NCT# 02451423

UNIVERSITY OF CALIFORNIA
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

STUDY TITLE: CC#14524: Phase II Study of Neoadjuvant Atezolizumab-based Immunotherapy for Patients with Urothelial Carcinoma (NEBULA)

Principal Investigator: Lawrence Fong, MD
Department: University of California San Francisco (UCSF), Genitourinary

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

For study participants at University of California San Francisco (UCSF): You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor, Lawrence Fong, MD, from the UCSF Department of Genitourinary [redacted].

For study participants at University of California Davis (UCD): You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor, Mamta Parikh, MD, from the UC Davis Department of Genitourinary [redacted] or after hours, 24-hour telephone number for the UC Davis Medical Center (UCDMC) Hospital Operator, 916-734-2011 (ask for the medical oncologist on call).

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the UCSF Institutional Review Board at 415-476-1814.

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.

INTRODUCTION

This is a clinical trial, a type of research study. Your research study doctor will explain the clinical trial to you.

Clinical trials include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your research study doctor.

You are being asked to take part in this research study because you have bladder cancer and you are unable to receive cisplatin-based chemotherapy before your surgery. Cisplatin-based chemotherapy is a type of treatment which is commonly used either before or after removal of the bladder. In large studies, patients who received cisplatin-containing chemotherapy before surgery were more likely to be cured of bladder cancer and were more likely to be alive 5 years later.

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Even if your doctor determines that you are able to receive cisplatin-based chemotherapy you may be eligible to enter this study if you decline to receive cisplatin- based chemotherapy prior to your surgery, understanding and recognizing the benefits described above. You will be asked to sign an acknowledgement of the potential benefits of cisplatin-based chemotherapy at the end of this consent form.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, an investigational drug called atezolizumab, alone or in combination with tiragolumab, has on patients with bladder cancer.

Your body's immune system has a certain natural ability to withstand tumor growth. Tumors partially resist the immune system by expressing a protein called PD-L1. **Atezolizumab** blocks PD-L1 and allows your immune system to better recognize and attack cancer cells. Atezolizumab is approved by the United States Food and Drug Administration (FDA) for the treatment of people with bladder cancer and lung cancer, but atezolizumab is not approved in combination with tiragolumab. Therefore, the use of atezolizumab in this study is considered experimental.

While initial results suggest that patients whose tumors express more PD-L1 are more likely to respond to atezolizumab, this study is open to all patients with bladder cancer regardless of PD-L1 status. Your tumor will not be tested until after you complete treatment.

Tumors can partially decrease the immune system from functioning properly using a pathway known as TIGIT. **Tiragolumab** acts by blocking the TIGIT protein, which may help boost your immune system and stop or reverse the growth of tumors. Tiragolumab is an experimental drug, which means that is not approved by the FDA.

There are 2 parts to this study. Part 1 is complete and the study is currently enrolling into Part 2.

- In Part 1, participants received atezolizumab before their surgery. In this part of the study, the researchers also evaluated what effects are associated with increasing the numbers of atezolizumab treatments.
- In Part 2, participants will receive atezolizumab in combination with tiragolumab before surgery. <u>If you choose to enroll in this study you will be in Part 2.</u>

This research study is being sponsored by UCSF, the NIH National Cancer Institute, the Bladder Cancer Advocacy Network (BCAN), and the Conquer Cancer Foundation of the American Society of Clinical Oncology. Genentech, the maker of atezolizumab and tiragolumab will provide the study drugs free of charge.

How many people will take part in this study?

Up to 27 people at UCSF and UC Davis will participate in Part 1 of this research study.

About 21-33 people at UCSF and UC Davis will participate in Part 2 of this research study.

What will happen if I take part in this research study?

Before you begin the main part of the study...
You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. Some of these procedures are part of regular cancer care and may be done even if you do not join the study. Others are being done specifically for research and are noted as "research purposes" in the list of procedures below. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

The screening visit will take place within 4 weeks (28 days) prior to starting the study. The visit will take approximately 7-8 hours. You will be asked to have the following tests done:

- Medical history and current medication use will be reviewed to ensure that there are no prior health conditions you have had or medications you are taking that would make it unsafe for you to participate in the study.
- Blood (approximately 2-3 tablespoons) will be drawn for:
  - Routine safety blood tests
  - C-reactive protein (CRP) test – the protein appears in higher amounts when there is swelling (inflammation) somewhere in your body
  - Creatine kinase (CK) test - the protein appears in higher amounts when there is muscle damage
- Pulse oximetry – to check the amount of oxygen in your blood. The doctor will place a soft clip on the end of your finger for about 1 minute.
- Urinalysis
- Electrocardiogram (ECG) – an ECG records the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. The ECG takes about 15-30 minutes.
- Imaging (CT or MRI) of the chest, abdomen, and pelvis for tumor/lesion assessment. These assessments may be performed up to 45 days prior to study entry.
  - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (very rare). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you

have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.

- An MRI scan takes an image of your skull or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the Radiology Department and takes approximately an hour and a half to complete.
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram - if clinically indicated

- Bone scan (technetium OR sodium-fluoride PET/CT) - only for subjects with clinical suspicion of bony metastatic disease
  - A Bone Scan is a test that makes detailed images of your bones and any tumors on them. Before the bone scan a small amount of radioactive substance is injected into your vein. About 3 hours later you will lie on a table under a machine which will make an image of your bones. The test itself will take about 1 hour, but the whole process takes up to 4 hours. This type of scan is considered part of your routine care.
  - A sodium-fluoride PET/CT scan is a special type of test to show how the organs and cells work in your body and is done to show activity of the cells in your tumor. For this procedure, an IV is started in the hand. A small amount of radioactive chemical (glucose) is injected into the blood stream. Once the glucose is injected, you will be asked to wait for about an hour to allow for glucose to distribute in the body. Then you will be asked to lie down on a table and the body is scanned. The total time one will spend at the clinic is about 2-3 hours. This type of bone scan is for research purposes.

- Review of the medications you are taking or have taken within the last 7 days, including all prescriptions, and all non-prescription medications (such as vitamins, herbal supplements and aspirin).
- A review of any side-effects you may be experiencing
- Physical examination including vital signs
- An assessment of how well you are able to perform ordinary tasks and daily activities

- Blood (approximately 2-3 tablespoons) will be drawn for
  - TBNK blood sample - a test to count the number of immune cells in your body

  - Hepatitis B and C and for the Epstein-Barr virus, which is one of the most common viruses in humans.
  - Human immunodeficiency virus (HIV)
  - Pregnancy test, if you are a female of childbearing potential (even if you have had a tubal ligation).
  - Thyroid function testing
  - Possible future testing of how your immune system is responding to the study drug. The blood will be saved ("banked") and frozen during screening and tested if there is clinical suspicion of immune system-related toxicity to the study drug.
- Urine sample for biomarker evaluation. Biomarkers are substances that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study treatment and whether your cells are becoming resistant (no longer responding) to the study treatment.
- Collection of leftover tumor from a prior surgery or biopsy. The tissue will be tested for immune characterization and tumor PD-L1 expression. PD-L1 protein may play a major role in suppressing the immune system's ability to react against foreign substances.
  - While participating in this study, if you undergo any additional surgeries or biopsies of your bladder tumor for routine care purposes, the study team would like to obtain a sample of the tissue.

During the main part of the study...

If the exams, tests, and procedures show that you can be in the research study and you choose to take part then you will be enrolled in the research study.

You will also have research-related exams, tests and procedures during these visits. Most of these exams, tests or procedures are part of your routine cancer care (unless noted otherwise as Research Purposes), but may be done more often because you are in this research study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Study Drugs

Atezolizumab is given intravenously (by IV) for 30-60 minutes on Day 1 of each cycle. Each cycle is 21 days (3 weeks). You will receive atezolizumab for 3 cycles.

Tiragolumab is given intravenously (by IV) for 30-60 minutes on Day 1 of each 21-day cycle, after the atezolizumab infusion is complete. You will receive tiragolumab for up to 3 cycles, depending on when you enroll in the study. Your study doctor will let you know how many cycles of tiragolumab you will receive.

While you are participating in this study, there are medications that should not be taken. Please see the list at the end of this consent form.

