected and shared with an outside collaborator for analysis. The data will be anonymized but identifiable through your study ID number. The data will be banked for future use.

Study Treatment Overview: Each study treatment cycle lasts 21 days

- **Oral Study Drug (abemaciclib):** All participants (except for the first 5 participants in Arm C) will take the oral study drug twice daily.
- **Infused Study Drug (atezolizumab):** Participants 1-5 in Arm C will be given the infused study treatment once every 21 days into your vein (by intravenous infusion) over about 60 minutes.
- **Pre-medications:** You may be pre-medicated with drugs to reduce the chance of having a sensitivity reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor.

If you take part in this research study you will be given a drug diary. You will be asked to document information in the drug diary about the study treatment you are being asked to take.

Study Visit: Day 1 of each cycle

This visit will involve the following:

- **Oral Study Drug**: Abemaciclib dispensation, diary review & reconciliation (all participants, except for the first 5 participants in Arm C)
- **Infused Study Drug:** Atezolizumab administration (Participants 1-5 in Arm C)
- **Pre-medications**
- **Clinical Exams:** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions

about any problems that you might be having and any medications you may be taking.
- **Performance status**
- **Routine Blood tests** for safety monitoring and PSA
- **Data Collection**

Study Visit: Cycle 1 day 1, Cycle 6 day 1, Cycle 9 day 1, and Cycle 12 day 1

This visit will involve the following:
- **Oral Study Drug**
- **Infused Study Drug**
- **Pre-medications**
- **Clinical Exams**
- **Performance status**
- **Routine blood tests** for safety monitoring and PSA
- **Research blood tests (approximately 6 teaspoons)** for biomarker studies
- **Biobanking**
- **Data Collection**

Study Visit: Cycle 3 day 1

This visit will involve the following:
- **Oral Study Drug**
- **Infused Study Drug**
- **Pre-medications**
- **Clinical Exams**
- **Performance status**
- **Routine blood tests** for safety monitoring and PSA
- **Research blood tests (approximately 6 teaspoons)** for biomarker studies
- **Tumor biopsy:** Around the time of this visit you will undergo biopsy of a metastatic tumor. An interventional radiologist will review images from your pre-treatment imaging studies to find a suitable site for image-guided biopsy. This is an outpatient procedure requiring local anesthesia and conscious sedation. Informed consent for this procedure will be obtained by the interventional radiology team, and you will be informed on the length of time you will need to hold aspirin, ibuprofen/naproxen, or blood thinners prior to the procedure.
- **Biobanking**
- **Data Collection**

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Study Visit: Cycle 4 day 1

This visit will involve the following:

- **Oral Study Drug**
- **Infused Study Drug**
- **Pre-medications**
- **Clinical Exams**
- **Performance status**
- **Routine blood tests** for safety monitoring and PSA
- **Data Collection**
- **Scans (or Imaging tests):** An assessment of your tumor by one or more of the following standard assessment tools: X-ray, CT (Computerized Tomography) scan, MRI (Magnetic Resonance Imaging) or Bone scan
- **Pulmonary (lung) function testing:** Around the time of this visit (about 3 months after starting on trial therapy) you will undergo repeat lung function testing to see if there is any evidence that the study drugs are leading to inflammation of your lungs (called pneumonitis).

Study Visit: Cycle 7 day 1, Cycle 10 day 1 and every 3 cycles thereafter

This visit will involve the following:

- **Oral Study Drug**
- **Infused Study Drug**
- **Pre-medications**
- **Clinical Exams**
- **Performance status**
- **Routine blood tests** for safety monitoring and PSA
- **Data Collection**
- **Scans (or Imaging tests)**

Study Visit: End of Treatment (EOT)

This visit will involve the following:

- **Clinical Exams**
- **Performance status**
- **Routine blood tests** for safety monitoring and PSA
- **Research blood tests (approximately 6 teaspoons)** for biomarker studies
- **Biobanking**
- **Data Collection**

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Research Study Plan:

Procedures	Screening	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Cycle 5+ Day 1	EOT	Follow -Up
Physical Exam, Vital Signs	X	X	X	X	X	X	X	
Toxicity Assessment	X	X	X	X	X	X	X	X
Routine blood draw	X	X	X	X	X	X	X	
PSA	X	X	X	X	X	X	X	
Tumor scans (every 3 cycles)	X				X	X		X
Pulmonary function test (Screening and after 3 months)	X				X			
Research blood (Screening, Cycle 1 day 1, Cycle 3 day 1, Cycle 6 day 1, Cycle 9 day 1, Cycle 12 day 1, EOT)	X	X		X		X	X	
Archival Tumor Tissue	X							
On-treatment Tumor Biopsy				X				
Abemaciclib (Dispensation, Diary Review & Reconciliation)		X	X	X	X	X	X	
Atezolizumab Administration		X	X	X	X	X		
Survival Status								X

Planned Follow-up:

We would like to keep track of your medical condition. If you stop the study intervention for any reason you will be asked to return for an end of treatment visit within 30 days of your last dose of the study intervention.

After you complete the end of treatment visit you will have an office visit or be contacted by a member of the study team every 3 months for up to 24 months. Keeping in touch with you and checking your condition helps us look at the long-term effects of the research study.

In addition, you can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from the study.

C. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**
Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function, particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug(s) taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take. There may also be some foods that you should avoid while on this research study and your research doctor will review this information with you.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

Risks Associated with Abemaciclib

Likely (More than a 50% chance that this will happen)

- Loose stools (diarrhea)
- Lack of energy (fatigue)
- Feeling sick to the stomach with a sense of wanting to throw up (nausea)

Frequent (Between a 11-50% chance that this will happen)

- Low appetite (decreased appetite)
- Decreased number of white blood cell count in the blood (neutropenia; leukopenia); this may make infections more likely to occur. Symptoms of infection may include:
    i. Fever
    ii. Pain
    iii. Redness
- Difficulty breathing
- Being sick to the stomach (vomiting)
- Low red blood cell count in the blood that may make you feel more tired (anemia)
- Decreased number of platelets in the blood (thrombocytopenia); this may cause
    i. Bruising
    ii. Difficulty with clotting of blood
    iii. Bleeding easily
- Dry mouth
- Inflammation or ulcers inside the mouth (stomatitis)
- Taste changes or bad taste in the mouth (dysgeusia)
- Hair loss (alopecia)

Occasional (Between a 1-10% chance that this will happen)

• Decreased number of lymphocytes in the blood (lymphocytopenia); this may make infections more likely to occur

• Inflammation of the lungs causing coughing and difficulty breathing (interstitial lung disease/pneumonitis)

Rare (Less than a 1% chance that this will happen)

• Fever with decreased number of white blood cells in the blood (neutropenia) has been reported in less than 1% of patients exposed to abemaciclib across trials. This can lead to severe generalized infection (sepsis) with side effects involving several organs in your body (for example, liver, kidney, lungs, and bone marrow), causing a serious condition, which could lead to hospitalization, life-threatening

circumstances, or even death. Two deaths due to neutropenic sepsis were observed in a study of abemaciclib called MONARCH 2.

Very often, increases in creatinine levels, a substance in the blood that measures kidney function, were noted by laboratory testing. While abemaciclib does not decrease kidney function, creatinine increases may indicate the need for other tests of kidney function.

Risks Associated with Atezolizumab

Atezolizumab is designed to increase the number of immune system cells in your body that can fight cancer. These cells may cause inflammation within the tumor, as well as in normal tissue (immune-related side effects). Therefore, by taking atezolizumab, you may develop a condition where there is inflammation against a part of your own body (an autoimmune condition).

Common (More than a 10% chance that this will happen)

- Fatigue
- Joint pain (arthralgia)
- Weakness
- Decreased appetite
- Diarrhea
- Shortness of breath (dyspnea)
- Urinary tract infection
- Cough
- Itching of the skin
- Nausea
- Fever
- Rash
- Vomiting
- Muscle and bone pain (myalgia, musculoskeletal pain, and bone pain)
- Loose stools (diarrhea)

Less Common (Between a 1-10% chance that this will happen)

- Chills
- Difficult swallowing (dysphagia)
- Inflammation of the liver. May cause you to feel not hungry, tired, have a mild fever, muscle or joint aches, nausea and vomiting and stomach pain.
- Allergic reaction or intolerance to medication (hypersensitivity). Symptoms could include nausea, vomiting, skin reactions (hives or

rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability.
- Low levels of potassium in the blood which can cause an abnormal heart rate. This could cause an irregular heartbeat, which can be serious and life threatening.
- Decreased level of sodium in the blood (hyponatremia), which can cause confusion, seizures, fatigue and low levels of consciousness.
- Low blood pressure (hypotension), which may cause dizziness, lightheadedness, or fainting.
- Underactive thyroid gland (hypothyroidism), which may cause fatigue, weight gain, fluid retention, sensitivity to cold, hair loss, headache, change in mood and mental apathy. Can be serious or life threatening.
- Nasal congestion
- Inflammation of the intestines (colitis). Symptoms may include diarrhea, blood in stool, and pain in stomach area.
- Decreased oxygen supply in the body, resulting in shortness of breath, confusion, or drowsiness (hypoxia)
- Flu-like symptoms
- Infusion-related reactions (events occurring during or within 1 day of infusion), including dizziness or fainting (low blood pressure), sudden reddening of the face, neck or chest, (flushing), rash, fever, chills, shortness of breath or feeling sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.
- Inflammation of the lungs (pneumonitis), which may can cause shortness of breath and difficulty breathing. Symptoms may also include new or worsening cough and chest pain. If severe, this can be life threatening.
- Decreased platelet counts in the blood (thrombocytopenia), which increases the risk of bleeding and bruising or makes bleeding more difficult to stop. Bleeding may be serious or life threatening and may require a blood transfusion.
- Inflammation of the liver (hepatitis). Symptoms may include yellowing of skin, pain in stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin, and dark urine.
- Stomach area pain

Rare but potentially serious (Less than a 1% chance that this will happen)
- Decreased production of hormones by the adrenal glands, which are glands located above the kidneys. This may cause weakness and/or low blood pressure (adrenal insufficiency). Symptoms may include

dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods.

- Diabetes
- Overactive thyroid gland (hyperthyroidism). May cause weight loss, rapid heartbeat, sweating, trouble with heat, nervousness, change in mood. May require medical intervention to resolve symptoms.
- Inflammation of the brain and the thin tissue surrounding the brain and spinal cord (meningoencephalitis). Symptoms include headache, fever, chills, neck stiffness, sensitivity to light, vomiting, seizures, trouble thinking clearly, personality changes, irritability, unusual behavior and/or unconsciousness. This infection may become life-threatening and in severe cases cause long-term brain damage including trouble thinking, controlling movement, hearing, seeing, or speaking. This infection is usually treated with IV anti-viral medications but in severe cases long-term care and medications would be needed.
- Inflammation of the pituitary gland (hypophysitis). Symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision. Side effects that may occur at the same time include hypothyroidism and adrenal insufficiency (see above for details).
- Inflammation of the heart muscle (myocarditis). Symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of ankles or legs, irregular heartbeat and fainting.
- Inflammation of the lining of the heart (pericarditis). Symptoms may include chest pain, shortness of breath, decreased exercise tolerance, fatigue, cough, fever, swelling of ankles or legs, swelling of the belly (abdomen) and irregular heartbeat.
- Inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure of the kidneys.
- A disorder called Guillain-Barré syndrome in which the body's immune system attacks part of the peripheral nervous system. Symptoms of this disorder include varying degrees of weakness, fatigue or tingling sensations in the toes and legs with difficulty walking. In many instances, the weakness and abnormal sensations spread to the fingers, arms and upper body. These symptoms can increase in intensity until certain muscles cannot be used at all and, when severe, the subject is almost totally paralyzed. In these cases, the disorder is life threatening, potentially interfering with breathing and, at times, with blood pressure or heart rate.
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis). Symptoms may include weakness in the

arm and leg muscles, double vision, and difficulties with speech and chewing.
- Inflammation of the pancreas (pancreatitis). Symptoms may include abdominal pain, nausea, vomiting, and fever.
- Increase in pancreatic enzymes, which may indicate inflammation of the pancreas (increase in amylase and lipase)
- Severe high levels of sugar and acids in the blood or urine (diabetic ketoacidosis).
- Inflammation or damage of the muscles (myositis, myopathies including rhabdomyolysis). Symptoms may include muscle pain and weakness, urine with a dark brown or reddish color, nausea, and vomiting.
- Severe inflammation or damage of the skin (severe cutaneous adverse reactions) including disorders called erythema multiforme, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or drug rash with eosinophilia and systemic symptoms (DRESS). Symptoms may include skin rash, itching, redness, pain, and peeling of skin and mucosal membranes that can increase risk of severe infections.

Allergic Reactions
Allergic reactions may occur with atezolizumab in rare instances and typically occur while it is being given into your vein or shortly after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability. If you experience any of these symptoms, your study doctor will interrupt, or even stop, the delivery of atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

Side Effects Potentially Associated with Atezolizumab
The following are side effects that may be associated with atezolizumab:
- Development of antibodies to atezolizumab (proteins made in the body that respond to a substance that is foreign to the body) by your immune system. If you develop these special antibodies, it may affect your body's ability to respond to atezolizumab in the future.
- Potential to cause harm to a developing fetus
- Inflammation of the eye (uveitis). Symptoms may include eye pain and redness, vision problems, and blurry vision.
- Inflammation of the blood vessels that can lead to damage of different organs (vasculitis); symptoms may include fever, fatigue, weight loss,

weakness, general aches and pains, rash, headache, lightheadedness, shortness of breath, and numbness.
- Breakdown of red blood cells (autoimmune hemolytic anemia); symptoms may include fatigue, fever, lightheadedness, paleness of the skin, yellowing of the skin and/or eyes, weakness, and inability to do physical activity.
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptoms may include severe skin or mucosal blistering, shedding, scaling, and death of the skin or mucosa.

Systemic Immune Activation

In rare situations, when atezolizumab is combined with another drug that also increases your body's immune response (immune-modulating drugs), a more than-normal (excessive) immune response can occur. Like other immune-mediated conditions, excessive systemic immune activation can cause side effects related to severe inflammation and/or generalized infection (sepsis) that may involve several organs in your body (for example, liver, kidney, lungs, and bone marrow), causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Abemaciclib may be an immune-modulating drug that when combined with atezolizumab could increase the risk of sepsis resulting in death, so the combination of atezolizumab with abemaciclib is no longer being studied. Symptoms of systemic immune activation may include:

- Very low blood pressure that does not respond to standard treatment, including fluids given through the veins
- High-grade fever (more than 38.5° Celsius or 101.3° Fahrenheit)
- Cough
- Severe shortness of breath (respiratory distress) requiring oxygen therapy and/or mechanical help (intubation)
- Severe dizziness
- Confusion
- Weakness
- Decreased urination with failure of the kidneys (renal failure)
- Significantly high levels of liver enzymes (liver failure)
- Very low blood cell counts
- Bleeding within the organs.

If you experience any of these symptoms, you should notify your doctor immediately, as you may need immediate treatment and hospitalization. Your study doctor may give you drugs to treat these symptoms.

Vaccinations
You should also talk to your study doctor about any vaccinations you have had recently. Talk to your study doctor before you get any vaccinations or start any new drug or treatment. You should not receive live vaccines (e.g., influenza, measles, mumps, rubella, varicella, etc.) or be in close contact with people who have received live vaccines while you are taking atezolizumab to reduce the risk of infection from the vaccine.

Risks Associated with Biopsies:
Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

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.

Radiation Risks Associated with Scans:

While you are in this research study, CT scans, MRI scans, Bone Scans, and/or other scans utilizing radioactivity may be used to evaluate your disease.

In the long term, over many years, there is a very low risk of developing a new cancer as a result of the radiological evaluation and treatment for your cancer.

Risks Associated with MRI Scans:
When having an MRI (Magnetic Resonance Imaging) scan, you will lie still on a table that slides into a tunnel slightly wider than your body. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow cylinder. If you feel uncomfortable in confined spaces, please tell your research doctor. Your doctor may give you a medication to make you feel more comfortable. As images are taken, a loud banging noise will be produced. Earplugs or headphones will be available if needed. The MRI can be stopped at any time at your request, but the scan may not be complete.

Risks Associated with Contrast Agents Used During Scans:
There is a small risk with using a contrast agent that is injected into a vein during the MRI or CT scan. The contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.

Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.

Reproductive Risks:
The study drugs can affect your reproductive system, resulting in sperm production becoming irregular or stopping permanently. In addition, you may experience erectile dysfunction or a decreased desire for sex during treatment. Talk to your study doctor about options for treating erectile dysfunction. You may want to consider sperm banking if you may wish to have a child in the future. Discuss these options with your study doctor. You should not donate sperm or semen while taking the study drugs. Exposure of an unborn child to these medications could cause birth defects; therefore, you should not father a child while on these medications.

It is important that you understand that you need to use birth control from the time you sign this consent and continuing throughout the course of treatment and for at least 150 days after atezolizumab or 21 days after abemaciclib, whichever is later, is discontinued.

We can provide counseling about preventing pregnancy for either male or female study participants. Let your doctor know immediately if you become pregnant or find out that you are going to be the father of a child.

If your partner becomes pregnant while you are on the study, it may be critical to share information regarding your participation in this research study with that person. Your research doctor should also be told if this happens.

Risks of Tissue Collection for Biobanking:

Generally, hospitals will keep some of your tissue. There is a small risk that when this tissue is collected and the sample is submitted to the biobank, your tissue could be used up and unavailable for use in the future.

Non-Physical Risks:
Because of side effects or the time required for tests and clinic visits while you are on this research study, you may be unable to keep up with your normal daily activities.

The questionnaires used in this study may be upsetting. If you find the questionnaires upsetting, you may speak with the research doctor or ask to be referred for additional emotional support.

D. WHAT WILL HAPPEN IF I AM REMOVED FROM THE STUDY OR DECIDE TO END MY PARTICIPATION IN THE RESEARCH?

You may be taken off the research study for any reason including:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- There is any problem with following study treatments and procedures
- Your condition worsens
- A decision is made to end the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

You can also choose to stop participating in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

It is important to tell the research doctor if you are thinking about stopping so your research doctor can evaluate the risks from stopping the study drugs.

In some cases, the abrupt stopping of a drug can have risks in itself. Another reason to tell your research doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

It is important to note that although you may withdraw from study participation, the FDA requires that any information collected up to the point of your withdrawal cannot be removed from study records. Additionally, the research doctor may consult public records after you have withdrawn from the study.

If you have agreed to allow your tissue and blood specimens to be kept for future research with identifying information that could link your sample to you, you may withdraw your permission at any time. We ask that you contact your study doctor and let them know you are withdrawing your permission for your identifiable blood and tissue specimens to be used for future research.

E. WHAT ARE THE BENEFITS OF THIS RESEARCH STUDY?

You may not receive any direct personal benefits from being in this study. Some of the possible benefits to you as a participant in this study are that your cancer may respond favorably to the investigational study treatment, improvement in the quality of your life, and/or prolonged life. Others may benefit from the knowledge gained from this study.

F. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

You will not be paid for participating in this study.

We may use your samples and information to develop a new product or medical test to be sold. The sponsor and hospital may benefit if this happens. There are no plans to pay you if your samples are used for this purpose.

G. WHAT ARE YOUR COSTS?

Taking part in this research study may lead to added costs to you or your insurance company. This may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your disease. You may:

- Have more travel costs
- Need to take more time off work
- Have other additional personal costs

You will not be charged for research related assessments and study drugs.

It is possible that study drugs may not continue to be supplied free for some reason. If this would occur, your research doctor will talk with you about your options.

You or your insurance company will be charged for portions of your care during this research study that are considered standard care, such as office visits as well as laboratory and imaging assessments. Standard of care is the care that

you would receive regardless of whether you were enrolled in the study or not. You may be responsible for co-payments, co-insurance, premiums and deductibles that are typical for your insurance coverage. This includes the cost of tests, procedures, or medicines to manage any side effects. The pulmonary (lung) function testing performed prior to starting on study and at 3 months on study treatment), as well as the tumor biopsy are done for research only and are performed at no charge.

If you have questions about your insurance coverage, or the items you might be required to pay for, please call financial services for information. The contact information for financial services are:

- Dana-Farber Cancer Institute: (617) 632-3455
- Beth Israel Deaconess Medical Center: (617) 667-5661

The National Cancer Institute provides an online resource to help people participating in cancer clinical trials understand which services their insurance company is required by law to pay. This can be found at the website below or can be provided by the study team:

www.cancer.gov
or 1-800-4-CANCER (1-800-422-6237)

H. WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments may be billed to you or your insurance company. You will be responsible for deductibles, co-payments and co-insurance. There are no plans to pay you or give you other compensation for the injury.

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

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of

birth, gender, social security number or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in this research. If possible, you should give them a copy of this consent form.

I. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

Dana-Farber Cancer Institute:
- Atish Choudhury, MD, PhD at 617-632-6328

Beth Israel Deaconess Medical Center:
- David J. Einstein, MD: (617) 667-2100

24-hour contact:
- Dana-Farber Cancer Institute: Atish Choudhury, MD, PhD at 617-632-6328 or page at (617) 632-3352 beeper 41868.
- Beth Israel Deaconess Medical Center: Please call the page operator at 617-667-4700 and ask for Dr. David Einstein, MD to be paged.

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt under pressure to enroll in this research study or to continue to participate in this research study.

J. RETURN OF RESEARCH RESULTS

Tests done on samples in this research study are only for research and have no clear meaning for your health care. For this reason, your study doctor will not share the results with you.

K. CLINICALTRIALS.GOV (CT.GOV)

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.

L. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. Any personal identifiers will be removed before they are shared, and identifiable only through your study ID number. The study ID can only be linked to your medical record through a key stored on a secure server accessible only by the study team.

Investigators, including investigators from collaborating institutions, can request this data and samples for new research. Samples and data may also be shared with outside non-profit academic investigators as well as with for-profit pharmaceutical investigators or commercial entities, with whom we collaborate.

You will not be asked to provide additional informed consent for the use of your anonymized information or samples in future research.

Future research studies may include genetic research. Your genes are unique to you. At this time, you cannot be identified through this research, if the samples and specimens are anonymized. There is a risk that you might be reidentified in the future as genetic research progresses.

M. CONFIDENTIALITY

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee complete confidentiality of study data.

Medical information created by this research study may become part of your hospital medical record and may be forwarded to your primary doctor. Information that does not become part of your medical record will be stored in your study file. It may also become part of a research database.

Participation in this study involves providing a specimen of your tissue; please know that if the research doctor leaves the institution, the research and the tissue might remain at the research doctor's current institute or might be transferred to another institution.

The study team plans to publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

Your anonymized specimens or genetic data may also be placed into one or more publicly-accessible scientific databases. Through such databases, researchers from around the world will have access to anonymized samples or data for future research.

There is a risk that anonymized research data that is shared with outside collaborators may be reidentified. When anonymized data and specimens are shared with outside collaborators agreements limit what the outside collaborators can do with the information to help prevent reidentification.

N. FINANCIAL DISCLOSURES

Dana-Farber Cancer Institute has a financial interest in the investigational compound used in this trial, Atezolizumab. This financial interest could be affected by the outcome of this research. Additional information is provided in the Patient Information Sheet available to participants.

It is possible that certain researchers on this study may have earned money from, or own some publicly-traded stock in, the company that makes or is developing the study drugs. The amount of money that a researcher may earn and still take part in research is limited by the Harvard Medical School Faculty of Medicine Policy on Conflicts of Interest and Commitment. If you have further questions, please speak with a member of the study team or contact the Dana-Farber Cancer Institute Office of Research Integrity at 617-432-4557 or researchintegrity@dfci.harvard.edu.

O. GENETIC RESEARCH

This research will involve genomic and germline testing.

The Genetic Information Nondiscrimination Act of 2008 (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health, and may prevent discrimination by health insurers and employers based on genetic information. GINA is intended to ease concerns about discrimination that might keep some people from getting genetic tests that could benefit their health, and enable people to take part in research studies such as this without fear that their DNA information might be used against them by health insurers or their workplace. This protection does not extend to disability or life insurance. Additional information can be found at http://www.genome.gov/10002328.

As part of this study, your anonymized specimens or genetic data may be placed into one or more publicly-accessible scientific databases, such as the National Institutes of Health's Database for Genotypes and Phenotypes (dbGaP). Through such databases, researchers from around the world will have access to anonymized samples or data for future research.

P. PRIVACY OF PROTECTED HEALTH INFORMATION (HIPAA AUTHORIZATION)

The Health Insurance Portability and Accountability Act (HIPAA) is a federal law that requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. What protected health information about me will be used or shared with others during this research?

- Existing medical records, including mental health records.
- New health information created from study-related tests, procedures, visits, and/or questionnaires

2. Why will protected information about me be used or shared with others?

The main reasons include the following:

- To conduct and oversee the research described earlier in this form;
- To ensure the research meets legal, institutional, and accreditation requirements;
- To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
- To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
- To better understand the diseases being studied and to improve the design of future studies; and,
- Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, representatives, business partners, and its agent(s): Genentech and Eli Lilly
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable
- Broad Institute

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed, because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities such as oversight, or that is needed to ensure quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”
- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: “Whom do I contact if I have questions about the research study?”

Q. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

☐ *As someone who understands both English and the language used by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.*

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate