INFORMED CONSENT DOCUMENT

Project Title: **A phase Ib study of combination of Avelumab and Taxane based chemotherapy in platinum refractory or ineligible metastatic urothelial cancer (AVETAX study)**

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This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have metastatic urothelial cancer and either can't receive cisplatin-based chemotherapy or have already received cisplatin-based chemotherapy and have had return of your disease.

The purpose of this research study is to see if the combination of Avelumab and Docetaxel will be effective in treating your urothelial cancer. Avelumab is an immunotherapy drug that is currently approved for the treatment of metastatic urothelial cancer. However, the way it's being given in this research study (10 mg/m2 every 3 weeks) is not the standard of care for patients with metastatic urothelial cancer.

Docetaxel is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic urothelial cancer. The dose of Docetaxel will be determined based on when you enter the study.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 25 people will take part in this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement could last several years. This study consists of

treatment "cycles" and each cycle during the Induction phase when you receive both Avelumab and Docetaxel is 21 days long. You will have 6 cycles during the Induction phase. Each cycle during the Maintenance phase when you receive Avelumab alone is 14 days long. You will continue to receive Avelumab alone until you experience disease progression or unacceptable side effects. You will return to the hospital for treatment on Day 1 of each cycle in both phases of the study. Visits will range from 3-6 hours in length.

You will have an End-of-Treatment visit approximately 30 days after your last dose of study drug. At that visit, you will have a physical examination, labs drawn and CT and/or MRI scan as standard of care. After that, we will either schedule a visit or contact you by telephone after 3 months. If you have not had progression of your disease, you will have a clinic visit and a CT or MRI scan every 3 months for 2 years as standard of care. If you have had progression of your disease or if you've started another treatment, we will contact you by telephone or check your medical record every 3 months for 2 years, then every 6 months to see how you are doing.

WHAT WILL HAPPEN DURING THIS STUDY?

Before you begin the study treatment

You will need to have some tests done to find out if you can continue to be in the study. Some of these tests are part of regular cancer care and may be done even if you do not join the study treatment. If you have had some of them recently, they may not need to be repeated. This is up to your doctor.

- Physical examination including vital signs, height and weight.
- Electrocardiogram (ECG) to check the function of your heart.
- Blood will be drawn to determine blood counts, thyroid function and liver function.
- Urinalysis
- Pregnancy test (if you are a woman of child-bearing potential).
- Biopsy to confirm diagnosis
- CT and/or MRI scan of the chest, abdomen and pelvis.
- MRI scan of the brain will be done if clinically indicated.

During your study treatment

Induction

If the tests show you can proceed, you will begin receiving infusions of Avelumab and Docetaxel every 3 weeks for 6 cycles. Each cycle is 3 weeks long during this part of the study. Each Avelumab infusion will take approximately 1 hour to complete, although the first two infusions will be given over 90 minutes to decrease the risk of an infusion reaction. The infusion of Docetaxel will take approximately 1 hour to complete.

Maintenance

After 6 cycles of treatment with the combination of drugs, you will then have infusions of Avelumab alone every 2 weeks. Cycles are 2 weeks long during this part of the study. Each Avelumab infusion

will take approximately 1 hour to complete. You can continue to receive Avelumab alone as long as you don't have unacceptable side effects and your disease doesn't progress.

- You will visit your doctor for a physical examination, vital signs and standard-of care labs on Day 1 of each cycle in induction and maintenance, prior to each infusion of Avelumab.
- At the end of Cycles 3, 6 and 12 you will have a CT or MRI of the chest, abdomen and pelvis, then every 6 cycles thereafter.
- Females of child-bearing potential will have a pregnancy test on Day 1 of Cycles 2, 4, 6, etc.
- A urinalysis will be done on Day 1 of Cycles 5, 9, 13 and every 4 cycles thereafter.

<u>After your study treatment</u>

- You will have a follow-up appointment in the Holden Comprehensive Cancer Center about 30 days after your final infusion. It is very important you keep this appointment. You will have a physical exam, blood drawn for standard-of-care labs and a CT scan and/or MRI scan.
- If you have not had progression of your disease, you will have a clinic visit and a CT or MRI scan every 3 months for 2 years as standard of care. If you have had progression of your disease or if you've started another treatment, we will contact you by telephone or check your medical record every 3 months for 2 years, then every 6 months to see how you are doing.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

For Avelumab:

Risks Associated with Avelumab

Three types of risks are associated with avelumab: general signs and symptoms, reactions that occur during or following the infusion, and immune side effects. The following side effects have been observed among 1738 patients treated with avelumab according to the results from two oncology clinical studies in patients with various solid tumors.

