A Phase II trial with copanlisib plus avelumab as a maintenance therapy for metastatic bladder cancer after platinum-based chemotherapy

NCT05687721

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Participant Name: _____ Date:_____

Title of Study: A Phase II trial with copanlisib plus avelumab as a maintenance therapy for metastatic bladder cancer after platinum-based chemotherapy

Principal Investigator: Chong-xian Pan, MD, PhD, MS VA Facility: VA Boston Healthcare System

Principal Investigator for Multisite Study: Chong-xian Pan, MD, PhD, MS

KEY SUMMARY INFORMATION ABOUT THIS STUDY

You are being invited to take part in a research study that is being funded by Veterans Affairs Office of Research & Development (ORD). Before you decide to take part, it is important for you to know why the research is being done and what it will involve. This includes any potential risks to you, as well as any potential benefits you might receive. Taking part in this study is completely voluntary.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we expect to learn the effectiveness and safety of combination of two drugs, avelumab and copanlisib, for the treatment of advanced bladder cancer (aBC) after chemotherapy.

Avelumab is a kind of immunotherapy that has been approved by the Food and Drug Administration (FDA) as the standard of care for the treatment of aBC after chemotherapy. It is given through intravenous infusion every other week for two years. In this study, it will be used as a standard of care. Currently copanlisib is FDA approved for relapsed (recurred) follicular lymphoma (a type of blood cancer), but not for bladder cancer. In combination with avelumab, copanlisib will be given as the drug under study (investigational treatment) for your condition. Laboratory research suggests that combination of copanlisib and immunotherapy similar to avelumab is more effective than immunotherapy alone. However, the exact efficacy and safety is not known. Copanlisib itself has anti-cancer activity which means it can be used to treat cancer on its own. Furthermore, it may strengthen the anti-cancer action of avelumab.

If you agree, you will be given copanlisib and avelumab intravenous (in the vein) infusion for the treatment of your aBC. Avelumab is FDA approved for the treatment of aBC for up to two years. You will receive avelumab intravenous infusion on day 1 and day 15 every four weeks and copanlisib intravenous infusion on Day 1, 8 and 15 every 4 week. This means that you will receive one additional intravenous infusion every 4 weeks for up to two years. You will be included in this trial if your cancer does not become worse after chemotherapy. Twenty-nine (29) patients from four Department of Veterans Affairs (VA) centers at Boston, Chicago, Philadelphia and Seattle, will participate in this trial. Since it is the standard of care, you will be recommended treatment with avelumab regardless of your participation in the study. The study drug copanlisib will be provided by Bayer Pharmaceuticals. Your participation in this research will last up to two years if you decide to stay for the whole study.

In this study, copanlisib will be combined with avelumab to determine whether the combination works better than avelumab alone in aBC. We will also determine the harmful effect of this combination as this combination has not been tested in human patients.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

There is no guarantee that you will directly or personally benefit from this study. This study will use two drugs. Avelumab is an FDA-approved immunotherapy that will be used as the standard of care for your bladder cancer. It has been shown that avelumab treatment can significantly improve the overall survival and cause tumor shrinkage in some patients.

This study will add copanlisib to avelumab with the hope that two medications work better than one medication. Laboratory research suggests that a two-drug combination works better than one drug.

However, there are no known direct benefits to you for being in this study with this combination as it has not been tested in humans. The knowledge obtained from this study may help treat other patients with your condition in the future.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

There is no guarantee that you will benefit from being treated with Copanlisib. It is possible that the combination of two drugs may lead to adverse side-effects. For a complete description of risks, refer to the Detailed Consent below. This study is completely voluntary, and you do not have to take part in it.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer. Your decision not to take part will not affect the relationship you have with your doctor or other staff, and it will not affect the usual care that you receive as a patient.

If you decide to participate in the study, but change your mind for any reason, you may discontinue taking part at any time without any penalty or loss of benefits. You may withdraw and still receive the same standard of care that you would otherwise have received.

After your discontinuation, this study will not collect further information except for public records, such as survival data. For the data already collected prior to your withdrawal, the investigators may continue to review.

For the tissue specimens already collected, the investigators may continue to use them for research purposes unless you specifically request to discard or destroy. Some of the specimens, if they have already been analyzed, may not be able to be discarded or destroyed.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Dr. Chong-xian Pan at the VA Boston Healthcare System. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, his/her contact information is:

Office Telephone: (857)203-5737.

Office address: West Roxbury VA Medical Center, 1400 VFW Parkway, West Roxbury, MA 02132.

DETAILED INFORMATION ABOUT THE STUDY

WHAT IS THE PURPOSE OF THIS STUDY?

By doing this study, we hope to learn the effectiveness and safety of combination of two drugs, avelumab and copanlisib, for the treatment of advanced bladder cancer (aBC) after chemotherapy. Bladder cancer is the tenth most common malignancy and the fourteenth most common cause of cancer death worldwide. Currently, chemotherapy followed by avelumab maintenance is the standard of care for aBC. Though maintenance avelumab therapy has improved survival of patients, bladder cancer progresses in most patients in a few months.

Currently copanlisib is FDA approved for relapsed (recurred) follicular lymphoma (a type of blood cancer), but not for bladder cancer. In combination with avelumab, copanlisib will be given as the drug under study (investigational treatment) for your condition. Laboratory research suggests that combination of copanlisib and immunotherapy is more effective than immunotherapy alone. However, the exact efficacy and safety is not known. Copanlisib itself

has anti-cancer activity which means it can be used to treat cancer on its own. Furthermore, it may strengthen the anti-cancer action of avelumab.

In this study, copanlisib will be combined with avelumab to determine whether the combination works better than avelumab alone in aBC. We will also determine the harmful effect of this combination as this combination has not been tested in human patients.

HOW LONG WILL I BE IN THE STUDY?

If you agree to participate, it will last up to two years if you decide to stay for the whole study. You will receive avelumab intravenous infusion on day 1 and day 15 every four weeks and copanlisib intravenous infusion on Day 1, 8 and 15 every 4 week. This means that you will receive one additional intravenous infusion every 4 weeks for up to two years.

You will be included in this trial if your cancer does not become worse after chemotherapy. Twenty-nine (29) patients from four Department of Veterans Affairs (VA) medical centers at Boston, Chicago, Philadelphia and Seattle, will participate in this trial.

WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

BEFORE YOU BEGIN THE STUDY

Before you begin this study, you will have a series of tests to determine if you are eligible for this study. Your doctor will take a detailed history and perform a physical examination. You will need blood tests, a computed tomography (CT) or magnetic resonance imaging (MRI) or positron emission tomography (PET) of your body to evaluate bladder cancer. All these tests are routine tests that you will do even if you do not participate in this study.

- Sign and date this consent form
- You will be asked to give your personal information, such as your name, date of birth, etc.
- You will be asked about your medical history, your current disease, and treatments you received before, and any other medications you are taking.
- Complete physical exam to check your vital signs, including height, weight, heart and breathing rate, blood pressure and temperature.
- Approximately two teaspoons of blood will be collected to test blood counts, blood sugar levels, kidney function, liver function, and other organ function.

- Urine test
- Electrocardiogram (EKG) to test heart rhythm
- Pregnancy blood test for women who are capable of having children (requiring approximately 1 teaspoon of blood). The study doctor or study staff will tell you if the pregnancy test results are positive. The results of the pregnancy test must be negative in order for you to be in the study.
- Imaging studies, such as chest X-ray, CT, MRI and/or PET. If you have bone pain, a bone scan may also be performed.

Results from these screening tests will be used by the study doctor to find out if you qualify for the research study. If the screening tests show that you are not eligible to continue in the research study, then you will not be able to take part in the study.

