Are you participating in any other research studies? _____ Yes _____No

INTRODUCTION TO RESEARCH STUDIES

You are invited to voluntarily participate in a research study of durvalumab a treatment for bladder cancer (urothelial carcinoma), being conducted by Sandy Srinivas, MD, at the Stanford Cancer Center. You were selected as a possible participant in this study because your bladder cancer is invading the surrounding tissues of your bladder and is an uncommon type of bladder cancer known as "variant histology bladder cancer". There are several types of "variant" bladder cancer such as: squamous differentiation; glandular differentiation; nested variant; microcystic variant; micropapillary variant; lymphoepithelioma-like carcinoma; plasmacytoid and lymphoma-like variants; sarcomatoid variant/carcinosarcoma; giant cell variant; trophoblasitic differentiation; clear cell variant; lipid cell variant; and undifferentiated carcinoma. These variant types of bladder cancer are not well studied and may need treatment that is not included in the treatment of "regular" bladder cancer. Variant histology bladder cancer can be difficult to treat with standard treatments. This study adds durvalumab to standard treatments to test whether the addition of durvalumab leads to better outcomes for variant bladder cancer patients.

Durvalumab is still in the development stage for the treatment of Muscle Invasive Bladder Cancer and is not approved for treatment of Muscle Invasive Bladder Cancer except for use in research studies like this. However, durvalumab is approved by the FDA and the European Medicines Agency (EMA) for the treatment of patients with locally advanced non-small cell lung cancer after chemoradiation therapy and extensive-stage small cell lung cancer in combination with chemotherapy.

This document is to be used as a guide for a discussion between you and your Study Doctor and the study team. This form, called an informed consent document, was designed to help you understand why this study is being done; what part of the study is "research" or "experimental;" what will be asked of you if you choose to participate; possible risks; any inconveniences or discomforts you may experience; and other important information. This form may also be helpful as a reference if you choose to participate, as a reminder of what your role in the study is, and who to contact if you have questions at any time during your participation. You are urged to discuss any and all questions you have about this study with members of the study team. If you wish, you can also discuss this study and your role with your family doctor or medical provider.

PURPOSE OF RESEARCH

The proposed study is called a Phase 2 "neoadjuvant" chemotherapy study. Neoadjuvant treatment, means to receive chemotherapy and/or radiation therapy before surgery. The study team hopes to learn if durvalumab, administered in combination with standard

chemotherapy, is safe, and if there is any beneficial effect of durvalumab in combination with chemotherapy to treat variant histology bladder cancer.

Your doctor recommends chemotherapy as the best treatment choice that is available to you at this time. Other than durvalumab administration, there are no other research aspects of this study. Your normal medical care for your bladder cancer would be the same or similar chemotherapy. The current standard anti-cancer treatment for your cancer includes combinations of drugs known as methotrexate; gemcitabine; carboplatin; cisplatin; vinblastine; and doxorubicin.

Using current therapies, some patients with variant histology bladder cancer receive treatment benefit but are not cured of their disease. Your normal medical care would also include medical exams, blood tests, and medical scans to check the status of your cancer such as positron emission tomography (PET); computed tomography (CT); or magnetic resonance imaging (MRI) scans. Your normal medical care might also include radiation treatments, depending on the details of your cancer. This study does not include radiation treatment.

The other parts of this study that are research (experimental, not part of your regular care) are the use and administration of durvalumab. Durvalumab is approved by FDA as "Imfinzi" for the treatment of people with locally-advanced or metastatic urothelial carcinoma that progressed (got worse) during or after platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. "Neoadjuvant" therapy means to receive chemotherapy and/or radiation therapy before surgery. "Adjuvant" therapy means having the surgery first, followed by chemotherapy and/or radiation therapy. For this study, durvalumab will be provided by the drug manufacturer AstraZeneca/MedImmune.

If you decide to terminate your participation in this study, you should notify Dr Srinivas at 650-725-2078.

This research study is looking for up to 24 patients with variant histology bladder cancer. The study is being done at about only at the Stanford University Medical Center.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

DURATION OF STUDY INVOLVEMENT

It is planned that each participant will take part in this study for up to about 5 months.

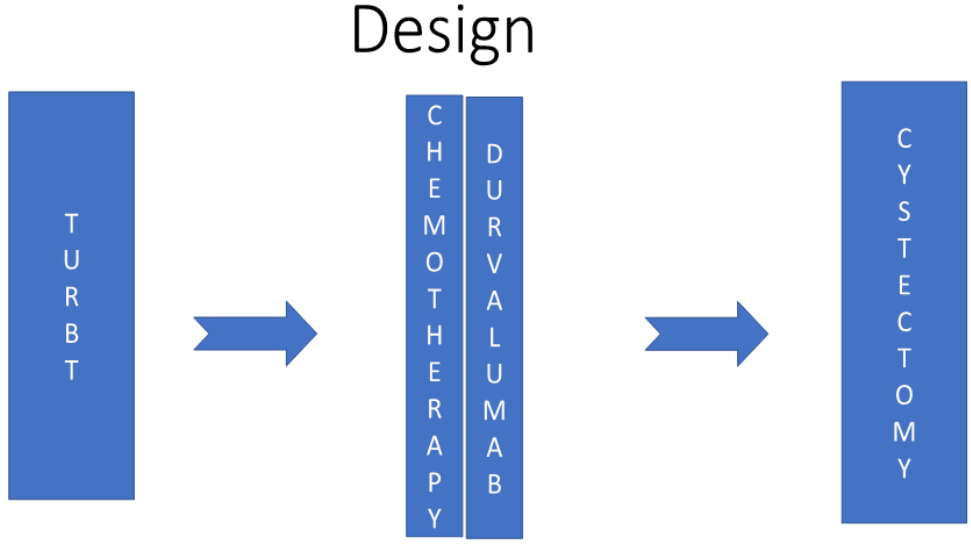
Information about the end of your participation in the study is provided under "Withdrawal from the study."

PROCEDURES

It may be harmful to enter this study while receiving some medications, therefore, you may need to stop taking certain medications. Your Study Doctor will review your medications and provide you with specific instructions.
Before you join this study, Dr Srinivas and/or the research study team will review this document with you, and ask you to sign this informed consent document. After you have signed this document, and received a signed copy, the study will begin with a Screening Visit.
Research studies are usually dividing into at least 3 parts, typically consisting of:

1. Testing to see if you are eligible to participate in the study ("Screening");
2. Testing during study treatment to monitor your health and the effects of the study treatment ("Study Evaluation Procedures"); and
3. Testing after your treatment is complete ("Follow-up"). Testing/procedures for each of these parts are described separately below.

Following is an image that illustrating this study.



The first part of the study is screening. Eligible patients will continue to receive durvalumab and chemotherapy, and then have their bladder and remaining tumor removed (cystectomy).
Most of the examinations, tests, or procedures will be part of your regular medical care, would be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated.

Screening Visit

If you choose to participate, the first activity will be Screening. During the Screening Visit, you will be asked to have the following tests and activities or assessments.

General information: Information about you, such as date of birth; gender (sex); and ethnic origin ("demographic information")

Medical history: Your complete medical history will be reviewed, including:

- Review of all medicines and/or supplements you are taking or have been taking
- Questions about any medical symptoms you are having
- Surgery and cancer history
- Tobacco and alcohol use
- Reproductive status

Physical examination: A complete physical exam will be performed, including:

- Your vital signs, including height; weight; breathing rate; heart rate; blood pressure; temperature; and other measurements
- General examination of your body systems, such as heart and lungs; ear, nose, and throat; skin; muscles and joints; stomach and gastrointestinal tract; and nervous system
- You will be asked how well you are able to perform normal daily living activities (such as bathing, driving, shopping, working, etc)

Electrocardiogram (ECG or EKG): An ECG scan will be performed according to standard practice to measure and record the electrical activity of your heart. This assessment is performed entirely from outside the body, meaning you do not have to have an injection or incision (noninvasive). The procedure is called a 12-lead ECG because 12 wires will be attached to your chest near your heart, and at your wrists/arms and ankles/legs with adhesive pads. You will be asked to lie still during the procedure. A computer will make a recording of your heart's electrical activity, which will tell doctors information about how well your heart is working. The results of this test may be used in combination with other imaging procedures described below.