Side effects observed in 10% or more of patients

General signs or symptoms: Tiredness; Nausea; Loose or watery stools (diarrhea); Constipation; Reduced appetite; Decrease in weight; Vomiting; Low number of red blood cells (anemia); Belly pain; Cough; Fever; Shortness of breath; Swelling of feet and legs; Back pain; Joint pain.

Reactions that occur during or following the infusion: may include chills or shaking, fever, flushing, back pain, belly pain, shortness of breath, or wheezing, decrease in blood pressure, hives. These infusion reactions are mostly mild or moderate and generally resolve with a slowdown or discontinuation of the infusion and administration of such as anti-allergic and pain-killer drugs. In some cases these reactions may be severe or life-threatening (in less than 1% of patients) and can require intensive medical care.

Immune side effects: Immune side effects result from an increased activity of the immune system. Most

of these side effects are reversible, which means they will stop gradually AFTER treatment with avelumab is discontinued but some side effects, such as pituitary damage, may be permanent However, in some cases these reactions may be severe (approximately 2% of patients) and may lead to death in rare cases. The reactions that are more severe require treatment with drugs that decrease the immune system function, also called immunosuppressant drugs (like corticosteroids or more potent drugs). No immune side effects were observed in 10% or more of patients. Avelumab may worsen any immune diseases you might have had prior to Avelumab therapy and may induce new autoimmune diseases such as psoriasis or pemphigus.

Immune side effects observed in 5% to less than 10% of patients

- **Abnormal function of the thyroid gland** (could include low or high function or inflammation of the thyroid gland): may include rapid heartbeat; increased sweating; extreme tiredness; weight gain or weight loss; hair loss; changes in mood or behavior such as irritability or forgetfulness; feeling cold; constipation; voice gets deeper.
- **Inflammation of the skin (rash):** may include skin rash, itchy skin, skin redness, skin blisters, or peeling.

Immune side effects observed in 1% to less than 5% of patients

- **Inflammation of the large intestine (colitis):** may include diarrhea (loose stools) or more frequent bowel movements than usual; blood in stools or dark, tarry, sticky stools; severe stomach area (abdomen) pain or tenderness.
- **Inflammation of the lungs (pneumonitis):** may include new or worsening cough, shortness of breath, chest pain.

Immune side observed in less than 1% of patients

- **Inflammation of the liver (hepatitis):** may include yellowing of skin or of the whites of eyes; severe nausea or vomiting; pain on the right side of stomach area (abdomen); drowsiness; dark urine (tea colored); bleeding or bruising more easily than normal; feeling less hungry than usual.
- **Inflammation of the kidneys (nephritis):** may include urinating less than usual; blood in urine; swelling in ankles; loss of appetite.
- **Low function of the adrenal glands (glands on top of the kidneys), which may be due to the reduced function of the pituitary gland (a gland in the head):** may include very low blood pressure; extreme tiredness.
- **Increase in blood sugar (diabetes):** may include urinating more often than usual; feeling more hungry or thirsty than usual; nausea or vomiting; stomach area (abdomen) pain.
- **Inflammation of the eyes (uveitis):** may include changes in eyesight.
- **Inflammation of the muscles (myositis):** may include severe or persistent muscle or joint pain; severe muscle weakness.
- **Inflammation of the heart (myocarditis):** may include chest pain or tightness; tiredness; changes in heartbeat, such as beating fast, or seeming to skip a beat, or pounding sensation; swelling of feet and legs; trouble breathing.
- **Inflammation of the nerves (Guillain-Barre syndrome):** may include “pins and needles” sensations in arms and legs; weakness in legs that spreads to the upper body and may lead to temporary paralysis.

- **Inflammation of the pancreas (pancreatitis):** may include abdominal pain which may radiate to the back, nausea and vomiting, chills and fever, lethargy and weakness, tenderness of the abdomen.

For Docetaxel:

Possible Side Effects and Risks of Docetaxel (Taxotere™).

During the study you may receive an anti-cancer drug called docetaxel (Taxotere™).

This drug considered investigational as it is not been approved by the FDA; however, it is a treatment option for bladder cancer according to National Comprehensive Cancer Network guidelines and the Micromedex database. The drug is given as an infusion directly into a vein. The infusion time will be about 1 hour every 3 weeks. Like many other anti-cancer chemotherapy drugs, docetaxel can cause side effects and some can be serious. Infusion reactions can include shortness of breath, wheezing, hypotension and flushing (which can rarely lead to hospitalization). Other immune reactions (hypersensitivity) can later develop.