Description of Tests/Procedures:

- **Blood drawing (venipuncture):** a blood sample will be drawn by inserting a needle into a vein in your arm. Each sample will be approximately 2 teaspoons. The total amount of blood to be drawn will depend on how long you are in the study.

- **Electrocardiogram (EKG or ECG)**: EKG is a test that checks for problems with the electrical activity of your heart. An EKG shows the heart's electrical activity as line tracings on paper. The spikes and dips in the tracings are called waves. The heart is a muscular pump made up of four chambers.

- C**hest x ray:** Chest X ray is a fast and painless imaging test that uses certain electromagnetic waves to create pictures of the structures in and around your chest. This test can help diagnose and monitor conditions such as pneumonia, heart failure, lung cancer, tuberculosis, sarcoidosis, and lung tissue scarring, called fibrosis. In this study, chest X ray will be taken to rule out spread of cancer (metastasis) to your lung.

- **CT scan:** You will have a computed tomography (CT) [also known as computerized axial tomography (CAT)] scan of your chest, abdomen and pelvis done after your chemotherapy, but before you receive the first treatment of the study to determine how your cancer responds to chemotherapy. A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. You will need to lie still on a table inside a large doughnut-shaped machine. The table will move and the machine will make clicking and whirring noises as the pictures are taken. Each CT scan will take about 15 minutes to a half hour. This CT scan will be done even if you are not on a clinical trial as it is needed to evaluate your cancer status.

- **MRI:** [if needed] you will have a Magnetic Resonance Imaging (MRI) exam. For the MRI exam, you will lie down on a narrow bed, which will then be placed in a tunnel that is 6 feet long by 22 inches wide and open at each end. You will need to lie there quietly for about one hour, during which time there will be a loud banging noise. You may feel warm during this procedure. MRI is not routinely done for this study. You will only need MRI if indicated by your disease and as determined by your doctor.

- **Bone scan**: [if needed] You may have a bone scan of your whole body before you receive the first treatment of the study. A bone scan uses a radioisotope to determine if your cancer spreads to your bones. After you receive an injection of an isotope, you will need to lie still on a table and a machine will scan your whole body. Bone scan is done only if you have new bone pain. It is not routinely done in patients with advanced bladder cancer.

DURING THE STUDY

This is a single-arm study. This means that all patients will receive treatment. There is no placebo control. This study has two drugs. Avelumab is the standard of care. It will be given through intravenous infusion over 1-2 hours on Day 1 and Day 15 of every 4-week cycle for up to two years.

The study medication, copanlisib, will be given through intravenous infusion over 1-2 hours on Day 1, 8 and 15 of every 4-week cycle for up to two years or until you meet the criteria to be taken off from the trial, or if you choose to withdraw, whichever comes first.

Regarding follow-up schedule, each cycle is 4 weeks. You will be seen by a physician, and/or clinical trial coordinator and receive treatment on Day 1, 8 and 15 in each cycle.

Imaging studies, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), will be performed before you start the trial and once every 2-3 months after you start the trial. This imaging studies will be done even if you do not participate in the trial.

Less than one tablespoon of blood will be taken before and at every two cycles (8 weeks) while on the study. You will need one more blood draw at the end of the trial or at two years after starting the trial, whichever comes first. Before each treatment, you will need blood tests that is part of the routine care of your cancer.

All patients (about 12) enrolled at VA Boston Healthcare System (VABHS) will undergo a biopsy after two cycles (8 weeks) of treatment. This biopsy is for the research use, but may

also reveal useful information to guide the treatment. Information extracted from these tissue samples will help establish new treatment targets and drug combination that might effectively cure patients with similar cancer type as you.

If you are a male patient and able to father children, or if you are a female patient of childbearing potential and at risk for pregnancy, you must agree to use 2 highly effective methods of contraception throughout the study and for at least 60 days after the last dose of assigned treatment.