Echocardiogram (ECHO) scan: An ECHO scan will be performed according to standard practice to evaluate your heart's function and structures. This assessment is performed entirely from outside the body, meaning you do not have to have an injection or incision (noninvasive). An ECHO scan is a non-radiation procedure, and is similar to the sonogram procedure a woman might have during pregnancy. The procedure includes ECG recordings as described above. A microphone-like device called a transducer will send out ultrasound waves into your chest. Like a dog whistle, ultrasound is too high for you to hear. The ultrasonic sound waves "echo" off of the heart structures, and a computer converts the echoes into images. Generally, no calming medications (sedation) or fasting are needed. Tell the study team if you have any medical devices implanted, such as a pacemaker. Electrodes will be attached to your

skin to record the echoes. The ECHO technician will place a gel on your chest. The technician will apply varying amounts of pressure with the transducer probe. The amount of pressure should not be uncomfortable, but if it does, tell the technician.

Blood collection: Blood collection will typically be from a vein in your arm, using a blood collection needle. This is called venipuncture. If you have an implanted venous access port, this may be used for blood collection. Standard aseptic (clean) techniques will be used.
About 2 tablespoons (30 mL) of blood will be collected for:

- **Complete blood count (CBC) with differential**, including red blood cells (RBC, oxygen-carrying cells): white blood cells (WBC, infection-fighting cells); platelets; and other blood components.
- **Serum chemistry or "Comprehensive Metabolic Panel,"** consisting of tests for blood chemicals that indicate how well your body and organs are working, and if you have any significant diseases.
- **Research blood sample**. A blood sample will be drawn to measure tumor markers as detected by cancer cell DNA.
- **Serum pregnancy test** (if you are a woman who can become pregnant). The pregnancy test must be negative within 30 days before joining the study.
- **Blood test for certain types of viral infections**, including hepatitis viruses and the human immunodeficiency virus ["HIV;" the virus that causes acquired immunodeficiency syndrome (AIDS)]. People who are HIV-positive or have hepatitis may be still be eligible. These tests are required in order to participate in this study. HIV and hepatitis may be a reportable disease where you live. If you test positive for HIV, counseling will be provided. Please ask your study doctor for details if you have concerns about this.

Disease status / Tumor Assessment: The size and severity of your tumor will be assessed during the physical exam above (within 30 days of starting study treatment), and by a radiologic evaluation (scan imaging) within 28 days of starting study treatment. These scans look at the blood flow and the extent and activity of your cancer, and are a part of your regular medical care (Standard-of-Care, SOC). The radiologic evaluation may be computed tomography (CT) scan; positron emission tomography (PET) scan; magnetic resonance imaging (MRI), or an alternate scan as medically necessary. Regardless of which scan will be conducted, these scans are part of your regular medical care for a patient with bladder cancer. These procedures are described below:

CT imaging: A CT scan with contrast may be performed according to standard practice within 28 days before the expected 1st day of treatment. This scan is part of your regular medical care. You may be asked to not drink or eat anything ("fast") for a couple hours before the scan. The scan will take about 30 to 60 minutes. The type of scan that you will have is called a CTCAP, meaning **c**omputed **t**omography of the **c**hest, abdomen, **a**nd **p**elvis.

A **bone scan** will be performed according to standard practice to detect or rule out bone lesions. This scan is part of your regular medical care. If you have had an X-ray using a barium contrast material (such as a barium enema) or have taken a medicine that contains bismuth (such as Pepto-Bismol) within the past 4 days, tell the Study Doctor or study team as barium or bismuth can interfere with the scan results (ask if you need more information about this). It is not necessary to fast before the bone scan, but it is best to avoid eating a meal or drinking large amounts of fluids before the test. A tourniquet will be applied to your arm to help find a vein, and a radioactive tracer will then be injected into a vein.
A radioactive tracer is a combination agent that has a radioactive element attached. The tracer circulates through the body part of interest, and the pattern of the signal from the radioactive element tells the doctor information about that body part. You will have to wait 2 to 3 hours after the injection before the scan can be performed. You will lie on your back on a bench within the scanner and must be as still as possible during the scan. You may be asked to assume various positions on the table in order for all of the necessary images to be taken. The scanner will move back and forth slowly, recording images for about 1 hour. After the scan, you should drink plenty of fluids.

Women of Childbearing Potential
If you are pregnant or currently breast-feeding, you may not participate in this study. The chemotherapy you will receive in not safe for fetus (unborn child) or a breast-fed baby. It is also not known whether the durvalumab is safe for a fetus (unborn child) or a breast-fed baby.

Study Treatment

All participants in this study will receive the experimental anti-cancer study drug durvalumab. You may know durvalumab by the tradename Imfinzi. This study tests whether adding durvalumab to several possible anti-cancer chemotherapy drug regimens improves the overall anti-cancer effect. Based on the assessment of your medical condition, the study doctor will select 1 of the 3 different treatments described below. All the treatments will be administered into vein (intravenously (IV)).

- Treatment "DD MVAC" (dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin). DD MVAC treatment occurs on a 14-day cycle.
  - Day 1 of each cycle. Durvalumab at a fixed dose of 750 mg, plus methotrexate at a fixed dose of 30 mg/m^2.
  - Day 2 of each cycle. Vinblastine at 3 mg/m^2; plus doxorubicin at 30 mg/m^2, plus cisplatin 70 mg/m^2.

- Treatment "Cis-Gem," or "Carbo-Gem," consisting of gemcitabine with either cisplatin or carboplatin. "Cis-Gem and Carbo-Gem treatment occurs on a 21-day cycle.
  - Day 1 of each cycle. Durvalumab at a fixed dose of 1500 mg, plus gemcitabine 1,000 mg/m^2 IV and either cisplatin 70 mg/m^2 or carboplatin at a dose of "AUC 5."
  - Day 8 of each cycle. Gemcitabine 1,000 mg/m^2.

In the remainder of this document, the term "Study Drug" refers to the experimental treatment, ie, durvalumab.

Study Evaluation Procedures

During the study, you will come into the clinic on Day 1 of each cycle to receive your treatment, and for tests to assess how well the treatments are working. You will also come into the clinic on Day 2 or Day 8 of each cycle, depending on your treatment group. At all clinic visits the doctors will ask about the medicines you are taking, and if you have any side effects. The tests that will occur on Day 1 of each cycle are described below.

Physical examination: A physical exam will be performed, as described above.

Blood collection: Blood will be collected, as described above. Up to about 2 tablespoons (30mLs) will be collected.
Assessments on Day 2 or Day 8 of each cycle (depending on treatment assignment) will be limited to checking about the medicines you are taking, and if you have any side effects.

During this study, you will have your bladder cancer surgically removed by cystectomy (surgical removal of your bladder). Before the surgery, your medical condition will be checked by a CT-CAP scan, as described above, and a small sample of blood will be collected (about 1 teaspoon, 5 mL). The study team will also check about the medicines you are taking, and if you have any side effects.

Additional tests may be ordered by the doctor as determined medically necessary.

End-of-Study

The end of this study is planned to be the visit about 30 days after the surgery. Your medical condition will be checked by a CT-CAP scan, as described above, and a small sample of blood will be collected (about 1 teaspoon, 5 mL). The study team will also check about the medicines you are taking, and if you have any side effects.