The most common side effects (occurring ≥10%) in subjects with any tumor type include:

- Low red or white blood cell count
- Changes in your sense of taste or smell
- Infection
- Fever
- Constipation
- Weight loss
- Difficulty swallowing
- Stomach cramping
- Heart burn
- Anorexia
- Swelling of your hands, face, or feet
- Feeling weak or tired
- Joint and muscle pain
- Nausea and vomiting
- Diarrhea (can become very severe and lead to bleeding or colon perforation)
- Mouth or lips sores
- Hair loss
- Rash including redness and swelling of your arms and legs with peeling of your skin
- Neurological symptoms including numbness, tingling, or burning of your hand and feet
- Changes in finger nails or toe nails
- Redness of the eye, excess tearing
- Amenorrhea
- Abnormal liver function tests

This is not a complete list of possible side effects. If you would like to learn more about the possible side effects of this drug, please ask your doctor.

Interactions occur with many common medications. You should check your current medications with the doctor and report any new medications you are considering. It is not safe to take grapefruit juice with Docetaxel.

Serious side effects include:

- Acute Myeloid Leukemia (AML), a type of blood cancer ≤ 0.4%
- Pneumonitis with cough and shortness of breath <1%. You should call your physician if this occurs.
- Blood disorders. Changes in blood counts due to leukemia and other blood disorders may occur years after treatment with Docetaxel. (Low neutrophil (white blood cell) count ≤84%, Low thrombocyte (platelet) count ≤5%)
- Skin reactions including redness and swelling of your arms and legs with peeling of your skin ≤1%
- Neurologic symptoms including numbness, tingling, or burning in your hands and feet ≤1%
- Vision problems including blurred vision or loss of vision (exact % incidence not available)
- Rarely, Docetaxel has been associated with heart toxicity and an abnormal heart rhythm.

Women Capable of Becoming Pregnant

Avelumab has been associated with an increased risk of miscarriage. It is contraindicated during pregnancy as it is a drug which can pass from the mother to the developing baby. Docetaxel poses likely risks to the developing baby as well, particularly in the first trimester. Neither of these drugs are safe to use while breastfeeding.

If you are a woman who is capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to your fetus, or risks to your fetus that we did not anticipate, associated with being in the study. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. If you believe or know you have become pregnant while participating in this research study, please contact **Dr. Rohan Garje at 319-356-7831** as soon as possible.

Are there any other risks?

Other less common side effects have been reported with the use of the drugs in this study. The study doctor or staff can discuss these with you.

There may be other side effects or risks that are not known at this time.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because the knowledge gained might help to develop better treatments for urothelial cancer.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could have the option of other chemotherapy treatment or other investigational research studies. You also have the option of receiving no treatment for your cancer. Please talk to your doctor about these options.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You may have costs for being in this research study. The study drug, Avelumab, will be provided to you free-of-charge by Pfizer. The cost of Docetaxel will be the responsibility of you or your insurance carrier. All of the tests and procedures done as standard of care for your disease will be the responsibility of you or your insurance carrier.

We encourage you to determine your health insurer's policy about paying for treatment in a research study.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

Pfizer is providing the study drug, Avelumab, for this research study. The University of Iowa is receiving no additional funding for this research study

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- the U.S. Food and Drug Administration
- Pfizer
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

In the future, Pfizer may continue to use your health information that is collected as part of this study. For example, Pfizer may combine information from this study with the results of other studies to re-analyze the safety and effectiveness of the study medication, to evaluate other products or therapies, to develop a better understanding of a disease, or to improve the design of future research studies. Pfizer may also share information from the study with regulatory agencies in foreign countries.

To help protect your confidentiality, we will use unique identification code numbers only on data forms, have locked storage areas, and use password-protected computer files. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document your participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.
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.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires your health care provider to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study and for your treatment. Once your health care provider has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, and Pfizer.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes your health care provider to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by

sending a written notice to:

Rohan Garje, MD
University of Iowa Hospitals and Clinics
200 Hawkins Drive, C-32 GH
Iowa City, IA 52242
Phone: 319-356-7831

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

You are free to stop participating in this study at any time. If you stop, you will not lose any medical benefits except for any benefits that you might have been receiving in connection with this study. All information collected from you before you stop the study may still be used by the study doctor.

If you want to stop participating in the study, please tell the study doctor. He can tell you about stopping all or part of the study activities and what other care is available for you.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because in our judgment, it would not be safe for you to continue because your condition has become worse, you need treatment not allowed by the study, we have decided to stop the research, you were non-compliant with the study therapy regimen or because you may benefit from a new therapy.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Rohan Garje at 319-356-7831. If you experience a research-related injury, please contact: Dr. Rohan Garje at 319-356-7831. If it is after 5 PM or on a weekend, please call 319-356-1616 and ask for the Hematology/Oncology Fellow on call.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail

irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 06/11/21.

_____ _____
(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)