The following procedures are part of regular care and may be done even if you do not join the study:

- History and physical examination
- Vital signs (heart rate, temperature, breathing rate, blood pressure, height and weight)
- Chest X-ray, CT scan (or MRI or PET). CT scans are a way for your doctor to get a picture of the inside of your body.
- Bone scan to check for cancer in your bones only if you have new bone pain.
- Standard blood work to look at your blood count, liver function, kidney function, and electrolytes, after screening. These tests will require less than 2 teaspoons of blood.
- Urine tests to check for infection and, for female patient, pregnancy.
- EKG
- Treatment with avelumab

The following procedures are NOT part of regular care and will only be done if you join the study:

- Treatment with copanlisib
- Collection of tumor specimen for research purposes
- Blood draws (1-2 teaspoon) before the study starts, on the first day of every even cycle and at the end of study
- Some of your blood samples will be sent to outside labs to determine the impact of this new tretament on cancer cells and immune system. The results will not be shared with you. This process is for research purpose only.

Another way to find out what will happen to me during the study is to read the chart/table below.

Treatment/Test/Procedure	**Frequency**
Treatment	Avelumab intravenous infusion on Day 1 and 15 Copanlisib infusion on Day 1, 8 and 15 of every 4 weeks for up to two years.
Physical exam including vitals	Pre-study, and before each treatment
Blood draws for routine blood tests	Pre-study and before each treatment
Urine test	Pre-study
CT, MRI or PET	Pre-study, every 2-3 months
Bone scan (clinically necessary)	If clinically indicated
ECG aka EKG (electrocardiogram)	Pre-study

Study location:

VA Boston Healthcare System at Jamaica Plain, 150 S Huntington Ave, Boston, MA 02130. Occasionally the treatment is given at VA West Roxbury, 1400 VFW Parkway, West Roxbury, MA 02132.

VA Puget Sound Healthcare System at Seattle VA Medical Center, 1660 South Columbian Way Seattle, WA 98108.

VA Chicago Healthcare System at Jesse Brown VA Medical Center, 820 South Damen Avenue Chicago, IL 60612

VA Philadelphia Healthcare system at Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center, 3900 Woodland Avenue Philadelphia, PA 19104

WHAT IS EXPECTED OF ME IF I TAKE PART IN THIS STUDY?

- Keep your doctor appointments. If you miss an appointment, please contact the investigator or research staff to reschedule as soon as you know you will miss the appointment.
- Report to study doctors any changes in your physical or mental condition, especially if you think these changes may be due to the study drug or treatments you receive from the study. This is important for your own safety and the value of the study.
- Tell the investigator or research staff if you believe you might be pregnant or might have gotten your partner pregnant.
- Ask questions as you think of them.
- Tell the study doctor or staff if you change your mind about remaining in this study.
- While participating in this research study, do not take part in any other research project without approval from the investigators. This is to protect you from possible injury from things such as extra blood drawing, extra X-rays, or potential drug interactions. Taking part in other research studies without first discussing it with the investigators of this study may invalidate the results of this study, as well as that of the other studies.

WHAT POSSIBLE RISKS OR DISCOMFORTS MIGHT I HAVE IF I TAKE PART IN THIS STUDY?

Any medication has possible risks and discomforts. The medications in this study may cause all, some, or none of the risks or side effects listed. Rare, unknown, or unexpected risks also may occur.

Risks associated with study drug

Patient taking copanlisib, the investigational medication, may develop certain side effects. As the combination of avelumab and copanlisib is investigational in your illness, there may be unknown or unforeseeable safety risks and side effects. You should discuss any concerns you have with your doctor.