Study Follow-Up Procedures

Your Tissue / Data Samples for Research and Genetic Testing

Research using tissues, such as from your research blood sample, is an important way to try to understand human disease. Sometimes, research may include the testing and study of genes, also known as DNA, and related materials called RNA, proteins, and/or metabolites. This type of testing is also called "genetic analysis" or called "pharmacogenomic research." You are being given this information because the Study Doctors want to include a sample of your blood in a research project and because they want to save the samples for future research. A previously-collected tumor sample may be adequate for this, or your doctor may need to collect a fresh sample of your tumor tissue for testing, which will include genetic analysis.

There are several things you should know before participating in this study and … allowing your blood to be studied. This subject is complicated, and there are many considerations. Ask for more information if you do not understand any part of this information.
Genes are in every cell of your body. Your genes were inherited from your biological parents and carry instructions for the body to grow, develop, and survive. Genes are made of a substance called DNA. Most genes and DNA are identical among human beings, but there are small variations between different people. These small genetic differences are why people have their own unique characteristics, such hair color, eye color, height, and other characteristics.
Some traits affected by genetics are not visible, such as why different people have different responses, including side effects, to the same drug, or are more likely to get certain diseases or conditions. The proteins in your body were determined by your genes, and control how your body works. Differences in genes and therefore proteins can affect the way a disease develops, the way drugs act against the disease, or the way your body uses the drugs.
The purpose of this type of research is to understand the cause of disease, such as cancer, or the body's response to the treatments (such as safety findings or drug level patterns). In this study, the genetic research is being done learn more about variant histology bladder cancer, and what might be effective to improve treatment of this type of cancer.

The data from your sample for this genetic research project will be used for research purposes only. This genetic research sample may be used for additional research including: additional studies of cancer; as a comparison sample ("control sample") in other cancer studies or in a group of other patients' samples to determine the natural difference in genes and proteins in groups of people with cancer; or to develop new gene research techniques. The results of future studies could trigger the need to test or re-test the genetic research samples; therefore, the sample and data generated from them will be held by Stanford and the company supporting this study (AstraZeneca/MedImmune) for many years. These samples, and the data generated from them, may be shared with other researchers or entered into databases, provided confidentiality is upheld (you are not identified), and they are used only for research on the topics described in this document. The information in these databases may be kept forever, however, information that could directly identify you will not be included in these databases.

However, your privacy is very important to us and we will use safety measures to protect it. Despite all of the safety measures that we will use, we cannot guarantee that your identity will never become known.

Although you will be told the results of study tests that are part of your regular medical care, the genetic testing described here will not be used for decisions about your medical care, and there may be no results from this genetic research for many years, therefore the results of the genetic testing may not be given to you, your doctor, or any other staff at the study center.

Providing genetic information to others

Sometimes patients have been required to furnish information from genetic testing for health insurance, life insurance, and/or a job. A Federal law, the Genetic Information Nondiscrimination Act of 2008 (GINA), generally makes it illegal for health insurance companies, group health plans, and employers with 15 or more employees to discriminate against you based on your genetic information.
Be aware that that GINA 2008 does not specifically protect you against genetic discrimination by companies that sell life insurance; disability insurance; or long-term care insurance.

Handling of your Tissue Samples

Your samples will be sent outside of Stanford for analysis. Your blood sample will be stored and identified by your unique study number ("study identifier") only, and not your name. This study identifier will be a series of numbers and/or letters. Donors of samples do not retain any property rights to the samples.
You have the right to refuse to allow your tissues to be studied now or saved for future study. However, agreeing to provide this blood sample is required in order to participate in this study. If you choose not to provide the sample, you cannot participate in the study. Regular medical care will be available to treat your condition.
You may withdraw from this study at any time. The Study Doctors might retain the identified samples, eg, as part of your routine clinical care, but not for additional research.
An authorization statement for your initials is provided on the signature page of this document.

Adverse event monitoring will be performed as part of the procedures described above. During the treatment period, the Study Doctors will monitor you for any potential side effects. If the side effects are severe, the Study Doctors may temporarily stop study medication; change the dosage of your study medication; or withdraw your medication completely.

If, at any time, you have any symptom; side effect; or injury affecting you physically or mentally during the study, **you should tell the Study Doctors or nurses right away**, even if you do not think it was caused by the study medication.
If you have to go to the hospital for any reason, please tell the hospital staff that you are participating on a research study, and give them the contact information for the study team. You may be provided with a card with the study team contact information.

STUDY CALENDAR BY COHORT (all receive durvalumab)

Dose-Dense Methotrexate, Vinblastine, Doxorubicin, Cisplatin cohort ("DD MVAC" 14-day Cycle)

Procedure	**Screening[a]**	**Cycle 1 Day 1[c]**	**Cycle 1 Day 2[c]**	**Cycle 2 Day 1 [c]**	**Cycle 2 Day 2 [c]**	**Cycle 3 Day 1 [c]**	**Cycle 3 Day 2 [c]**	**Cycle 4 Day 1 [c]**	**Cycle 4 Day 2 [c]**	**EOT Safety Visit**	**Surgery**	**ctDNA Collection**	**End of Study Visit**
Scheduling Window (Days)	**-30 to -1**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**(+2)**	**4 weeks[m] (+/- 2 weeks)**		**4 weeks post-cystectomy (+/- 2 weeks)**	**12 weeks post-cystectomy (+/- 2 weeks)**
Informed Consent[h]	**X**												
Medical history	**x**												
Physical exam	**X**	**X**		**X**		**X**		**X**					
Vital signs, weight, & height[d]	**X**	**X**		**X**		**X**		**X**					
ECOG Performance Status	**X**	**X**		**X**		**X**		**X**					
Complete blood count w/differential	**X[f]**	**X**		**X**		**X**		**X**					
Comprehensive metabolic panel including Mg[i]	**X[f]**	**X**		**X**		**X**		**X**					
Coagulation (PT, PTT, INR)	**X**												
TSH	**X**												
Urinalysis	**X**												
Hepatitis B serology	**X**												
Hepatitis C serology	**X**												

HIV serology	X												
Pregnancy test	X												
Biomarkers[k]	X	X								X		X	X
12-lead ECG[g]	X												
ECHO	X												
Tumor specimen testing	X										X		
CT or MRI of abdomen and pelvis[e]	X									X			X[L]
CT or X-ray of chest[e]	X												
Bone scan (if alk phos is elevated)	X												
Adverse event collection		X		X		X		X		X	X	X	X
Concomitant medications	X	X		X		X		X		X	X	X	X
TREATMENT													
Durvalumab (750mg)		X		X		X		X					
Methotrexate		X		X		X		X					
Vinblastine			X		X		X		X				
Doxorubicin			X		X		X		X				
Cisplatin			X		X		X		X				
Cystectomy[j]											X		

Cisplatin plus Gemcitabine cohort ("Cis-Gem," 21-day cycle)

Procedure	Screening[a]	Cycle 1 Day 1 [b]	Cycle 1 Day 8	Cycle 2 Day 1 [b]	Cycle 2 Day 8	Cycle 3 Day 1 [b]	Cycle 3 Day 8	Cycle 4 Day 1 [b]	Cycle 4 Day 8	EOT Safety Visit	Surgery	ctDNA Collection	End of Study Visit
Scheduling Window (Days)	**-30 to -1**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**4 weeks[m] (+/- 2 weeks)**		**4 weeks post-cystectomy (+/- 2 weeks)**	**12 weeks post-cystectomy (+/- 2 weeks)**
Informed Consent[h]	X												
Medical history	X												
Physical exam	X	X		X		X		X					
Vital signs, weight, & height[d]	X	X		X		X		X					
ECOG Performance Status	X	X		X		X		X					
Complete blood count w/differential	X[f]	X		X		X		X					
Comprehensive metabolic panel including Mg[i]	X[f]	X		X		X		X					
Coagulation (PT, PTT, INR)	X												
TSH	X												
Hepatitis B serology	X												
Urinalysis	X												
Hepatitis C serology	X												
HIV serology	X												
Pregnancy test	X												
Biomarkers[k]	X	X								X		X	X
12-lead ECG[g]	X												
ECHO	X												