All cycles, Day 1

Your clinic visits will take about 1-3 hours.

- Physical examination including vital signs and pulse oximetry
- Blood (approximately 2-3 tablespoons) will be drawn for
  - Routine safety tests
  - C-reactive protein
- Urinalysis
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Urine sample for biomarker evaluation
- Blood (approximately 5 tablespoons) will be drawn for
  - TBNK blood sample - a test to count the number of immune cells in your body
  - Pharmacodynamic biomarkers. Biomarkers are substances in your tissues that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study treatment and whether your cells are becoming resistant (no longer responding) to the study treatment.
- Tiragolumab and/or Atezolizumab infusion(s)

End of Treatment (before your cystectomy)

Within 30 days of the last dose of study treatment and before your cystectomy, you will have the following exams and tests. This visit will take approximately 1-2 hour.

- Physical examination including vital signs and pulse oximetry
- Blood (approximately 2-3 tablespoons) will be drawn for
  - Routine safety tests
  - C-reactive protein
- Urinalysis
- CT or MRI of your abdomen and pelvis
- Chest X-ray or CT of your chest – if clinically indicated
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram - if clinically indicated.
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Urine sample for biomarker evaluation
- Blood (approximately 5 tablespoons) will be drawn for:

  - Thyroid function tests
  - TBNK blood sample
  - Pharmacodynamic biomarkers
- Collection of leftover tumor from cystectomy

Follow-up visits post-cystectomy

The study team will continue to follow your health after your cystectomy for up to 2 years from the time of your cystectomy or until your disease progress, the study ends, or you withdraw from the study, whichever occurs first. During the follow-up phase, you will be asked to return to the clinic every 4 weeks for 12 weeks, and then every 12 weeks thereafter. At these visits, you will have the following assessments:

- Physical examination including vital signs and pulse oximetry
- Blood (approximately 1-2 tablespoons) will be drawn for
  - Routine safety tests
- Urinalysis
- CT or MRI of your abdomen and pelvis
- Chest X-ray or CT of your chest
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram if clinically indicated.
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Blood (approximately 5 tablespoons) will be drawn for
  - TBNK blood sample
  - Pharmacodynamic biomarkers.
  - C-reactive protein
- Urine sample for biomarker evaluation
- Tumor tissue collection
  - Collection of tissue from your cystectomy for immunologic characterization
  - Tumor biopsy at first sign of disease recurrence. You may decide to opt-out of this procedure.

Off Study Visit

Once you finish participating in the study (whether because your disease progresses, it is 2 years following your cystectomy, the study ends, or you withdraw from the study), you will be asked to return to the clinic for one final visit. At this visit, you will have the following assessments:

- Physical examination including vital signs and pulse oximetry

- Blood (approximately 1-2 tablespoons) will be drawn for
  - Routine safety tests
- Urinalysis
- CT or MRI of your abdomen and pelvis (only if not performed within the last 8 weeks)
- Chest X-ray or CT of your chest (only if not performed within the last 8 weeks)
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram if clinically indicated.
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Blood (approximately 5 tablespoons) will be drawn for
  - TBNK blood sample
  - For Pharmacodynamic biomarkers.
  - C-reactive protein
- Urine sample for biomarker evaluation
- Tumor tissue collection
  - Collection of tissue from your cystectomy for immunologic characterization
  - Tumor biopsy at first sign of disease recurrence. You may decide to opt-out of this procedure

How will my lifestyle be affected if I take part?

A type of vaccine, known as *live* vaccine, is not permitted during the study, including up to 4 weeks before your first dose of study drug and for at least 3 months after the last dose of the study drug. A *live* vaccine contains small amounts of the *living* virus, such as FluMist (for influenza) and the Measles, Mumps, Rubella vaccine. Please note that these restrictions only apply to *live* vaccines. Inactivated vaccines (or killed vaccines), such as RNA- or protein-based COVID-19 vaccines, are not subject to these restrictions. If you know that you will need a vaccination during the study, please tell your doctor. The study drugs may have some side effects that may overlap with some of the side effects caused by other medications that also stimulate the immune system. It may be dangerous to take both of these drugs at the same time. It is important to tell your doctor the last time you took any medication that may affect your immune system, including any herbal supplements. It is also important that you do not take any other drugs that may alter your immune system for 10 weeks after your last dose of study drug.

Study location:

UCSF: All research study procedures will be done at UCSF Helen Diller Family Comprehensive Cancer Center. Some of the imaging scans for your routine care may be done outside of UCSF.

UC Davis: All study procedures will be done at UC Davis Comprehensive Cancer Center and UC Davis Medical Center. Some of the imaging scans for your routine care may be done outside of UC Davis.

How long will I be in the study?

Depending on when you enroll in the study, you will receive up to 3 cycles of atezolizumab and tiragolumab. After you are finished taking the study treatment or your disease has progressed, the study doctor will ask you to visit the office for follow-up exams within 30 days after the last dose of study treatment or from the date of your disease progression. If your disease has not progressed, you will continue to receive scans to monitor your disease.

You will also be contacted by phone or asked to come in to your physician's office about every 3 months for 2 years after your cystectomy so that your health can be monitored and information collected on any additional anti-cancer treatments you may be receiving.

Can I stop being in the study?

Yes. You may decide to stop at any time. Tell the research study doctor if you are thinking about stopping or decide to stop. He will tell you how to stop your participation safely.

It is important to tell the research study doctor if you are thinking about stopping so any risks can be evaluated by your research study doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The research study doctor may stop you from taking part in this research study at any time if he believes it is in your best interest, if you do not follow the research study rules, if you need a treatment that is not allowed by the study, or if the research study is stopped.

If you decide to stop being in the study or if your study doctor stops you from taking part in the study, your study doctor will ask you to come back for a final study visit.

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

You may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all of the side effects that could occur. Your study doctors may give you drugs to help lessen side effects. Many side effects go away soon after you stop what is causing them. In some cases, side effects can be serious and may be long lasting or

may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects you have while taking part in the study.

Atezolizumab Risks

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 MPDL3280A, you may develop a condition where there is inflammation against a part of your own body (an autoimmune condition).

Risks and Side Effects of Atezolizumab

Very Common (occurs in 10% or more of people)

- Fatigue
- Joint pain (arthralgia)
- Lack of energy (asthenia)
- Decreased appetite
- Cough
- Diarrhea
- Shortness of breath (dyspnea)
- Constipation
- Headache
- Swelling of the limbs (peripheral edema)
- Urinary tract infection
- Itching of the skin (pruritus)
- Nausea
- Fever
- Rash
- Vomiting
- Muscle and bone pain (myalgia, musculoskeletal pain and bone pain)

Common (occurs in 1%-10% of people)

- Chills
- Difficulty swallowing (dysphagia)
- Increase in liver enzymes, which may indicate inflammation of the liver
- Allergic reaction or intolerance to medication (hypersensitivity)
- Decreased level of potassium in blood (hypokalemia)
- Decreased level of sodium in blood (hyponatremia)
- Low blood pressure (hypotension)
- Underactive thyroid gland (hypothyroidism)
- Inflammation of the intestines (colitis)
- Decreased oxygen supply in body resulting in shortness of breath (hypoxia)

- Flu-like symptoms
- Infusion-related reaction
- Muscular weakness
- Inflammation of the lungs (pneumonitis)
- Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia)
- Nasal congestion
- Inflammation of the liver (hepatitis)
- Abdominal pain

Less common but potentially serious side effects (occurs in less than 1% of people)

- High levels of sugar in the blood (hyperglycemia)
- Nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)
- Decreased production of hormones by the adrenal glands (adrenal insufficiency)
- Diabetes
- Overactive thyroid gland (hyperthyroidism)
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis)
- Inflammation of the pituitary gland (hypophysitis)
- Inflammation of the heart muscle (myocarditis)
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome)
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis)
- Inflammation of the pancreas (pancreatitis)
- 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 of the kidneys (nephritis); symptoms may include frequent urination, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- 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
- Increased blood level of a liver pigment (bilirubin), often a sign of liver problems
- Bone pain
- Increase in gamma glutamyl transferase (an enzyme found in tissues mainly in the liver, kidney, and pancreas) increased
- Scarring (fibrosis) of the lungs (interstitial lung disease)

Side effects of special interest

Among the side effects known to be associated with atezolizumab, Genentech and your study doctors would like you to pay more attention to the following:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood in stool, and pain in stomach area
- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptoms may include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal glands (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- 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 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
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light
- 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
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficulty walking
- Inflammation of the lungs (pneumonitis); symptoms may include new or worsening cough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest
- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain, nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue

Side effects potentially associated with atezolizumab

- Development of special 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. Blood samples will be drawn to monitor for the development of these antibodies during the study and at your study drugs discontinuation visit.
- 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

Allergic Reactions

Allergic reactions may occur with atezolizumab and typically occur while it is being given into your vein or shortly after it is given. No events of allergic reactions to atezolizumab have been reported. 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.

Immune reaction

In rare situations, an immune reaction can occur with administration of atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection. Several organs in your body (for example liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may include very low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or mechanical help (intubation), severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs. This immune reaction is thought to be due to cytokine release syndrome (CRS).

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.

Risks and side effects of tiragolumab:

Tiragolumab has had limited testing in humans. The known side effects of this drug, as well as potential side effects based on human and laboratory studies or knowledge of similar drugs, are listed below. There may be side effects that are not known at this time.

Side Effects Known to be associated with Tiragolumab

Reactions associated with the infusion (occurring during or within 1 day of infusion) have occurred in patients receiving tiragolumab. Symptoms have included fever, chills, shortness of breath, rash, headache, nausea, or vomiting, and changes in blood pressure. These reactions have been mild but could potentially be severe. If you experience these symptoms, your study doctor may slow down, interrupt, or even stop the delivery of tiragolumab into your vein. Your study doctor may give you some medications to treat these symptoms and may also give you some medication before your next infusion to prevent or lessen such symptoms.

Side effects potentially associated with Tiragolumab

Tiragolumab may potentially be associated with immune-mediated side effects, as seen with other drugs that stimulate the immune system. The immune system may cause inflammation in your tumor but also may cause damage to normal tissue, and may affect any part of the body. Tiragolumab may also be associated with a decrease in lymphocytes, a type of white blood cell.

Treatment with tiragolumab alone may have contributed to one death due to severe liver injury. Your study doctor will monitor your liver function with blood tests throughout the study. Treatment with tiragolumab combined with atezolizumab may have contributed to one death due to reactivation of Epstein-Barr virus (EBV) that led to a severe immune reaction (described as a potential side effect for atezolizumab; see "Immune Reaction"). People with an active EBV infection cannot participate in this study. If you experience symptoms described in the "Immune Reaction" section, you should notify your doctor immediately.

Other risks related to this study include:

Surgery Delay: Side effects related to the study drugs could delay your regular care surgery, such that surgery is not possible. Your study doctors will do their best to avoid delay of your surgery. You should discuss this risk with the study doctor.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.

Infusion risks: As with most intravenous products, you may experience pain, irritation, swelling or bruising, or a slight chance of infection at the site where the intravenous catheter (small tube) is inserted into your vein. These side effects may also be observed at the site where blood is drawn for laboratory tests.

Radiation risks: This research study involves exposure to radiation. Not all this radiation exposure is necessary for your medical care and is for research purposes only. The additional amount of radiation that you will receive as a result of participating in this study will be a maximum of approximately 23 mSv, which is equivalent to almost 8 times the yearly natural background of radiation in the US, which is 3 mSv (a mSv, or milliSievert, is a measurement of radiation). This amount of radiation may involve a low risk of cancer. If you are pregnant, you SHOULD NOT participate in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

Electrocardiogram (ECG): The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own.

CT scan risks: CT scans involve the risks of radiation (see above). In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The research study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from

happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the research study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this research study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

Bone Scan: The bone scan involves exposure to radiation. The bone scan involves an injection, in a vein in your arm, of a radiotracer (radioactive compound that localizes in the bone). As with all injections, it may feel like a small sting and there may be possible bruising at the injection site. You may become uncomfortable lying still for the duration of the examination. See Radiation Risks.

Tissue biopsy: The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure

can be unsuccessful and require a repeat biopsy to get enough tissue. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

Reproductive risks:

For Women: If you are pregnant or become pregnant, or if you are currently breastfeeding, you cannot take part in this study because you or your child may be exposed to an unknown risk.

If you are a woman who can become pregnant (even if you have had a tubal ligation), you must have a blood test that shows you are not pregnant before you can be enrolled in this study. In addition, you must agree to use highly effective form(s) of contraception (e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly) while in this study and for 5 months after your last dose of study drug. Check with your study doctor about the methods of birth control to use.

Tell your study doctor right away if you suspect that you have become pregnant while in the study or within 6 months after your last dose of study drug. The study doctor or research staff will advise you of the possible risks to your unborn child and the options available to you.

For Men: If you are a man who is able to father a child, you must agree to use birth control while in this study and for 5 months after your last dose of study drug to avoid exposing your child to an unknown risk. Check with your study doctor about the methods of birth control to use.

Tell your study doctor right away if your partner becomes pregnant during the study or within 6 months after your last dose of study drug. The study doctor or research staff will advise you of the possible risks to your unborn child and will make an effort to contact your partner to get her permission to collect information about the pregnancy. No matter what your partner decides, you can continue to take part in this study.

HIV and Hepatitis Testing Risks: Being tested for HIV and Hepatitis may cause anxiety regardless of the test results. A positive test result means that you have been infected with the HIV virus, but no one can say for certain when, if ever, you will become sick with AIDS or a related condition. Receiving positive results may make you very upset. If other people learn about your positive test results, you may have trouble obtaining insurance or employment. If your test is negative, there is still the possibility that you could be infected with the HIV or Hepatitis virus and test positive at some time in the future. There is always the possibility that the test results could be wrong.

Unknown Risks: The experimental treatments may have side effects that no one knows about. You will be told about any important new findings that may affect your

decision to remain in the research study.

For more information about risks and side effects, ask your research study doctor.

Are there benefits to taking part in the study?

There is no guarantee that you will receive any benefits from this study, and taking part in this study may or may not cause your health to improve. Information from this study may help doctors learn more about atezolizumab and tiragolumab and the treatment of bladder cancer. This information may benefit other patients with bladder cancer or a similar condition in the future.

How will my specimens and information be used?

Researchers will use your specimens and information to conduct this study. Once the study is done using your specimens and information, we may share them with other researchers so they can use them for other studies in the future. We will not share your name or any other personal information that would let the researchers outside of UCSF and UC Davis know who you are. We will not ask you for additional permission to share the de-identified information and specimens.

Your specimens will be stored in a repository, also called a 'tissue bank', at UCSF and UC-Davis. The manager of tissue bank and select tissue bank staff members will have access to your specimens and information about you, but they will not release any identifying information about you to researchers using your specimens. We may give your specimens and certain medical information about you (for example, diagnosis, blood pressure, age if less than 85) to other scientists or companies not at UCSF or UC-Davis including to an unrestricted or controlled-access government health research database, but we will not give them your name, address, phone number, or any other identifiable information. Your specimens and information will be kept indefinitely until they are used up or destroyed. Research results from these future studies will not be returned to you and will not be put in your medical record. Future research performed on your de-identified samples will not change the care you receive.

Researchers may use your specimens (for example, blood, tissue, saliva, etc.) to look at all of your DNA (this is called "whole genome sequencing. DNA contains information that determines things like eye color, height, or disease risk that are passed on from parent to child. Genetic information (also known as genotype data) and the medical record data (also known as phenotype data) may be shared broadly in a coded form for future genetic research or analysis.

Donating data and specimens may involve a loss of privacy, but information about you will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Genetic information that results from this study does

not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. It is possible that future research could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

There will be no direct benefit to you from allowing your data and specimens to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease. If the data or specimens, or any new products, tests or discoveries that result from this research have potential commercial value, you will not share in any financial benefits. If you decide later that you do not want your information to be used for future research, you can notify the investigator in writing or by phone at:

UCSF PI: Lawrence Fong, MD
[redacted]

UC-Davis PI: Mamta Parikh, MD
[redacted]

and any remaining data will be destroyed. However, we cannot retract any data has been shared with other researchers.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a research study. Treatment available off study include cisplatin-based chemotherapy, an FDA approved therapy for the treatment of bladder cancer that cannot be treated with surgery or radiation therapy alone. Cisplatin-based combination chemotherapy regimens are the standard of care for stage IV bladder cancer.
- Taking part in another research study.
- Getting no treatment.
- Getting comfort care, also called palliative care.

Please talk to your doctor about your choices before deciding if you will take part in this research study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is

kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this research study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Genentech and their associates
- The University of California
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

California Confidentiality Statement

California regulations require laboratories to report new cases of HIV, hepatitis B, and hepatitis C infection to the county public health department. The reports include the patient's name, social security number, and other identifying information. Information about these new infections is used to track these diseases statewide and nationwide. Other than this required reporting, your results will be treated confidentially by the study staff. Personally identifying information will not be reported to other departments or agencies.

What are the costs of taking part in this study?

Genentech, the manufacturers of atezolizumab and tiragolumab, will provide the study drugs at no cost.

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

If you have questions about what costs you will be responsible for, please talk with the study investigator before deciding to enroll in the study. Depending on the type of study, some of your costs could be substantial.

Will I be paid for taking part in this study?

You will not be paid for taking part in this research study.

What happens if I am injured because I took part in this study?

It is important that you tell your research study doctor if you feel that you have been injured because of taking part in this research study. You can tell the doctor in person or contact your study doctor by phone:

UCSF PI: Lawrence Fong, MD [redacted]

UC-Davis PI: Mamta Parikh, MD [redacted]

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the UCSF Office of the Institutional Review Board at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this research study is your choice. You may choose either to take part or not to take part in the research study. If you decide to take part in this research study, you may leave the research study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the research study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about significant new information or changes in the research study that may affect your health or your willingness to continue in the research study.

In the case of injury resulting from this research study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your research study doctor about any questions, concerns, or complaints you have about this research study. Contact your research study doctor.

If you wish to ask questions about the research study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the research study, please call the UCSF Office of the Institutional Review Board at 415-476-1814.

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.

Please note: This section of the consent form concerns cisplatin-eligibility.

As stated in the beginning of this consent form, cisplatin-based chemotherapy is a type of treatment which is commonly used either before or after removal of the bladder. In large studies, patients who received cisplatin-containing chemotherapy before surgery were more likely to be cured of bladder cancer and were more likely to be alive 5 years later.

If your doctor determines that you are able to receive cisplatin-based chemotherapy and you have declined to receive cisplatin-based chemotherapy prior to your surgery, understanding and recognizing the benefits described above, please indicate your decision below. You may be eligible to enter this study if you decline to receive cisplatin-based chemotherapy prior to your surgery.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence, put your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care.

1. *I am declining cisplatin-based chemotherapy, understanding and recognizing the benefits of treatment before surgery, OR my provider has informed me that I am not able to receive cisplatin.*

YES	*NO*

Reason for declining chemotherapy: _____

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OPTIONAL RESEARCH PARTICIPATION

This section of the informed consent is about optional future contact of participants in the main study. You can still be in the main study even if you say "no" to allowing optional future contact.

Future Contact

We want to know if we may contact you in the future to see if you are interested in participating in other research studies.

If you agree and we contact you to tell you about a study, you have no obligation to actually participate in any study. You can decide when you are told about the study if you want to receive more information about the study. There would be a new consent process for that study.

If at any time you decide you no longer want to be contacted about future studies, please let us know [redacted].

Making Your Choice

Please read the sentence below and mark your choice by putting your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care or your participation in the main study.

1. *Someone may contact me in the future about taking part in more research.*

YES	*NO*

****

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
	Participant's Printed Name
Date	Person Obtaining Consent
Date	Witness – Only required if the participant is a non-English speaker

STUDY TITLE: CC#14524: Phase II Study of Neoadjuvant Atezolizumab-based Immunotherapy for Patients with Urothelial Carcinoma (NEBULA)

List of Prohibited Medications

The following are a list of commonly used medications which are prohibited while you are participating in this study:

- *Live* vaccines – A *live* vaccine is a type of vaccine that contains small amounts of the *living* virus, such as FluMist (for influenza) and the Measles, Mumps, Rubella vaccine. You should not receive any *live* vaccines while you are participating in this study, including up to 4 weeks before your first dose of study drug and for at least 3 months after the last dose of the study drug. Please note that these restrictions only apply to *live* vaccines. Inactivated vaccines (or killed vaccines), such as RNA- or protein-based COVID-19 vaccines, are not subject to these restrictions. Please let the study doctor know before you receive any vaccinations.
- Denosumab (Prolia, XGEVA) – a drug approved for the treatment of osteoporosis and treatment-induced bone loss
- Any traditional herbal medication
- Any immune stimulants. These include interferon alpha or gamma, or interleukin-2 (IL-2)
- Any medication that may suppress your immune system. These include:
    - Medicines commonly known as "steroids" or "corticosteroids":
        - Prednisone
        - Prednisolone
        - Hydrocortisone
        - Dexamethasone
    - Cyclophosphamide (Cytoxan)
    - Azathioprine (Imuran)
    - Methotrexate (Rheumatrex, Trexall)
    - Thalidomide (Thalomid)
    - Infliximab (Remicade)
    - Etanercept (Enbrel)
    - Adalimumab (Humira)
    - Certolizumab (Cimzia)
    - Golimumab (Simponi)
- Steroid creams and ointments (i.e hydrocortisone, clobetasol, betamethasone) used for skin conditions are allowed while you are on the study
- Inhaled steroids (i.e. fluticasone, Flovent) used for asthma or bronchitis are allowed while you are on the study.
- Certain steroids (fludricortisone) are allowed if used for adrenal insufficiency. Tell your doctor if you take, or are planning to take these medications.

There may be other medications that can suppress or enhance your immune system and should not be taken while you are on the study. If you are unsure please ask your doctor before starting any new medication.

Even if your doctor determines that you are able to receive cisplatin-based chemotherapy you may be eligible to enter this study if you decline to receive cisplatin- based chemotherapy prior to your surgery, understanding and recognizing the benefits described above. You will be asked to sign an acknowledgement of the potential benefits of cisplatin-based chemotherapy at the end of this consent form.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, an investigational drug called atezolizumab, alone or in combination with tiragolumab, has on patients with bladder cancer.

Your body's immune system has a certain natural ability to withstand tumor growth. Tumors partially resist the immune system by expressing a protein called PD-L1. **Atezolizumab** blocks PD-L1 and allows your immune system to better recognize and attack cancer cells. Atezolizumab is approved by the United States Food and Drug Administration (FDA) for the treatment of people with bladder cancer and lung cancer, but atezolizumab is not approved in combination with tiragolumab. Therefore, the use of atezolizumab in this study is considered experimental.

While initial results suggest that patients whose tumors express more PD-L1 are more likely to respond to atezolizumab, this study is open to all patients with bladder cancer regardless of PD-L1 status. Your tumor will not be tested until after you complete treatment.

Tumors can partially decrease the immune system from functioning properly using a pathway known as TIGIT. **Tiragolumab** acts by blocking the TIGIT protein, which may help boost your immune system and stop or reverse the growth of tumors. Tiragolumab is an experimental drug, which means that is not approved by the FDA.

There are 2 parts to this study. Part 1 is complete and the study is currently enrolling into Part 2.

- In Part 1, participants received atezolizumab before their surgery. In this part of the study, the researchers also evaluated what effects are associated with increasing the numbers of atezolizumab treatments.
- In Part 2, participants will receive atezolizumab in combination with tiragolumab before surgery. <u>If you choose to enroll in this study you will be in Part 2.</u>

This research study is being sponsored by UCSF, the NIH National Cancer Institute, the Bladder Cancer Advocacy Network (BCAN), and the Conquer Cancer Foundation of the American Society of Clinical Oncology. Genentech, the maker of atezolizumab and tiragolumab will provide the study drugs free of charge.

How many people will take part in this study?

Up to 27 people at UCSF and UC Davis will participate in Part 1 of this research study.

About 21-33 people at UCSF and UC Davis will participate in Part 2 of this research study.

What will happen if I take part in this research study?

Before you begin the main part of the study...
You will need to have the following exams, tests or procedures to find out if you can be in the main part of the study. Some of these procedures are part of regular cancer care and may be done even if you do not join the study. Others are being done specifically for research and are noted as "research purposes" in the list of procedures below. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

The screening visit will take place within 4 weeks (28 days) prior to starting the study. The visit will take approximately 7-8 hours. You will be asked to have the following tests done:

- Medical history and current medication use will be reviewed to ensure that there are no prior health conditions you have had or medications you are taking that would make it unsafe for you to participate in the study.
- Blood (approximately 2-3 tablespoons) will be drawn for:
  - Routine safety blood tests
  - C-reactive protein (CRP) test – the protein appears in higher amounts when there is swelling (inflammation) somewhere in your body
  - Creatine kinase (CK) test - the protein appears in higher amounts when there is muscle damage
- Pulse oximetry – to check the amount of oxygen in your blood. The doctor will place a soft clip on the end of your finger for about 1 minute.
- Urinalysis
- Electrocardiogram (ECG) – an ECG records the electrical activity of your heart. Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity. The ECG takes about 15-30 minutes.
- Imaging (CT or MRI) of the chest, abdomen, and pelvis for tumor/lesion assessment. These assessments may be performed up to 45 days prior to study entry.
  - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). The contrast material may be given orally, intravenously, or rectally (very rare). Oral contrast material is given to you to drink and is used to help outline the stomach and intestines. Intravenous (IV) contrast material is given to you by injecting the contrast material into a line which is attached to a needle in your arm, and is used to get clearer pictures of your body cavity. A rectal contrast fills up the loops of your lower bowel so the doctors can see your tumor better. After you

have been given the contrast material (either by mouth, by vein, or rectum), you will lie flat on a table that will move you into the CT scan machine. You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.

- An MRI scan takes an image of your skull or body to observe the location and size of your tumor. For the MRI scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). Gadolinium is contrast material that causes some tumors to appear much brighter than normal tissue on MRI scans (these tumors may not be visible without gadolinium). The contrast material may be given to you in your arm through an intravenous catheter (a tiny tube inserted into a vein). You will then lie down on a narrow bed which will be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will lie there quietly for about one hour, during which time you will hear a loud machine-like noise. The MRI scan is done in the Radiology Department and takes approximately an hour and a half to complete.
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram - if clinically indicated

- Bone scan (technetium OR sodium-fluoride PET/CT) - only for subjects with clinical suspicion of bony metastatic disease
  - A Bone Scan is a test that makes detailed images of your bones and any tumors on them. Before the bone scan a small amount of radioactive substance is injected into your vein. About 3 hours later you will lie on a table under a machine which will make an image of your bones. The test itself will take about 1 hour, but the whole process takes up to 4 hours. This type of scan is considered part of your routine care.
  - A sodium-fluoride PET/CT scan is a special type of test to show how the organs and cells work in your body and is done to show activity of the cells in your tumor. For this procedure, an IV is started in the hand. A small amount of radioactive chemical (glucose) is injected into the blood stream. Once the glucose is injected, you will be asked to wait for about an hour to allow for glucose to distribute in the body. Then you will be asked to lie down on a table and the body is scanned. The total time one will spend at the clinic is about 2-3 hours. This type of bone scan is for research purposes.

- Review of the medications you are taking or have taken within the last 7 days, including all prescriptions, and all non-prescription medications (such as vitamins, herbal supplements and aspirin).
- A review of any side-effects you may be experiencing
- Physical examination including vital signs
- An assessment of how well you are able to perform ordinary tasks and daily activities

- Blood (approximately 2-3 tablespoons) will be drawn for
  - TBNK blood sample - a test to count the number of immune cells in your body

  - Hepatitis B and C and for the Epstein-Barr virus, which is one of the most common viruses in humans.
  - Human immunodeficiency virus (HIV)
  - Pregnancy test, if you are a female of childbearing potential (even if you have had a tubal ligation).
  - Thyroid function testing
  - Possible future testing of how your immune system is responding to the study drug. The blood will be saved ("banked") and frozen during screening and tested if there is clinical suspicion of immune system-related toxicity to the study drug.
- Urine sample for biomarker evaluation. Biomarkers are substances that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study treatment and whether your cells are becoming resistant (no longer responding) to the study treatment.
- Collection of leftover tumor from a prior surgery or biopsy. The tissue will be tested for immune characterization and tumor PD-L1 expression. PD-L1 protein may play a major role in suppressing the immune system's ability to react against foreign substances.
  - While participating in this study, if you undergo any additional surgeries or biopsies of your bladder tumor for routine care purposes, the study team would like to obtain a sample of the tissue.

During the main part of the study...

If the exams, tests, and procedures show that you can be in the research study and you choose to take part then you will be enrolled in the research study.

You will also have research-related exams, tests and procedures during these visits. Most of these exams, tests or procedures are part of your routine cancer care (unless noted otherwise as Research Purposes), but may be done more often because you are in this research study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Study Drugs

Atezolizumab is given intravenously (by IV) for 30-60 minutes on Day 1 of each cycle. Each cycle is 21 days (3 weeks). You will receive atezolizumab for 3 cycles.

Tiragolumab is given intravenously (by IV) for 30-60 minutes on Day 1 of each 21-day cycle, after the atezolizumab infusion is complete. You will receive tiragolumab for up to 3 cycles, depending on when you enroll in the study. Your study doctor will let you know how many cycles of tiragolumab you will receive.

While you are participating in this study, there are medications that should not be taken. Please see the list at the end of this consent form.

All cycles, Day 1

Your clinic visits will take about 1-3 hours.

- Physical examination including vital signs and pulse oximetry
- Blood (approximately 2-3 tablespoons) will be drawn for
  - Routine safety tests
  - C-reactive protein
- Urinalysis
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Urine sample for biomarker evaluation
- Blood (approximately 5 tablespoons) will be drawn for
  - TBNK blood sample - a test to count the number of immune cells in your body
  - Pharmacodynamic biomarkers. Biomarkers are substances in your tissues that may provide information on any changes to your genes or DNA, how your cancer cells are responding to study treatment and whether your cells are becoming resistant (no longer responding) to the study treatment.
- Tiragolumab and/or Atezolizumab infusion(s)

End of Treatment (before your cystectomy)

Within 30 days of the last dose of study treatment and before your cystectomy, you will have the following exams and tests. This visit will take approximately 1-2 hour.

- Physical examination including vital signs and pulse oximetry
- Blood (approximately 2-3 tablespoons) will be drawn for
  - Routine safety tests
  - C-reactive protein
- Urinalysis
- CT or MRI of your abdomen and pelvis
- Chest X-ray or CT of your chest – if clinically indicated
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram - if clinically indicated.
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Urine sample for biomarker evaluation
- Blood (approximately 5 tablespoons) will be drawn for:

  - Thyroid function tests
  - TBNK blood sample
  - Pharmacodynamic biomarkers
- Collection of leftover tumor from cystectomy

Follow-up visits post-cystectomy

The study team will continue to follow your health after your cystectomy for up to 2 years from the time of your cystectomy or until your disease progress, the study ends, or you withdraw from the study, whichever occurs first. During the follow-up phase, you will be asked to return to the clinic every 4 weeks for 12 weeks, and then every 12 weeks thereafter. At these visits, you will have the following assessments:

- Physical examination including vital signs and pulse oximetry
- Blood (approximately 1-2 tablespoons) will be drawn for
  - Routine safety tests
- Urinalysis
- CT or MRI of your abdomen and pelvis
- Chest X-ray or CT of your chest
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram if clinically indicated.
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Blood (approximately 5 tablespoons) will be drawn for
  - TBNK blood sample
  - Pharmacodynamic biomarkers.
  - C-reactive protein
- Urine sample for biomarker evaluation
- Tumor tissue collection
  - Collection of tissue from your cystectomy for immunologic characterization
  - Tumor biopsy at first sign of disease recurrence. You may decide to opt-out of this procedure.

Off Study Visit

Once you finish participating in the study (whether because your disease progresses, it is 2 years following your cystectomy, the study ends, or you withdraw from the study), you will be asked to return to the clinic for one final visit. At this visit, you will have the following assessments:

- Physical examination including vital signs and pulse oximetry

- Blood (approximately 1-2 tablespoons) will be drawn for
  - Routine safety tests
- Urinalysis
- CT or MRI of your abdomen and pelvis (only if not performed within the last 8 weeks)
- Chest X-ray or CT of your chest (only if not performed within the last 8 weeks)
- Imaging of the upper tracts with an intravenous pyelogram, CT urography, renal ultrasound with retrograde pyelogram, ureteroscopy, or MRI urogram if clinically indicated.
- A review of any side effects you may be experiencing
- Review of the medications you are taking
- An assessment of how well you are able to perform ordinary tasks and daily activities
- Blood (approximately 5 tablespoons) will be drawn for
  - TBNK blood sample
  - For Pharmacodynamic biomarkers.
  - C-reactive protein
- Urine sample for biomarker evaluation
- Tumor tissue collection
  - Collection of tissue from your cystectomy for immunologic characterization
  - Tumor biopsy at first sign of disease recurrence. You may decide to opt-out of this procedure

How will my lifestyle be affected if I take part?

A type of vaccine, known as *live* vaccine, is not permitted during the study, including up to 4 weeks before your first dose of study drug and for at least 3 months after the last dose of the study drug. A *live* vaccine contains small amounts of the *living* virus, such as FluMist (for influenza) and the Measles, Mumps, Rubella vaccine. Please note that these restrictions only apply to *live* vaccines. Inactivated vaccines (or killed vaccines), such as RNA- or protein-based COVID-19 vaccines, are not subject to these restrictions. If you know that you will need a vaccination during the study, please tell your doctor. The study drugs may have some side effects that may overlap with some of the side effects caused by other medications that also stimulate the immune system. It may be dangerous to take both of these drugs at the same time. It is important to tell your doctor the last time you took any medication that may affect your immune system, including any herbal supplements. It is also important that you do not take any other drugs that may alter your immune system for 10 weeks after your last dose of study drug.

Study location:

UCSF: All research study procedures will be done at UCSF Helen Diller Family Comprehensive Cancer Center. Some of the imaging scans for your routine care may be done outside of UCSF.

UC Davis: All study procedures will be done at UC Davis Comprehensive Cancer Center and UC Davis Medical Center. Some of the imaging scans for your routine care may be done outside of UC Davis.

How long will I be in the study?

Depending on when you enroll in the study, you will receive up to 3 cycles of atezolizumab and tiragolumab. After you are finished taking the study treatment or your disease has progressed, the study doctor will ask you to visit the office for follow-up exams within 30 days after the last dose of study treatment or from the date of your disease progression. If your disease has not progressed, you will continue to receive scans to monitor your disease.

You will also be contacted by phone or asked to come in to your physician's office about every 3 months for 2 years after your cystectomy so that your health can be monitored and information collected on any additional anti-cancer treatments you may be receiving.

Can I stop being in the study?

Yes. You may decide to stop at any time. Tell the research study doctor if you are thinking about stopping or decide to stop. He will tell you how to stop your participation safely.

It is important to tell the research study doctor if you are thinking about stopping so any risks can be evaluated by your research study doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The research study doctor may stop you from taking part in this research study at any time if he believes it is in your best interest, if you do not follow the research study rules, if you need a treatment that is not allowed by the study, or if the research study is stopped.

If you decide to stop being in the study or if your study doctor stops you from taking part in the study, your study doctor will ask you to come back for a final study visit.

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

You may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not know all of the side effects that could occur. Your study doctors may give you drugs to help lessen side effects. Many side effects go away soon after you stop what is causing them. In some cases, side effects can be serious and may be long lasting or

may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects you have while taking part in the study.

Atezolizumab Risks

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 MPDL3280A, you may develop a condition where there is inflammation against a part of your own body (an autoimmune condition).

Risks and Side Effects of Atezolizumab

Very Common (occurs in 10% or more of people)

- Fatigue
- Joint pain (arthralgia)
- Lack of energy (asthenia)
- Decreased appetite
- Cough
- Diarrhea
- Shortness of breath (dyspnea)
- Constipation
- Headache
- Swelling of the limbs (peripheral edema)
- Urinary tract infection
- Itching of the skin (pruritus)
- Nausea
- Fever
- Rash
- Vomiting
- Muscle and bone pain (myalgia, musculoskeletal pain and bone pain)

Common (occurs in 1%-10% of people)

- Chills
- Difficulty swallowing (dysphagia)
- Increase in liver enzymes, which may indicate inflammation of the liver
- Allergic reaction or intolerance to medication (hypersensitivity)
- Decreased level of potassium in blood (hypokalemia)
- Decreased level of sodium in blood (hyponatremia)
- Low blood pressure (hypotension)
- Underactive thyroid gland (hypothyroidism)
- Inflammation of the intestines (colitis)
- Decreased oxygen supply in body resulting in shortness of breath (hypoxia)

- Flu-like symptoms
- Infusion-related reaction
- Muscular weakness
- Inflammation of the lungs (pneumonitis)
- Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia)
- Nasal congestion
- Inflammation of the liver (hepatitis)
- Abdominal pain

Less common but potentially serious side effects (occurs in less than 1% of people)

- High levels of sugar in the blood (hyperglycemia)
- Nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)
- Decreased production of hormones by the adrenal glands (adrenal insufficiency)
- Diabetes
- Overactive thyroid gland (hyperthyroidism)
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis)
- Inflammation of the pituitary gland (hypophysitis)
- Inflammation of the heart muscle (myocarditis)
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome)
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis)
- Inflammation of the pancreas (pancreatitis)
- 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 of the kidneys (nephritis); symptoms may include frequent urination, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- 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
- Increased blood level of a liver pigment (bilirubin), often a sign of liver problems
- Bone pain
- Increase in gamma glutamyl transferase (an enzyme found in tissues mainly in the liver, kidney, and pancreas) increased
- Scarring (fibrosis) of the lungs (interstitial lung disease)

Side effects of special interest

Among the side effects known to be associated with atezolizumab, Genentech and your study doctors would like you to pay more attention to the following:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood in stool, and pain in stomach area
- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptoms may include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal glands (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- 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 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
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light
- 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
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficulty walking
- Inflammation of the lungs (pneumonitis); symptoms may include new or worsening cough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest
- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain, nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue

Side effects potentially associated with atezolizumab

- Development of special 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. Blood samples will be drawn to monitor for the development of these antibodies during the study and at your study drugs discontinuation visit.
- 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

Allergic Reactions

Allergic reactions may occur with atezolizumab and typically occur while it is being given into your vein or shortly after it is given. No events of allergic reactions to atezolizumab have been reported. 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.

Immune reaction

In rare situations, an immune reaction can occur with administration of atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection. Several organs in your body (for example liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may include very low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or mechanical help (intubation), severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs. This immune reaction is thought to be due to cytokine release syndrome (CRS).

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.

Risks and side effects of tiragolumab:

Tiragolumab has had limited testing in humans. The known side effects of this drug, as well as potential side effects based on human and laboratory studies or knowledge of similar drugs, are listed below. There may be side effects that are not known at this time.

Side Effects Known to be associated with Tiragolumab

Reactions associated with the infusion (occurring during or within 1 day of infusion) have occurred in patients receiving tiragolumab. Symptoms have included fever, chills, shortness of breath, rash, headache, nausea, or vomiting, and changes in blood pressure. These reactions have been mild but could potentially be severe. If you experience these symptoms, your study doctor may slow down, interrupt, or even stop the delivery of tiragolumab into your vein. Your study doctor may give you some medications to treat these symptoms and may also give you some medication before your next infusion to prevent or lessen such symptoms.

Side effects potentially associated with Tiragolumab

Tiragolumab may potentially be associated with immune-mediated side effects, as seen with other drugs that stimulate the immune system. The immune system may cause inflammation in your tumor but also may cause damage to normal tissue, and may affect any part of the body. Tiragolumab may also be associated with a decrease in lymphocytes, a type of white blood cell.

Treatment with tiragolumab alone may have contributed to one death due to severe liver injury. Your study doctor will monitor your liver function with blood tests throughout the study. Treatment with tiragolumab combined with atezolizumab may have contributed to one death due to reactivation of Epstein-Barr virus (EBV) that led to a severe immune reaction (described as a potential side effect for atezolizumab; see "Immune Reaction"). People with an active EBV infection cannot participate in this study. If you experience symptoms described in the "Immune Reaction" section, you should notify your doctor immediately.

Other risks related to this study include:

Surgery Delay: Side effects related to the study drugs could delay your regular care surgery, such that surgery is not possible. Your study doctors will do their best to avoid delay of your surgery. You should discuss this risk with the study doctor.

Blood drawing (venipuncture) risks: Drawing blood may cause temporary discomfort from the needle stick, bruising, and infection.

Infusion risks: As with most intravenous products, you may experience pain, irritation, swelling or bruising, or a slight chance of infection at the site where the intravenous catheter (small tube) is inserted into your vein. These side effects may also be observed at the site where blood is drawn for laboratory tests.

Radiation risks: This research study involves exposure to radiation. Not all this radiation exposure is necessary for your medical care and is for research purposes only. The additional amount of radiation that you will receive as a result of participating in this study will be a maximum of approximately 23 mSv, which is equivalent to almost 8 times the yearly natural background of radiation in the US, which is 3 mSv (a mSv, or milliSievert, is a measurement of radiation). This amount of radiation may involve a low risk of cancer. If you are pregnant, you SHOULD NOT participate in this study. If you have any questions regarding the use of radiation or the risks involved, please consult the physician conducting the study.

Electrocardiogram (ECG): The ECG involves placing electrodes on the skin. You may experience an allergic reaction to the adhesive used to attach the electrodes to the skin. These symptoms are generally mild and clear up on their own.

CT scan risks: CT scans involve the risks of radiation (see above). In addition, if contrast material (iodine dye) is used, there is a slight risk of developing an allergic reaction, from mild (itching, rash) to severe (difficulty breathing, shock, or rarely, death). The contrast material may also cause kidney problems, especially if you are dehydrated or have poor kidney function. The research study doctors will ask you about any allergies or related conditions before the procedure. If you have any of these problems, you may not be allowed to have a CT scan.

Having a CT scan may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia when placed inside the CT scanner, or by lying in one position for a long time. If contrast material is used, you may feel discomfort when it is injected. You may feel warm and flushed and get a metallic taste in your mouth. Rarely, the contrast material may cause nausea, vomiting or a headache.

MRI risks: Because the MRI machine acts like a large magnet, it could move iron-containing objects in the MRI room during your examination, which in the process could possibly harm you. Precautions have been taken to prevent such an event from

happening; loose metal objects, like pocket knives or key chains, are not allowed in the MRI room. If you have a piece of metal in your body, such as a fragment in your eye, aneurysm clips, ear implants, spinal nerve stimulators, or a pacemaker, you will not be allowed into the MRI room and cannot have an MRI.

Having an MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the research study. Temporary hearing loss has been reported from this loud noise. This is why you will be asked to wear ear plugs. At times during the test, you may be asked to not swallow for a while, which can be uncomfortable.

Because the risks to a fetus from MRI are unknown, pregnant women must not participate in this research study.

Contrast agent (gadolinium) risks: A few side effects of gadolinium injection such as mild headache, nausea, and local pain may occur. Rarely (less than 1% of the time) low blood pressure and lightheadedness occurs. This can be treated immediately with intravenous fluids. Very rarely (less than one in one thousand), patients are allergic to gadolinium. These effects are most commonly hives and itchy eyes, but more severe reactions have been seen which result in shortness of breath.

Patients with severe kidney disease sometimes have a bad reaction to gadolinium contrast. The condition is called nephrogenic systemic fibrosis (NSF). It can cause skin to tighten or scar and can damage internal organs. Sometimes it can be life-threatening. There are no reports of NSF in patients with normal kidney function. Before you have a MRI scan requiring an injection of gadolinium contrast, you will have a blood test in order to check the function of your kidneys. Based on your medical history and the results of the test, a doctor will decide whether it is safe for you to undergo the MRI scans.

Bone Scan: The bone scan involves exposure to radiation. The bone scan involves an injection, in a vein in your arm, of a radiotracer (radioactive compound that localizes in the bone). As with all injections, it may feel like a small sting and there may be possible bruising at the injection site. You may become uncomfortable lying still for the duration of the examination. See Radiation Risks.

Tissue biopsy: The biopsy has small but serious risks. While we make every effort to minimize the pain related to the procedure, the procedure is usually uncomfortable and sometimes painful. Wherever the biopsy is done in your body, it can lead to bleeding in that area, damage of organs near where the biopsy is done, or infection. While it is uncommon, sometimes bleeding or pain from the biopsy will require you to stay overnight in the hospital or require you to go to the operating room to control any bleeding. We check your laboratory values before the biopsy to make sure that the procedure is as safe as possible and to minimize your chance of having a complication. Additionally, if the biopsy involves the lungs, it can cause the lungs to deflate and if this occurs, you might require treatment to correct this. We try to take as little tissue as possible when we do the biopsy, and this means that sometimes the biopsy procedure

can be unsuccessful and require a repeat biopsy to get enough tissue. Other potential risks will be described to you and discussed with you by doctors who conduct these biopsies.

Reproductive risks:

For Women: If you are pregnant or become pregnant, or if you are currently breastfeeding, you cannot take part in this study because you or your child may be exposed to an unknown risk.

If you are a woman who can become pregnant (even if you have had a tubal ligation), you must have a blood test that shows you are not pregnant before you can be enrolled in this study. In addition, you must agree to use highly effective form(s) of contraception (e.g., surgical sterilization, a reliable barrier method, birth control pills, or contraceptive hormone implants) (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly) while in this study and for 5 months after your last dose of study drug. Check with your study doctor about the methods of birth control to use.

Tell your study doctor right away if you suspect that you have become pregnant while in the study or within 6 months after your last dose of study drug. The study doctor or research staff will advise you of the possible risks to your unborn child and the options available to you.

For Men: If you are a man who is able to father a child, you must agree to use birth control while in this study and for 5 months after your last dose of study drug to avoid exposing your child to an unknown risk. Check with your study doctor about the methods of birth control to use.

Tell your study doctor right away if your partner becomes pregnant during the study or within 6 months after your last dose of study drug. The study doctor or research staff will advise you of the possible risks to your unborn child and will make an effort to contact your partner to get her permission to collect information about the pregnancy. No matter what your partner decides, you can continue to take part in this study.

HIV and Hepatitis Testing Risks: Being tested for HIV and Hepatitis may cause anxiety regardless of the test results. A positive test result means that you have been infected with the HIV virus, but no one can say for certain when, if ever, you will become sick with AIDS or a related condition. Receiving positive results may make you very upset. If other people learn about your positive test results, you may have trouble obtaining insurance or employment. If your test is negative, there is still the possibility that you could be infected with the HIV or Hepatitis virus and test positive at some time in the future. There is always the possibility that the test results could be wrong.

Unknown Risks: The experimental treatments may have side effects that no one knows about. You will be told about any important new findings that may affect your

decision to remain in the research study.

For more information about risks and side effects, ask your research study doctor.

Are there benefits to taking part in the study?

There is no guarantee that you will receive any benefits from this study, and taking part in this study may or may not cause your health to improve. Information from this study may help doctors learn more about atezolizumab and tiragolumab and the treatment of bladder cancer. This information may benefit other patients with bladder cancer or a similar condition in the future.

How will my specimens and information be used?

Researchers will use your specimens and information to conduct this study. Once the study is done using your specimens and information, we may share them with other researchers so they can use them for other studies in the future. We will not share your name or any other personal information that would let the researchers outside of UCSF and UC Davis know who you are. We will not ask you for additional permission to share the de-identified information and specimens.

Your specimens will be stored in a repository, also called a 'tissue bank', at UCSF and UC-Davis. The manager of tissue bank and select tissue bank staff members will have access to your specimens and information about you, but they will not release any identifying information about you to researchers using your specimens. We may give your specimens and certain medical information about you (for example, diagnosis, blood pressure, age if less than 85) to other scientists or companies not at UCSF or UC-Davis including to an unrestricted or controlled-access government health research database, but we will not give them your name, address, phone number, or any other identifiable information. Your specimens and information will be kept indefinitely until they are used up or destroyed. Research results from these future studies will not be returned to you and will not be put in your medical record. Future research performed on your de-identified samples will not change the care you receive.

Researchers may use your specimens (for example, blood, tissue, saliva, etc.) to look at all of your DNA (this is called "whole genome sequencing. DNA contains information that determines things like eye color, height, or disease risk that are passed on from parent to child. Genetic information (also known as genotype data) and the medical record data (also known as phenotype data) may be shared broadly in a coded form for future genetic research or analysis.

Donating data and specimens may involve a loss of privacy, but information about you will be handled as confidentially as possible. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security. Genetic information that results from this study does

not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. Taking part in a genetic study may also have a negative impact or unintended consequences on family or other relationships. It is possible that future research could one day help people of the same race, ethnicity, or sex as you. However, it is also possible through these kinds of studies that genetic traits might come to be associated with your group. In some cases, this could reinforce harmful stereotypes.

There will be no direct benefit to you from allowing your data and specimens to be kept and used for future research. However, we hope we will learn something that will contribute to the advancement of science and understanding of health and disease. If the data or specimens, or any new products, tests or discoveries that result from this research have potential commercial value, you will not share in any financial benefits. If you decide later that you do not want your information to be used for future research, you can notify the investigator in writing or by phone at:

UCSF PI: Lawrence Fong, MD
[redacted]

UC-Davis PI: Mamta Parikh, MD
[redacted]

and any remaining data will be destroyed. However, we cannot retract any data has been shared with other researchers.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a research study. Treatment available off study include cisplatin-based chemotherapy, an FDA approved therapy for the treatment of bladder cancer that cannot be treated with surgery or radiation therapy alone. Cisplatin-based combination chemotherapy regimens are the standard of care for stage IV bladder cancer.
- Taking part in another research study.
- Getting no treatment.
- Getting comfort care, also called palliative care.

Please talk to your doctor about your choices before deciding if you will take part in this research study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record is

kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this research study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Genentech and their associates
- The University of California
- The National Cancer Institute (NCI) and other government agencies, e.g., the Food and Drug Administration (FDA), involved in keeping research safe for people.

Participation in research may involve a loss of privacy, but information about you will be handled as confidentially as possible. A medical record will be created because of your participation in this study. Your consent form and some of your research test results will be included in this record. Therefore, your other doctors may become aware of your participation. Hospital regulations require that all health care providers treat information in medical records confidentially.

California Confidentiality Statement

California regulations require laboratories to report new cases of HIV, hepatitis B, and hepatitis C infection to the county public health department. The reports include the patient's name, social security number, and other identifying information. Information about these new infections is used to track these diseases statewide and nationwide. Other than this required reporting, your results will be treated confidentially by the study staff. Personally identifying information will not be reported to other departments or agencies.

What are the costs of taking part in this study?

Genentech, the manufacturers of atezolizumab and tiragolumab, will provide the study drugs at no cost.

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

If you have questions about what costs you will be responsible for, please talk with the study investigator before deciding to enroll in the study. Depending on the type of study, some of your costs could be substantial.

Will I be paid for taking part in this study?

You will not be paid for taking part in this research study.

What happens if I am injured because I took part in this study?

It is important that you tell your research study doctor if you feel that you have been injured because of taking part in this research study. You can tell the doctor in person or contact your study doctor by phone:

UCSF PI: Lawrence Fong, MD [redacted]

UC-Davis PI: Mamta Parikh, MD [redacted]

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the UCSF Office of the Institutional Review Board at 415- 476-1814.

What are my rights if I take part in this study?

Taking part in this research study is your choice. You may choose either to take part or not to take part in the research study. If you decide to take part in this research study, you may leave the research study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the research study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about significant new information or changes in the research study that may affect your health or your willingness to continue in the research study.

In the case of injury resulting from this research study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your research study doctor about any questions, concerns, or complaints you have about this research study. Contact your research study doctor.

If you wish to ask questions about the research study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the research study, please call the UCSF Office of the Institutional Review Board at 415-476-1814.

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.

Please note: This section of the consent form concerns cisplatin-eligibility.

As stated in the beginning of this consent form, cisplatin-based chemotherapy is a type of treatment which is commonly used either before or after removal of the bladder. In large studies, patients who received cisplatin-containing chemotherapy before surgery were more likely to be cured of bladder cancer and were more likely to be alive 5 years later.

If your doctor determines that you are able to receive cisplatin-based chemotherapy and you have declined to receive cisplatin-based chemotherapy prior to your surgery, understanding and recognizing the benefits described above, please indicate your decision below. You may be eligible to enter this study if you decline to receive cisplatin-based chemotherapy prior to your surgery.

Making Your Choice
Please read each sentence below and think about your choice. After reading each sentence, put your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care.

1. *I am declining cisplatin-based chemotherapy, understanding and recognizing the benefits of treatment before surgery, OR my provider has informed me that I am not able to receive cisplatin.*

YES	*NO*

Reason for declining chemotherapy: _____

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OPTIONAL RESEARCH PARTICIPATION

This section of the informed consent is about optional future contact of participants in the main study. You can still be in the main study even if you say "no" to allowing optional future contact.

Future Contact

We want to know if we may contact you in the future to see if you are interested in participating in other research studies.

If you agree and we contact you to tell you about a study, you have no obligation to actually participate in any study. You can decide when you are told about the study if you want to receive more information about the study. There would be a new consent process for that study.

If at any time you decide you no longer want to be contacted about future studies, please let us know [redacted].

Making Your Choice

Please read the sentence below and mark your choice by putting your initials in the "Yes" or "No" box. If you have any questions, please talk to your doctor or nurse, or call our research review board at 415-476-1814.

No matter what you decide to do, it will not affect your care or your participation in the main study.

1. *Someone may contact me in the future about taking part in more research.*

YES	*NO*

****

CONSENT

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
	Participant's Printed Name
Date	Person Obtaining Consent
Date	Witness – Only required if the participant is a non-English speaker

STUDY TITLE: CC#14524: Phase II Study of Neoadjuvant Atezolizumab-based Immunotherapy for Patients with Urothelial Carcinoma (NEBULA)

List of Prohibited Medications

The following are a list of commonly used medications which are prohibited while you are participating in this study:

- *Live* vaccines – A *live* vaccine is a type of vaccine that contains small amounts of the *living* virus, such as FluMist (for influenza) and the Measles, Mumps, Rubella vaccine. You should not receive any *live* vaccines while you are participating in this study, including up to 4 weeks before your first dose of study drug and for at least 3 months after the last dose of the study drug. Please note that these restrictions only apply to *live* vaccines. Inactivated vaccines (or killed vaccines), such as RNA- or protein-based COVID-19 vaccines, are not subject to these restrictions. Please let the study doctor know before you receive any vaccinations.
- Denosumab (Prolia, XGEVA) – a drug approved for the treatment of osteoporosis and treatment-induced bone loss
- Any traditional herbal medication
- Any immune stimulants. These include interferon alpha or gamma, or interleukin-2 (IL-2)
- Any medication that may suppress your immune system. These include:
    - Medicines commonly known as "steroids" or "corticosteroids":
        - Prednisone
        - Prednisolone
        - Hydrocortisone
        - Dexamethasone
    - Cyclophosphamide (Cytoxan)
    - Azathioprine (Imuran)
    - Methotrexate (Rheumatrex, Trexall)
    - Thalidomide (Thalomid)
    - Infliximab (Remicade)
    - Etanercept (Enbrel)
    - Adalimumab (Humira)
    - Certolizumab (Cimzia)
    - Golimumab (Simponi)
- Steroid creams and ointments (i.e hydrocortisone, clobetasol, betamethasone) used for skin conditions are allowed while you are on the study
- Inhaled steroids (i.e. fluticasone, Flovent) used for asthma or bronchitis are allowed while you are on the study.
- Certain steroids (fludricortisone) are allowed if used for adrenal insufficiency. Tell your doctor if you take, or are planning to take these medications.

There may be other medications that can suppress or enhance your immune system and should not be taken while you are on the study. If you are unsure please ask your doctor before starting any new medication.