Very common side effects (more than 10%)
In 100 people receiving copanlisib, more than 10 people may have:

- High blood pressure
- Fatigue

- Skin rash
- High blood sugar levels
- High blood triglyceride levels (a type of fat)
- Low phosphate level in your blood; this may cause muscle pains and bone pains
- High uric acid levels in your blood; this may cause swelling and painful joints
- Diarrhea
- Nausea
- Vomiting
- Mouth sores
- Decreased hemoglobin (content of red blood cells)
- Low white blood cells; this increases the chance of getting infections
- Low platelet count; this increases the chance of bruising and bleeding
- Serious infection
- Lower respiratory tract infection

Common side effects (1-10%)
In 100 people receiving copanlisib, about 1 to 10 people may have:

- Abnormal burning/prickling/tingling or aching sensations
- Very high blood sugar levels
- Very low white blood cell count
- Inflammation of lungs (pneumonitis)
- Lung infection

Very rare side effects (less than 1%), post-marketing and/or case reports:

- Severe skin rash (Exfoliative dermatitis)
- Lung infections due to a fungus (pneumocystis)
- Itching

<u>Risks associated with Avelumab (Standard of Care)</u>

Very common side effects (more than 10%)
In 100 people receiving copanlisib, more than 10 people may have:

- High blood pressure
- Skin rash
- Weight loss

- Abdominal pain
- Constipation
- Decreased appetite
- Diarrhea
- Nausea
- Vomiting
- Urinary tract infection
- Decreased hemoglobin (content of red blood cells)
- Low white blood cells: this increases the chance of getting infections
- Low platelet count: this increases the chance of bruising and bleeding
- Increased serum alanine aminotransferase (a sign of liver damage)
- increased serum aspartate aminotransferase (a sign of liver damage)
- Dizziness
- Fatigue
- Joint Pain
- Musculoskeletal pain
- Cough
- Shortness of breath
- Allergic reaction to the drug

Common side effects (1-10%)

In 100 people receiving copanlisib, about 1 to 10 people may have:

- High blood sugar level
- Low sodium levels
- Low thyroid hormone in blood
- increased amylase
- Inflammation of colon
- Intestinal obstruction
- Blood in urine
- Low neutrophils level (type of white blood cells)
- Increased serum bilirubin
- Headache
- Increased serum creatinine
- Renal failure
- Inflammation of lungs

Very rare side effects (less than 1%), post-marketing and/or case reports:

- Inflammation of the heart
- Inflammation of the blood vessels
- Adrenal insufficiency
- High thyroid hormone in blood
- Low parathyroid hormone in blood
- Pituitary insufficiency
- Inflammation of thyroid
- Type 1 diabetes mellitus (can present with diabetic ketoacidosis)
- Inflammation of stomach
- Inflammation of small bowel and pancreas
- Destruction of red blood cells
- Destruction of platelets
- Sarcoidosis
- Inflammation of liver
- Inflammation of the brain
- Inflammation of membranes covering the brain and spinal cord
- neuropathy (autoimmune)
- Inflammation of joints
- Inflammation of muscles
- Muscle pains and stiffness (polymyalgia rheumatica)
- Inflammation of kidneys

Some of the side effects may be severe and some patients may even die from complications. Some of the side effects may be permanent even after discontinuation of the study drug.

The combination of these two drugs has not been tested and some new or severe adverse events can happen.

As this is a new combination, we do not know all of its bad effects. You should contact Dr. Chong-xian Pan if you are concerned you might be experiencing side effects that result from your participation in this study. The contact information is given below.

Phone: (857)203-5737
West Roxbury VA Medical Center,
1400 VFW Parkway,
West Roxbury, MA 02132

Other Risks associated with the clinical trial

Blood draws and IV placement can cause pain and bruising.

CT and PET, even though they are regular care, are associated with radiation exposure.

Tumor biopsies can cause pain, infection, bleeding, damage to other organs and even death.

Patients will also need to travel to the clinic for evaluation and treatment.

There is the risk of your confidential personal health information being disclosed (steps to avoid this are discussed below).

If you or your partner are or become pregnant, the particular treatment or procedure might involve risks to the embryo or fetus, which are currently unforeseeable. If you or your partner become pregnant during the course of the study or within 60 days after you finish the study, the pregnancy will be followed till the delivery of the baby; the health of the baby will be monitored and the health information of the baby will be collected.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Those risks are not included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

WHAT ARE THE POSSIBLE BENEFITS OF THIS STUDY?