Tumor specimen testing	X										X		
CT or MRI of abdomen and pelvis[e]	X									X			X[L]
CT or X-ray of chest[e]	X												
Bone scan (if alk phos is elevated)	X												
Adverse event collection		X		X		X		X		X	X	X	X
Concomitant medications	X	X		X		X		X		X	X	X	X
TREATMENT													
Durvalumab (1500mg)		X		X		X		X					
Cisplatin		X		X		X		X					
Gemcitabine		X	X	X	X	X	X	X	X				
Cystectomy[j]											X		

Carboplatin plus Gemcitabine cohort ("Carbo-Gem," 21-day cycle)

Procedure	Screening[a]	Cycle 1 Day 1	Cycle 1 Day 8[b]	Cycle 2 Day 1	Cycle 2 Day 8[b]	Cycle 3 Day 1	Cycle 3 Day 8[b]	Cycle 4 Day 1	Cycle 4 Day 8[b]	EOT Safety Visit	Surgery	ctDNA Collection	End of Study Visit
Scheduling Window (Days)	**-30 to -1**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**(+/- 2)**	**(+2)**	**4 weeks[m] (+/- 2 weeks)**		**4 weeks post-cystectomy (+/- 2 weeks)**	**12 weeks post-cystectomy (+/- 2 weeks)**
Informed Consent[h]	X												
Medical history	X												
Physical exam	X	X		X		X		X					
Vital signs, weight, & height[d]	X	X		X		X		X					
ECOG Performance Status	X	X		X		X		X					
Complete blood count w/differential	X[f]	X		X		X		X					
Comprehensive metabolic panel including Magnesium[i]	X[f]	X		X		X		X					
Coagulation (PT, PTT, INR)	X												
TSH	X												
Urinalysis	X												
Hepatitis B serology	X												
Hepatitis C serology	X												
HIV serology	X												
Pregnancy test	X												
Biomarkers[K]	X	X								X		X	X
12-lead ECG[g]	X												
ECHO	X												

Participant ID:

Tumor specimen testing	X									X			
CT or MRI of abdomen and pelvis[e]	X									X			X[L]
CT or X-ray of chest[e]	X												
Bone scan (if alk phos is elevated)	X												
Adverse event collection		X		X		X		X		X	X	X	X
Concomitant medications	X	X		X		X		X		X	X	X	X
TREATMENT													
Durvalumab (1500mg)		X		X		X		X					
Carboplatin		X		X		X		X					
Gemcitabine		X	X	X	X	X	X	X	X				
Cystectomy[j]											X		

a: Subjects must be screened within 30 days prior to Cycle 1 Day 1 with the exception of some labs.
b: For Cis/Gem and Carbo/Gem cohorts there must be at least 7 days between Day 1 and Day 8.
c: Efforts should be made to conduct study visits on the day scheduled (+2 days). Delays in dosing will shift the following cycle so that there are at least 12 days between Day 8 of the previous cycle and Day 1 of the current cycle.
d: Assessments will include vital signs (resting BP HR, RR, and body temperature) and weight. Height will be recorded at screening.
e: PET CT for subjects with impaired renal function is an acceptable alternative.
f: within 28 days of Cycle 1 Day 1
g: ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value > 470 ms; 2 additional 12 lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.
h: Informed consent may be obtained greater than 30 days prior to first dose of study treatment.
i: Magnesium is to be performed at baseline on Day 1 and as clinically indicated
j: Within 6 weeks post completion of 4 cycles
k: Biomarkers sample to be collected at pre-initiation of neoadjuvant treatment, upon completion of neoadjuvant treatment and prior to surgical cystectomy, 4 weeks (+/- 2 weeks) post-cystectomy and 12 weeks (+/- 2 weeks) post cystectomy
L: May be completed within 7 days before the End of Study visit
m: within 4 weeks ± 2 weeks of completion of neoadjuvant treatment, typically at the subject's cystectomy pre-operative visit

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the Protocol Director and study team.
- Be sure to tell the study team all of your present and past diseases, allergies and any drugs or medications you are taking. This is for your safety. Other drugs or medications includes all prescription drugs; over-the-counter (OTC) drugs; herbal preparations; and nutritional supplements. These may interact with the study drug durvalumab or the chemotherapy. If any other medical provider prescribes new medications for you while you are on this study, please contact the study team before taking the new medicine, or have that medical provider contact the study team before prescribing it to you. You should not take any new non-prescription medicine while you are on this study unless you first check with the study team.
  - Ask questions as you think of them.
  - Tell the Study Doctor or study team if you change your mind about staying in the study.
  - Tell the Study Doctor or study team about any side effects, doctor visits, or hospitalizations that you may have.
  - Tell the Study Doctor or study team if you believe you might be pregnant or gotten your partner pregnant.
    - **Men** must use a medically-approved method of birth control, preferably a barrier method, for the duration of the treatment period and for at least 6 months after the last injection of durvalumab.
    - **Women** must use a medically-approved method of birth control, preferably a barrier method, for the duration of the treatment period and for at least 3 months after the last injection of durvalumab.
  - Keep your study appointments. If it is necessary to miss an appointment, please contact the Study Doctor or research study team to reschedule as soon as you know you will miss the appointment.

About Pregnancy

In order to participate in this study, you must agree to use medically-acceptable birth control. If you do not use the required birth-control method(s), you may be discontinued from this study. Please ask the Study Doctor or study team if you have any questions.

Regardless of whether you are a man or a woman, your birth control method(s) must be reviewed by the Study Doctor and determined to be effective, as well as to not interfere with the study. In particular, use of a hormonal contraception must be approved by the Study Doctor before you begin taking the Study Drug. There is a risk that pregnancy could still happen despite the responsible use of a reliable method of birth control. You agree to notify the Study Doctor as soon as possible of any failure of proper use of your birth control method, or if you become pregnant, either of which may result in your being withdrawn from the study.

Women of Childbearing Potential: If you are a woman capable of having children and choose to have sex, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk, for 3 months after your last dose of study drug. The only certain way to be 100% certain you will not get pregnant is to not have sex. You understand that if you are pregnant, if you become pregnant, or if you are breast-feeding during this study, you; the fetus (unborn child); or the child may be exposed to unknown risks. To confirm that you are not pregnant, you agree to have a pregnancy test done before beginning this research study.
During the study, if you become pregnant, or you think you may be, you must immediately stop taking the Study Drug and tell your Study Doctor. If you become pregnant during the study, the Study Drug may involve unforeseeable risks to the unborn baby, and your pregnancy will be followed to determine the outcome.

Men: If you are a man and your partner is able to become pregnant, for 6 months after your last dose of durvalumab, you must:

- Talk to the Study Doctor about birth control methods that you should use.
- Prevent pregnancy in your female partners
- Inform your female partners of the potential for harm to her or a fetus. They should know that if pregnancy occurs, they should promptly notify their doctors
- Not donate sperm for 6 months after your last dose of durvalumab.
- Tell the Study Team and your partner's physician immediately if your partner becomes pregnant

Your doctor will discuss with you whether your preference for birth control is considered adequate.

WITHDRAWAL FROM THE STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical care for your disease and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify Sandy Srinivas, MD at 650-725-2078. If you withdraw after starting treatment with the durvalumab, your Study Doctor will need to check on your health status afterwards. If you do not want the Study Doctor to check on your health status after withdrawing from the study, you should say so. Any information collected before you withdraw will be kept and used to complete the research.

To help you safely finish your participation in the study, the Study Doctors may ask you to have more tests and you will be asked to come into the clinic for an End-of-Treatment Visit after stopping durvalumab. The Study Doctor will discuss your treatment options with you at this time. If you withdraw from the study, or the study medication is stopped for any reason,

- Your cancer may get worse.
- To help you leave the study safely, the Study Doctors may ask you to have more tests.
- The Study Doctors may also ask if you wish to take part in the follow-up portion of the study. If you agree to continue with the follow-up portion of the study, information about your health will continue to be collected as described above in the Follow-up Procedures section.
- The Study Doctor will discuss with you the different withdrawal decisions, including your options for continued treatment.
- Data and information from your participation may not be removed from the research study database and may continue to be used to complete the research analysis. This is discussed in more detail under the heading "Authorization To Use Your Health Information For Research Purposes" on the following pages.

Your treatment in this study can continue until one of the following occurs:

- You withdraw your agreement to continue to take part in this research study;
- The Study Doctor withdraws you from the study, and the study medication is stopped, with or without your consent, for one or more of the following reasons:
  - Failure to follow the instructions of the Protocol Director and study team
  - The Study Doctor decides that continuing your participation could be harmful to you, or otherwise not in your best interest
  - Your cancer becomes worse (tumor progression)
  - If you have bad side effects during treatment with durvalumab, or if you or your doctor otherwise decide that the side effects are too severe or undesirable
  - You have a different illness that prevents further administration of durvalumab
  - You need treatment with drugs or procedures not allowed in the study.
  - You have become pregnant
  - The study is stopped by the company supporting the study (AstraZeneca/MedImmune); the Study Doctor; the Stanford Institutional Review Board (the IRB, a group of people who review the research to protect your rights), or by a regulatory agency such as the US FDA
  - Other administrative reasons
  - Unanticipated circumstances

When your participation in this study ends, you may be asked to return for a final visit to have some end-of-study evaluations or tests, or to allow medical information to be collected about your health after the trial treatment is stopped. After you finish the study, or stop taking the durvalumab for any other reason, you may continue to be checked regularly (physical exams; blood tests; tumor measurements; X-rays; other scans, etc) if you continue to have significant side effects from the treatment. This is called follow-up. Your Study Doctor will follow your

progress, in accordance with good medical care, for as long as it is felt to be necessary by both you and the doctor, unless you ask otherwise. Many if not all of these procedures will be part of your regular continued medical care. In addition, further treatment outside the study will be discussed with you.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There are risks, discomforts, and inconveniences associated with any research study. This section describes the reasonably foreseeable risks; discomforts; and inconveniences that you may experience. In addition, because this is a research study, there may be risks that are not yet known ("unforeseeable"), including a risk of death due to unknown risks. These deserve careful thought. You should talk with the Study Doctor if you have any questions.

You must tell the Study Doctor or study team about all side effects that you have. If you are not honest about your side effects, it may not be safe for you to stay in the study. Your Study Doctor may give you medications to try to help lessen some of the side effects. All patients in the study will be monitored for side effects.
If you experience serious problems, you may be asked to return to the study center for more tests.
If you experience the following symptoms of an allergic reaction, contact the Study Doctor or the Study Team immediately.

- Allergic reaction, including rash, hives, or blisters; increased heart rate (a fast pulse or tachycardia); or abnormal or increased sweating
- Swelling of the face, mouth, lips, gums, tongue or neck
- Wheezing or difficulty breathing
- Dizziness and fainting

Possible Risks Associated with Durvalumab
Most of the possible side effects seen with durvalumab are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment while others generally get better with treatment. You may need to delay doses of durvalumab to allow the side effects to get better. The most important possible side effects, which are listed below, may occur because of the way durvalumab works on the immune system and they have been seen in patients treated with durvalumab in clinical studies. Side effects like these have also been seen in clinical studies with other drugs that are very similar to durvalumab. Management of these side effects may require the administration of drugs such as steroids or other agents that can affect your immune system and reduce inflammation. It is very important to tell your study doctor right away if you have any of these symptoms.

Very common side effects (affects more than 1 in 10 people):

- ☐ Diarrhea
- ☐ Rash/dry itchy skin
- ☐ Liver problems: Increases in the blood level of substances called enzymes found within your liver cells may occur. The enzyme changes are unlikely to make you feel unwell. However, if these blood enzyme levels become very high, your study doctor may need to stop the study medication. You may develop inflammation of the liver called hepatitis, however this is uncommon. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normal.

In addition to the important possible risks described above, patients with different types of cancer who have been treated with durvalumab alone in clinical trials have very commonly (ie, more than 10% of patients) reported: feeling tired, nausea, vomiting, abdominal pain, accumulation of fluid causing swelling, upper respiratory tract infections, decreased appetite, shortness of breath, cough, pain in muscles and joints and, fever.

Common side effects (affects between 1 in 100 and 1 in 10 patients treated)

- Inflammation in the lungs (pneumonitis): Symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. **Tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.**
- Low thyroid (Hypothyroidism): This is when the thyroid gland produces less thyroid hormone than it should which causes the metabolism to run too slow. Symptoms may include but are not limited to fatigue, increased sensitivity to cold, constipation, dry skin, unexplained weight gain, puffy face, muscle weakness, slow heart rate, thinning hair, impaired memory. The condition can be treated with replacement thyroid hormone.
- High thyroid (Hyperthyroidism): This is when the thyroid gland produces too much thyroid hormone. Symptoms include anxiety or nervousness, weight loss, frequent and loose bowel movements, breathlessness, feeling hot and possibly having heart palpitations. Depending on the severity of the symptoms treatment may include just monitoring the symptoms, treating the symptoms themselves and/or giving medicine to block the thyroid hormone.
- Kidney problems: You may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- Nervous system problems: Symptoms can include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet. In rare situations there is the potential for the inflammation of the nervous system to be severe and cause damage to the nerve cells or breakdown in the communication between nerves and muscles. **Tell your study doctor right away** if you have problems swallowing, if you start to feel weak very quickly and you are having trouble breathing.
- Infusion Related Reactions: Reactions may occur during or after the infusion of study medication. The reaction may cause fever or chills and a change in blood pressure or

difficulty in breathing which might be serious. Tell your study doctor right away if you experience any of these symptoms even if it has been several days after the infusion has been completed.

- Inflammation of the intestine (colitis). It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening. **Tell your study doctor right away if you have any of these symptoms**.
- As well as the important possible risks described above patients with different types of cancer who have been treated with durvalumab in clinical trials have commonly (ie 1% to less than 10% of patients) reported: a hoarse voice, painful urination, night sweats, pneumonia, oral thrush, dental and oral soft tissue infection and, influenza.

Uncommon side effects (affects between 1 in 1,000 and 1 in 100 patients treated)

- Inflammation of the pancreas (pancreatitis): Pancreatitis usually causes symptoms of persistent upper abdominal pain (sometimes made worse by eating and drinking), nausea, vomiting and general weakness. Pancreatitis usually settles with simple measures but it can be a serious condition and can be fatal. **You should immediately tell your study doctor if you develop any unusual symptoms.** You may get an increase of lipase and amylase levels in a blood test (related to the pancreas) but not have any symptoms or feel unwell. Lipase and amylase are enzymes or protein markers that measure the function of your pancreas. Uncommonly these increases may be associated with pancreatitis.
- Allergic reactions: These can cause swelling of the face, lips and throat, breathing difficulties along with hives or nettle like rash. **You should immediately tell your study doctor if you develop any of these symptoms**.
- Problems with your adrenal glands (Adrenal Insufficiency): May cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement.
- Inflammation of the muscles or associated tissues, such as blood vessels that supply the muscles (Myositis/polymyositis). Symptoms can include muscle weakness andaches, tired feeling when standing or walking, muscle pain and soreness that does not resolve after a few weeks.

Rare side effects (affects between 1 in 10,000 and 1 in 1,000 patients treated)

- Type 1 Diabetes mellitus which may cause increased blood glucose levels (called 'hyperglycemia'): Symptoms may include weight loss, increased urination, increased thirst, and increased hunger. Type 1 diabetes will require replacement of insulin through injection. Tell your study doctor right away if you have any of these symptoms.
- Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and

trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement.

- Inflammation of the heart muscle (myocarditis). Symptoms can include chest pain, rapid or abnormal heart beat, shortness of breath and swelling of your legs. **Tell your study doctor right away if you experience any of these symptoms.**
- Blistering and break down of the skin, mouth, and other mucous membranes (called pemphigoid).

As well as the important possible risks described above, patients with different types of cancer who have been treated with durvalumab in clinical trials have rarely (i.e. less than 0.1% of patients) reported: inflammation of the membrane surrounding the heart, growths of tiny collections of inflammatory cells in different parts of the body, inflammation of the middle layer of the eye and other events involving the eye (e.g. Inflammation of the cornea and optic nerves), inflammation of the brain or the membranes that cover the brain and spinal cord, hardening and tightening of the skin and connective tissues and loss of skin color, and hematological events (e.g., abnormal breakdown of the red blood cells and low levels of platelets), inflammation of the blood vessels and rheumatological events (inflammatory disorder causing muscle pain and stiffness and autoimmune arthritis).

In addition to the possible risks identified in patients treated with durvalumab, other immune-mediated side effects are possible that have not been observed, and can result in inflammatory side effects in any organ or tissue.

Possible Risks associated with Surgery (Radical Cystectomy)
This type of surgery is commonly performed in your country for patients with muscle invasive bladder cancer. Your study doctor will explain the surgical procedure and possible side effect related to the surgical procedure. If you have any questions related to the surgery, your study doctor will be able to explain this in more detail.

Possible Risks Associated with Methotrexate, Vinblastine, Doxorubicin, Cisplatin, and Filgrastim (or Pegfilgrastim)

COMMON, SOME MAY BE SERIOUS **More than 20 out of 100 people receiving methotrexate, vinblastine, doxorubicin, cisplatin, and filgrastim (or pegfilgrastim) may have:**
• Low number of red blood cells (anemia) - This can lead to shortness of breath, weakness, and fatigue. • Low number of platelets which help the blood clot – This can lead to unexplained bruising or bleeding. • Low number of white blood cells – This can make you more vulnerable to infection. • Hair loss • Nausea • Vomiting • Skin irritation at site of drug injection which can be severe • Damage to kidneys • Damage to hearing • Changes in urine color (doxorubicin may discolor your urine for up to 1-2 days but this is harmless) • Soreness or painful ulcers of the mouth lasting a couple of days • Sensitivity to the sun • Blood measurements of kidney function (creatinine) and normal elements in the blood including blood sugar (glucose), potassium, magnesium, calcium, and sodium may become abnormal • Electrolytes, which are normal elements measured in the blood, including potassium, magnesium, and sodium may become low and possibly require replacement • Sores in mouth and/or throat • Bone pain

OCCASIONAL, SOME MAY BE SERIOUS **About 4 to 20 out of 100 people receiving methotrexate, vinblastine, doxorubicin, cisplatin, and filgrastim (or pegfilgrastim) may have:**
• Allergic reaction • Upset bowels – this can lead to either constipation or diarrhea • Loss of appetite • Weight loss • Strange taste - A metallic or bitter taste can occur during treatment. A flavored hard candy or mint will help to disguise this taste. • Flu-like symptoms (such as fever, aches, pains, and shivering) • Tingling and numbness in the fingers or toes • Ringing in the ears • High frequency hearing loss – This can be permanent • Skin and nail changes • Rash or irritation at the injection site • Weakness of the heart – This is uncommon and can happen with increasing doses of doxorubicin.

RARE, AND SERIOUS **About 3 or fewer out of 100 people receiving methotrexate, vinblastine, doxorubicin, cisplatin, and filgrastim (or pegfilgrastim) may have:**
• Sore eyes • Depression • Headaches • Jaw pain • Seizure • Cancer of the bone marrow caused by chemotherapy later in life. • Death – In rare cases, death can occur in patients with a severe allergic reaction to the chemotherapy or in patients who develop a life-threatening infection.

Possible Risks Associated with Gemcitabine, Cisplatin, and Pegfilgrastim

COMMON, SOME MAY BE SERIOUS
More than 20 out of 100 people receiving gemcitabine, cisplatin, and pegfilgrastim may have:

- Low white blood cell counts (may make you more likely to get an infection)
- Low red blood cell counts (may make you feel tired or weak)
- Low platelet counts (may make you more likely to bruise or bleed)
- Nausea
- Vomiting
- Loss of appetite
- Diarrhea
- Fatigue
- Blood measurements of kidney function (creatinine) and normal elements in the blood including blood sugar (glucose), potassium, magnesium, calcium, and sodium may become abnormal
- Lightheadedness
- Headaches
- Changes in blood pressure
- Skin irritation at site of drug injection
- Damage to kidneys
- Damage to hearing
- Rash
- Flu-like illness with fever on day of chemotherapy
- Electrolytes, which are normal elements measured in the blood, including potassium, magnesium, and sodium may become low and possibly require replacement
- Bone pain

OCCASIONAL, SOME MAY BE SERIOUS **About 4 to 20 out of 100 people receiving gemcitabine, cisplatin, and pegfilgrastim may have:**
• Sores in mouth and/or throat • Alterations in taste • Allergic reaction (including flushing, skin rash, changes in blood pressure and/or difficulty breathing) • Stomach cramps • Hair loss • Numbness in the hands and feet • Loss of blood supply to the intestines that may require surgery • Inflamed pancreas • Dizziness and shooting back pain when bending your neck forward • Confusion • Blurred vision or a sensation of flashing light • Mood changes • Liver damage and/or failure • Seizures • Fainting • Irregular heartbeat • Heart attack • Ringing in the ears • High frequency hearing loss – This can be permanent

RARE, AND SERIOUS **About 3 or fewer out of 100 people receiving gemcitabine, cisplatin, and pegfilgrastim may have:**
• Cancer of the bone marrow caused by chemotherapy later in life. • Seizure

Chemotherapy

This type of treatment is widely available in the United States. Your Study Doctor will explain how the chemotherapy is given.

Cisplatin/Gemcitabine: You may experience nausea and vomiting, cramps in the abdomen and injury to the kidneys, nerve damage, numbness and tingling of the hands and feet, and decrease in hearing. You may also experience a decrease in white blood cell count, red blood cell count and platelet count, which can increase the possibility of infection and bleeding.

Carboplatin/Gemcitabine: You may experience nausea and vomiting, stomach pain or cramps, electrolyte abnormalities, decrease in white blood cells, red blood cells and platelet count which

can increase possibility of infection, anemia and bleeding, feeling of tiredness or weakness, increase in urea (which may cause gout), and kidney damage.

Please notify your study doctor or nurse **immediately** of any side effects you may experience, not just those listed above, and if any of the side effects become serious.

In addition, there are other risks and possible discomforts you might experience from the study procedures. The following discusses procedure risks related only to the research, and does not include risks of procedures that should be discussed as part of your regular medical care.

- **Women of childbearing potential**: Based on its mechanism of action and data from animal studies, durvalumab can cause fetal harm when administered to a pregnant woman. If you believe you might be pregnant, or even if you experience a menses cycle ("have your period"), you must inform the Protocol Director or study team immediately.
- **General Reproductive Risk**: There may be known or unknown risks to a fetus (unborn child) or the pregnant woman, even if it is the man participating in this study. There is a risk that pregnancy could still result despite the responsible use of reliable method of birth control. Detailed information about preventing pregnancy is given elsewhere in this document.
- **Allergic reactions**: All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. You should get medical help and contact the Study Doctors right away if you think you have any of the following symptoms of a serious allergic reaction: trouble breathing, or swelling of the face, mouth, lips, gums, tongue or neck. Other allergic reactions may include rash, hives, or blisters.
- **Blood draws**: A blood draw may cause fainting; inflammation of the vein; stinging, discomfort, or pain; bruising; discomfort; redness; burning; or bleeding at the site where the needle is placed to draw the blood. There is a slight chance of infection. You may feel dizzy or you may faint. If you feel faint, you should immediately lie down to avoid falling.
- **ECG:** Risks from an ECG can include skin irritation and/or a rash from the gel, or from wearing or removing the patches.
- **ECHO scan**: An ECHO scan is very similar to a sonogram, such as a pregnant woman might receive, and is considered very safe. For some patients, having to lie still on the examination table for the length of the procedure may cause some discomfort or pain.
- **Radiologic imaging: X-ray / CT / Bone /PET scans**. These scans expose you to radiation (discussed below). These scans are part of your regular medical care. If a scanner is used, you may experience discomfort or anxiety due to be in the small space inside the machine, or from the loud noises the scanner makes. If you become anxious or concerned in tight spaces, or from loud noises, tell the study team or technician **before the scan**. You may receive a medication to calm you if you need help with this.
- **Injection of contrast agents**: A contrast agent or dye will be injected for the CT and MRI scans. Following are the risks associated with injection of contrast agents.
    - Allergic reaction, which can be severe and/or life-threatening.
    - Kidney problems or kidney failure, especially if you are taking Glucophage (metformin, a common medicine for diabetes).

  - After the injection, there is a risk of pain, discomfort, or a burning sensation at the injection site; a flushing sensation; a salty or metallic taste in the mouth; a brief headache; or nausea/vomiting.
  - If you are a smoker or exposed to cigarettes or nicotine, you may experience spasms in the arteries of your heart.
- **Radiation risks**: X-ray, CT, Bone, and PET scans used in this study will expose you to radiation. For this study, this exposure is part of your regular medical care for your condition.
- **Genetic research risks:** This research involves genetic studies and information. Procedures have been put into place that are designed to make it very difficult for the results from genetic research to be linked to you. However, even without your name or other identifiers, your genetic information is unique to you, and there is a remote possibility that someone could trace the information in a central database back, and identify you. If a genetic disorder is discovered in your genes, there is a remote possibility this information could become public and affect you or your family in an unfavorable way, including a possible risk of discrimination by employers or insurance providers.
- **Personal anxiety**: Following are some common concerns that research subjects may have.
  - You may be asked sensitive or private questions which you normally do not discuss. It may be necessary to answer some of these questions related to your health and medical status.
  - You may feel embarrassed during the physical exam. You may request that the physical exam be done by a clinician of the same gender.
  - You may be concerned about your personal information being revealed. Although the Study Team and FDA will do their best to protect your personal information, this can not be absolutely guaranteed.

It is important that you report <u>all symptoms and side effects</u> that you experience <u>as soon as</u> they occur, whether or not you think they are caused by the study drug durvalumab or study procedures. Contact the Study Team at the Nurse Coordinators at 650-498-6000 (24 hours). If you are unable to reach anyone at the number(s) listed above, and you feel you may need medical attention, **call 911** or go to the nearest emergency room.

POTENTIAL BENEFITS

- It is possible that your health or medical condition may improve because of your participation in this study. The use of the study treatment, durvalumab, may improve your response to treatment for your disease. However, there is no guarantee that you will benefit in this or any other way.

- Although you may not directly benefit from participation in this study, information learned from this study may help other people in the future, including other people with bladder cancer.

We cannot and do not guarantee or promise that you will receive any benefits from this study.

ALTERNATIVES

You do not have to be in this study to receive treatment for your variant histology bladder cancer. Possible alternative treatments and side effects of these treatments depend on the characteristics of your bladder cancer, but would include the standard treatments that are part of this study. The effectiveness and side effects of other treatments may be different for different people. Instead of taking part in this study, you may choose to:

- Surgically remove the tumor.
- Receive radiation therapy, but not as part of this study.
- Receive treatment with other chemotherapy drugs, including the standard treatments that are part of this study, or others. The study team will discuss which might be effective to treat your cancer. There are numerous treatments that may or may not be suitable for the specifics of your cancer.
- Receive treatment with other drugs called targeted therapies, which recognize specific features of certain cancers, and focus the treatment effect on those cells. The study team will discuss with you whether any of these might be effective to treat your cancer.
- Receive surgery plus 1 or more of the above therapies. There are specific names for the order in which this type of treatment is given.
    - Neoadjuvant treatment, which means to receive chemotherapy and/or radiation therapy before surgery. Having one or both of these before surgery may help shrink the tumor, which may be easier to remove during the surgery.
    - Adjuvant treatment, which means having a surgery first, then receiving chemotherapy and/or radiation therapy. The goal of adjuvant treatment is to kill any cancer cells that may be left in your body after the surgery. Even if there is no visible sign of cancer cells, your physician may suggest adjuvant treatment to kill remaining microscopic cancer, as this lowers the risk that the cancer may come back or spread.
- Participate in another research study with a different study drug or procedure
- While your type of cancer is treatable with currently approved and available medications and procedure, another alternative is to receive only comfort care, also called "palliative care," like painkillers. These types of treatments do not treat your cancer (ie, "are not curative"), and only make you comfortable ("symptom relief;" pain reduction; reduce tiredness, help with appetite problems or other problems caused by cancer). If you think you might prefer comfort care, please discuss this with your family, friends, and doctor.
  NOTE: The Study Doctors do not recommend this decision for you at this time, although it is and will remain your decision.

The Study Doctors will discuss with you the risks and benefits of these alternatives, including which other treatments might be suitable for you.
If you decide that you do not wish to take part in this study and wish to pursue any of these, or other alternatives, this will not change your regular medical care or the other treatment choices in any way.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the Protocol Director. You can also tell any other member of the study team.

You will be told of any significant new information that is learned during the course of this research study, which might affect your condition or your willingness to continue participation in this study. After you hear about this information, you have the right to withdraw from the program.

You will be told the results of tests that are part of your medical care, but you may not be told the results of the research tests, including any future research tests.

ClinicalTrials.gov

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

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law. However, there is always some risk that even de-identified information might be re-identified.

Your research records may be disclosed outside of Stanford, including in computer databases and by other electronic methods, but you will only be identified by your unique study identifier, and not your name. Information linking your study identifier to your name will be kept in a secure location at Stanford and access will be limited to the Study Doctor and authorized members of the Study Team.

Patient information may be provided to Federal and other regulatory agencies as required. The US FDA, for example, may inspect research records and learn your identity if this study falls within its jurisdiction.

The purpose of this research study is to obtain data or information on the safety and effectiveness of durvalumab; the results will be provided to the company providing durvalumab (AstraZeneca/MedImmune); the Food and Drug Administration (FDA); and other federal and regulatory agencies as required.

Authorization To Use Your Health Information For Research Purposes

Because information about you and your health is personal and private, it generally cannot be used in this research study without your written authorization. If you sign this form, it will provide that authorization. The form is intended to inform you about how your health information will be used or disclosed in the study. Your information will only be used in accordance with this authorization form and the informed consent form and as required or allowed by law. Please read it carefully before signing it.

What is the purpose of this research study and how will my health information be utilized in the study?

This study may help the study team; the company providing durvalumab (AstraZeneca/MedImmune); and FDA determine if durvalumab might improve treatment for people with bladder cancer. Information from this study will be submitted to the company paying for the study (AstraZeneca/MedImmune) and international regulatory agencies including the FDA. The results from this research study are expected to be presented at scientific or medical meetings or published in scientific journals. **You will not be personally identified in the publications, although representatives of the sponsor and FDA and other international regulatory agencies may need to know who you are**.

Do I have to sign this authorization form?

You do not have to sign this authorization form. But if you do not, you will not be able to participate in this research study, including receiving any research-related treatment (durvalumab).

Signing the form is not a condition for receiving any medical care outside the study.

If I sign, can I revoke it or withdraw from the research later?

If you decide to participate, you are free to withdraw your authorization regarding the use and disclosure of your health information (and to discontinue any other participation in the study) at any time. After any revocation, your health information will no longer be used or disclosed in the study, except to the extent that the law allows us to continue using your information (eg, necessary to maintain integrity of research). If you wish to revoke your authorization for the

research use or disclosure of your health information in this study, you must write to:

Sandy Srinivas, MD
875 Blake Wilbur Dr, MC 6559
Stanford, CA 94305-6559

What Personal Information Will Be Obtained, Used or Disclosed?
Your health information related to this study, may be used or disclosed in connection with this research study, including, but not limited to identifiers such as your name and initials; address including ZIP code; phone numbers; dates including date of birth; age; biological gender (your sex); race; ethnicity; medical record number (MRN); and other numbers or codes such as your unique study identifier that might identify you. During the study, researchers will also obtain information about your health status, life-style choices, medical history, and medical diagnoses, including family medical history and allergies; your current and past medications or therapies; your physical examination results including height and weight, blood pressure readings, heart rate, breathing rate and temperature; your laboratory test results including blood, urine, and pregnancy tests; results of procedures, such as tumor measurements or assessments, medical scans including ECHO, ECG, CT, and bone scans; results of genetic and biomarker testing; and medical reports, such as the discharge summary and radiology, post-operative, and pathology reports. **The researchers will also get information from your medical record (including hospital records from the Stanford Healthcare and your referring physician's records).**

Who May Use or Disclose the Information?
The following parties are authorized to use and/or disclose your health information in connection with this research study:

- The Protocol Director, Sandy Srinivas, MD
- Research Staff
- The Stanford University Administrative Panel on Human Subjects in Medical Research; the Stanford Data and Safety Monitoring Committee (DSMC); and/or any other unit of Stanford University as necessary
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Who May Receive or Use the Information?
The parties listed in the preceding paragraph may disclose your health information to the following persons and organizations for their use in connection with this research study:

- AstraZeneca/MedImmune, or their representatives
- The Food and Drug Administration (FDA) and/or other state or international regulatory authorities
- The Office for Human Research Protections (OHRP) in the US Department of Health and Human Services (DHHS)
- The US National Institutes of Health (NIH), including the National Cancer Institute (NCI) and/or the National Heart, Lung, and Blood Institute (NHLBI)
- Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported

Your information may be re-disclosed by the recipients described above, if they are not required by law to protect the privacy of the information.

When will my authorization expire?
Your authorization for the use and/or disclosure of your health information will end on 31 December 2068 or when the research project ends, whichever is earlier.

Will access to my medical record be limited during the study?
To maintain the integrity of this research study, you may not have access to any health information developed as part of this study until it is completed. At that point, you would have access to such health information if it was used to make a medical or billing decision about you (eg, if included in your official medical record).

_____
Printed Name of Adult Participant

_____ _____
Signature of Adult Participant Date

_____
If needed: Printed Name of LAR

_____ _____
Signature of LAR Date

_____
LAR's Authority to Act for Participant
(eg, parent, guardian, or conservator)

NOTE: *If using the Short Form Consent process for informed consent in another language pursuant to an "Alteration of HIPAA Authorization," neither the participant nor their LAR should sign the HIPAA "Authorization To Use Your Health Information For Research Purposes" above.*

FINANCIAL CONSIDERATIONS

Costs
If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with this study that are not a part of your routine medical care (eg, duvalumab and its administration). However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the Study Visits.
You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. **You will also be responsible for any co-payments and/or deductibles as required by your insurance**. Participation in this study is not a substitute for health insurance.

Some insurance companies or other 3rd-party payers may not pay for standard-of-care procedures or laboratory tests, including hospitalization, when they are done as part of a research study. You should consult with your health benefit plan to determine whether your medical costs associated with your care during this study are covered.

Payments
You will not be paid to participate in this research study. There is no reimbursement offered for any expenses related to your participation in this study.
This study includes the collection of research samples. Any of your samples which are used in research may result in new products; tests; or discoveries. In some instances, these products may have commercial value, and may be developed and owned by the study team;
Stanford University; AstraZeneca/MedImmune (and its affiliates and collaborators) and/or others. However, donors of samples do not retain any property rights to the samples or data derived from them. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Any of your samples which are used in research may result in new products, tests or discoveries. In some instances, these may have potential commercial value and may be developed and owned by the study team; Stanford University. However, donors of samples do not retain any property rights to the materials. Therefore, you would not share in any financial benefits from these products, tests or discoveries.

Sponsor and Funding Source
AstraZeneca/MedImmune is providing the study drug durvalumab for this study, and providing some funding for the conduct of this study.

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Consultative or Financial Relationships
Sandy Srinivas, MD, receives no direct compensation from AstraZeneca/MedImmune for the conduct of this study

COMPENSATION for Research-Related Injury

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Protocol Director and the research study team will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, reimbursement for all related costs of care first will be sought from your insurer, managed care plan, or other benefits program. **You will be responsible for any associated co-payments or deductibles as required by your insurance.**

If costs of care related to such an injury are not covered by your insurer, managed care plan or other benefits program, **you may be responsible for these costs**. If you are unable to pay for such costs, the Protocol Director and/or the research study staff will assist you in applying for supplemental benefits and explain how to apply for patient financial assistance from the hospital. You do not waive any liability rights for personal injury by signing this form.

CONTACT INFORMATION

Questions, Concerns, Complaints, or to Report an Injury or Side Effect: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should contact the Study Doctor, Dr Srinivas, at 650-725-2078. You should also contact her at any time if you feel you have been hurt by being a part of this study.
If you are unable to reach anyone at the number(s) listed above, and you feel you may need medical attention, call or go to the nearest emergency room.

Independent Contact: If you are not satisfied with how this study is being conducted, or if you have any concerns, complaints, or general questions about the research or your rights as a participant, please contact the Administrative Panels on Human Subjects in Medical Research ("Stanford IRB"); Research Compliance Office; Stanford University, to speak to someone independent of the research team at 650-723-5244 or toll free at 1-866-680-2906. You can also write to the Stanford IRB, Stanford University, 1705 El Camino Real, Palo Alto, CA 94306.

Appointment or Alternate Contact: If you need to change your appointment, or if you cannot reach the Study Doctor, please contact the Nurse Coordinators at 650-498-6000 (24 hours).

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

As a research participant you have the following rights. These rights include but are not limited to the participant's right to:

- Be informed of the nature and purpose of the experiment;
- Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- Be given a description of any attendant discomforts and risks reasonably expected;
- Be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- Be given a disclosure of any appropriate alternatives, drugs or devices that might be advantageous to the subject, their relative risks and benefits;
- Be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- Be given an opportunity to ask questions concerning the experiment or the procedures involved;
- Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- Be given a copy of the signed and dated consent form; and
- Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion or undue influence on the subject's decision.

May we contact you about future studies that may be of interest to you? ___**Yes** ___**No**

Signing your name means you agree to be in this study and that you will receive a copy of this signed and dated consent form.

_____
Printed Name of Adult Participant

_____ _____
Signature of Adult Participant Date

_____
If needed: Printed Name of Legally Authorized Representative (LAR)

_____ _____
Signature of LAR Date

_____
LAR's Authority to Act for Participant (eg, parent, guardian, or conservator)

_____
Printed Name of Person Obtaining Consent (POC)

_____ _____
Signature of POC Date

The following witness line is to be signed only if the consent is provided as a summary form and accompanied by a short-form foreign language informed consent document.

_____
Printed name of witness

_____ _____
Signature of witness Date

(eg, staff, translator/interpreter, family member, or other person who speaks both English and the participant's language)

The translated short form must be signed and dated by **BOTH** the participant (or their LAR) **AND** the witness.

The English consent form ("referred to as the "Summary Form" in the regulations"):

- Must be signed by **BOTH** the witness **AND** the Person Obtaining Consent (POC).
- The non-English speaking participant / LAR does **NOT** sign the English consent.
- The non-English speaking participant / LAR should **NOT** sign the HIPAA participant line.
- If the participant / LAR is non-English speaking, the POC must ensure that:
  1) The LAR's Description of Authority is completed, and
  2) Any questions or options presented by the consent form are documented and initialed by the