This study will add copanlisib to the standard of care medication with the hypothesis that two medications work better than one medication. Laboratory research suggests that a similar two-drug combination works better than one drug.

However, there are no known direct benefits to you for being in this study with this combination as it has not been tested in humans. The knowledge obtained from this study may help treat other patients with your condition in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

Other treatments may include avelumab injections alone without copanlisib and will be under the supervision of your doctor or caregiver. Avelumab is a standard of care as a maintenance therapy for patients with bladder cancer.

HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

Your personal health information can neither be collected nor used without your written permission in this consent. The personal health information that may identify you may include your medical history, physical examinations, blood and tumor specimens, imaging scans, and any other data collected or reviewed during this research study (e.g., copies of your medical records from other healthcare providers who have treated you before and after you take part in this study).

This information will be protected in the following ways:

- All patient reports and clinical samples will be assigned and identified by a code comprised of letters and/or numbers.
- The log of patients' codes, names, and contact information will be kept in a locked cabinet and on password-protected computers in the research office. The cabinets and computers are only accessed by VA-trained research personnel.
- Since this study consists of 4 VA sites across the US, the data shared between sites will be coded and sent through either a VA-approved courier or VA-encrypted email.

After that removal of all identifiers, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative. We will store biological samples taken from you (such as urine, blood, or tissue) in the study at Dr. Pan's lab. It will be protected by the VA keycard and a lock to his lab located at the West Roxbury campus of VA Boston Healthcare System (VABHS).

While this study is being conducted, you will not have access to your research related health records. This will not affect your VA healthcare including your doctor's ability to see your records as part of your normal care.

There are times when we might have to show your records and research data to other people. For example, someone from the Department of Veteran Affairs, Office of Human Research Protections, Data Safety Monitoring Committee, the Government Accountability Office, the

Office of the Inspector General, the VA Office of Research Oversight, the VA Central IRB, our local Research and Development Committee, Food and Drug Administration, US governmental agencies, and other study monitors may look at or copy portions of records that identify you. Your study records will be kept confidential, and except as required by the law, you will only be identified by your special research code. If your personal data is disclosed to a third-party entity, then all appropriate measures will be taken to protect it. However, because of the need to release information to these parties, total confidentiality cannot be guaranteed.

You have the right to access and rectify your personal data when possible.

We will include information about your study participation in your medical record. As a result, your primary care physician and other specialist who are treating you will be informed about your participation in this study. This is for your own safety. If you do not consent to this, you cannot participate in this study.

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

WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are being done for research purpose in this study.
If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications for procedure that are usual care and are not part of this study.

WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

Every reasonable safety measure will be used to protect your well-being. If you are injured as a result of taking part in this study, the VA will provide necessary medical treatment at no cost to you unless the injury is due to non-compliance by a study participant with study procedures or if the research is conducted for VA under contract with an individual or non-VA institution.

Depending on the circumstances underlying the cause of your injury, the costs of diagnosis and treatment may be covered by the local site. If the study doctor determines that your injury is solely due to the study treatment or procedure, not ordinary care, you will not be responsible for

the cost of the treatments given. No other compensation will be offered by your VA medical center for injuries related to this study.

DO I HAVE TO TAKE PART IN THE STUDY?

Participation is voluntary. Refusal to take part in the study will involve no penalty or loss of benefits to which the participant is otherwise entitled. You may stop treatment and study procedures at any time for any reason.

For the data already collected prior to the participant's withdrawal, investigators may continue to review the data already collected for the study but cannot collect further information, except from public records, such as survival data. For the samples already collected before your withdrawal from the study will continue to be used and will not be destroyed.

If you are a VA employee or student, refusal to take part in the study will in no way influence your employment, ratings, subsequent recommendations, or academic progress as applicable. You may discontinue taking part at any time without any penalty or loss of benefits. You may withdraw and still receive the same standard of care that you would otherwise have received.

If you plan to withdraw from the research, please let your physician know. He/she can then discuss with you regarding the treatment options and evaluate you for any adverse events associated with treatment. You may also be followed up and receive other standard of care treatment.

RIGHT OF INVESTIGATOR TO TERMINATE MY PARTICIPATION

Your participation could be stopped by the study doctor without your permission for any of the following reasons:

- Your cancer progresses.
- You have a serious side effect or abnormal laboratory result that would make it unsafe for you to continue the study.
- You have a change in your medical condition that prevents you from taking the study drug or may impact your overall well-being.
- The study doctor believes that it is in your best interest not to continue the treatment.
- You have a study-related injury.
- You do not follow the study doctor's instruction.

You can also stop participating in this study at anytime if you wish. You just need to let the study investigator now that you plan to discontinue the study.

The study may be discontinued at any time by the VA Central Institutional Review Board (IRB), VA Office of Research and Development (ORD), Office of Human Research Protections (OHRP), or other governmental agencies as part of their duties to ensure that research participants are protected.

WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

You have the right to ask questions about your participation in this study at any time. If you have any questions about the study, experience any problems (e.g., study-related injury, illness, or side effect), or have concerns about your participation, you can contact your research doctor or the study principal investigator Dr. Chong-xian Pan at 1-857-203-5737

If you have questions about your rights as a study participant, or you want to make sure this is a valid VA study, you may contact the VA Central Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the VA Central IRB toll free at 1-877-254-3130 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Sometimes during the course of a research study, new information becomes available about the treatment of your condition that might change a person's decision to stay in the study. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw from the study, your research doctor will arrange for your medical care to continue. If you decide to continue in the study, you might be asked to sign an updated informed consent form. Your research doctor could also decide it to be in your best interests to withdraw you from the study. If so, he or she will explain the reasons and arrange for your usual medical care to continue. The clinically relevant research results may not be disclosed to you.

FUTURE USE OF DATA AND RE-CONTACT

Your data will be entered into a data repository and may be used for future studies approved by an IRB. The data will be stored at firewall-protected VABHS computer server further protected with a strong password. It can only be accessed by the principal investigator of this study Dr. Chong-xian Pan or designated research staff members.

We may re-contact you in the future if further information is needed as part of your participation in this study or if future studies for you to participate in are available.

TISSUE BANKING

During the study, some of your blood specimens and tumor tissues will be collected to study how the treatment in this trial affects your cancer and your immune system. The specimens will be sent to outside labs without your identifiable information.

Samples collected will be stored in the principal investigator Dr. Chong-xian Pan's lab located at Building 3, 2nd floor, West Roxbury VA Medical Center, 1400 VFW Parkway, West Roxbury, MA 02132. Dr. Pan's lab is located inside the research suite that can be only accessed by authorized personnel and further protected with a lock.

All the samples will be analyzed during and after this study. We will not contact you or get your consent for future use of your specimens for research purpose. If any participants withdraw the consent form or request the samples to be destroyed, or if there are any samples left after the study is terminated, the samples will be destroyed according to standard protocols. You can also request to destroy your stored sample at any time.

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms_____ _____ has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

Participant Name: _____ Date:_____

Title of Study: A Phase II trial with copanlisib plus avelumab as a maintenance therapy for metastatic bladder cancer after platinum-based chemotherapy

Principal Investigator: Chong-xian Pan, MD, PhD, MS VA Facility: VA Boston Healthcare System

Principal Investigator for Multisite Study: Chong-xian Pan, MD, PhD, MS

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

I agree to participate in this research study as has been explained in this document.

_____ Participant's Name	_____ Participant's Signature	_____ Date

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PI/SC Approval Date: December 9, 2022

LSI Approval Date:

LSI Verification Date: