CONSENT FOR CANCER RESEARCH

Project Title: CASE 6819 A Phase II Study of Intermittent Checkpoint Inhibitor Therapy in Patients with Advanced Urothelial Carcinoma

Principal Investigator(s): Moshe C. Ornstein, MD, MA
Research Nurse: [redacted]
Research Nurse: _____

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC) Main Campus.

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you have bladder cancer that can be treated with immunotherapy, specifically a checkpoint inhibitor (CPI), which is considered standard of care.

What should I know about a research study?
- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this study is to test the safety and effectiveness of immunotherapy (checkpoint inhibitor therapy) in advanced bladder cancer when given intermittently.

Checkpoint inhibitors (CPI) are drugs that works by helping the immune system recognize and kill cancer cells. There are 5 CPIs already FDA-approved for treating patients with bladder cancer that has come back or spread; as well as 2 CPIs that are FDA approved for patients who have newly diagnosed bladder cancer who cannot take chemotherapy.

Typically, patients who are not in a study are started on checkpoint inhibitor therapy until their cancer progresses or until they develop intolerable side effects. Science has shown us that checkpoint inhibitor therapy can last within the body for a long period of time. We also know that patients who will respond to checkpoint inhibitor do so within 3 months of starting the drug.

Thus, we think that there are patients that respond to therapy who do not need to be on the drug indefinitely. We think that it is safe to stop therapy with close monitoring. We hope that we can figure out the best treatment schedule to help minimize side effects and help with quality of life.

This study will allow the researchers to know whether this different approach is the same, better, or worse than continued checkpoint inhibitor therapy. To be better, the study would show similar response rates compared to the usual approach. There is no investigational drug in this study.

One or more of the Investigators conducting this study serve as consultants for the company that makes products used in this study. These financial interests are within permissible limits established by the local institutional Conflict of Interest Policy. If you have any questions regarding conflicts of interest, please ask you study doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924 or University Hospitals Institutional Review Board at (216) 844-1529. [Select appropriate IRB(s)]

How long will the research last and what will I need to do?
You will be included in this trial only if you have had a good response to your current immunotherapy treatment. If your cancer has decreased by at least 30% then treatment will be held. If you are included in the trial with "stable disease" (tumor did not shrink by at least 30% but did not grow by more than 20%), you will continue on your current immunotherapy treatment as you have been. If your treatment has been on hold and the cancer grows you will restart the same immunotherapy treatment you were getting prior to your treatment being held.
After you finish the study, your doctor will continue to watch you for side effects and follow your condition for 30 days longer or until you start your next treatment.
More detailed information about the study procedures can be found under "What extra tests and procedures will I have if I take part in this study?"

Is there any way being in this study could be bad for me?

Yes. In addition to the routine side effects of CPI, which is considered standard for patients like you, this trial involves the potential for cancer growth. This cancer growth could be faster than if you stayed on therapy.

Additionally, CPI has its own set of risks, which are detailed below. These side effects are not increased compared to if you were not on study. While most patients treated with CPI therapy have some mild to moderate effects, some can have significant side effects. More detailed information about the risks of this study can be found below. The rest of your medical care will be according to our standard practice.

More detailed information about the risks of this study can be found under "What possible risks can I expect from taking part in this study?"

What possible benefits can I expect from taking part in this study?
We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may relief some symptoms related to treatment, improve your quality of life, lessen the amount of medications or visits for the treatment of CPI related side

effects, and decreased risk of hospitalization for rare complications of CPI use.

However, it is possible that your condition could worsen. Your participation in this study will help to obtain information about treating subjects with bladder cancer.

What is the usual approach to my bladder cancer?
The standard of care is for patients like yourself to start CPI therapy. You would continue this medication indefinitely, until disease progression or intolerable side effects.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- you may choose not to be treated for cancer. For example: comfort/palliative care

Detailed Information: The following is more detailed information about this study in addition to the information listed above.

What are the study groups?
All study participants will get the same study intervention. It will include holding CPI therapy if scans show a significant decrease in tumor size after 24 weeks of treatment with CPI therapy.

What extra tests and procedures will I have if I take part in this study?
Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there may be some extra tests that you will need to have if you take part in this study.

Biomarkers: At specified time points, blood samples will be collected to see whether the study drug is producing changes to the genes and proteins related to your cancer.

Immunogenicity (IG) tests determine if your body's immune system is mounting a response to the study drug. At each time point, about 3 teaspoons of blood will be drawn for research purposes.

Research biopsies
Tumor biopsies are recommended at different points in the study to check the characteristics of your tumor. Your tumor cells could be affected by the drug. If your tumor is accessible, a tumor biopsy will be done. Prior tumor biopsies obtained within 6 months of enrollment are allowed.

A tumor biopsy is the removal of a small (pencil eraser-sized) circle of tumor using a cookie cutter-like instrument. The duration of the biopsy procedure is approximately 30 minutes. The biopsy instrument may be placed into the tumor by your physician either in the office or in radiology. The procedure will be done using local anesthesia to minimize discomfort from the biopsy. During a biopsy of the abdomen (for example, biopsy of the liver or lymph nodes in the belly), you will be asked to lie flat and a doctor will clean the area on your belly. The doctor will then numb the area with a local anesthetic so that you do not feel the biopsy. The doctor will ask

you to hold your breath and not move while he or she places the needle into your tumor and withdraws a small core of tissue which remains trapped inside the needle. It is very important that you not move or breathe during the biopsy.

Before you begin the study:
You will need to have the following exams tests and procedures to find out if you can be in the study:

- CT (Computed tomography) scan of chest, abdomen, and pelvis to measure tumors
- Bone scan and/or brain scan if your doctor thinks it necessary
- Blood tests (blood counts, chemistries, thyroid tests, and research samples)
- Women of child bearing potential must have a blood or urine pregnancy test.
- Bone scan to measure tumors if present.
- CT or Magnetic Resonance Imaging to measure brain tumors if present.

An extra blood sample (about 3 teaspoons) will be taken for the study. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the research biomarker and immunogenicity blood draws that will be used for this study.

During the study the following will be additional research procedures:

- Research blood tests each time you have CT scans

What possible risks can I expect from taking part in this study?
If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss
- There is the potential for rapid growth of your cancer.
- There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

<u>You are currently receiving one of the approved checkpoint inhibitor therapies for bladder cancer:</u>

- <u>Atezolizumab (Tecentriq)</u>
- <u>Avelumab (Bevencio)</u>
- <u>Durvalumab (Imfinzi)</u>

- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)

The checkpoint inhibitor immunotherapies used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible side effects of checkpoint inhibitor immunotherapies, which is the usual approach for this type of cancer:

COMMON, SOME MAY BE SERIOUS In 100 people receiving CPI therapy, more than 20 and up to 100 may have:
▪ Fatigue ▪ Watery stools ▪ Skin itching ▪ Cough

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving CPI therapy, from 4 to 20 may have:
▪ Joint pain ▪ Fever ▪ Back pain ▪ Rash ▪ Pain in your belly ▪ Loss of skin color

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving CPI therapy, from 4 to 20 may have: ▪ Not enough thyroid hormone so you may feel tired, gain weight, feel cold, have infrequent or hard stools ▪ Low levels of salt in the blood that may cause you to feel tired, confused, have a headache, muscle cramps and/or feel sick to your stomach

UNCOMMON SIDE EFFECTS
Out of 100 people receiving CPI therapy, from 1 to 5 may have: • Inflammation of the lungs so you may feel short of breath and cough. • Too much thyroid hormone so you may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools • Infusion reaction, where you may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath or at the time of receiving your infusion (IV) or just after, or pain at the site of infusion • Inflammation of the bowels/gut which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus • Inflammation of the skin so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body which can cause severe infection.

RARE SIDE EFFECTS

Out of 100 people receiving CPI therapy, less than 1 may have:

- Inflammation of the nerves that may cause pain, weakness or tingling in your hands and feet, and may spread to your legs, arms and upper body leading to severe muscle weakness and possible temporary paralysis
- Inflammation of the muscles so you may feel weak or have pain in your muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, have a pain in the right side of your belly, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting.
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone which could cause tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan.
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination and weight loss. You are likely to need regular insulin shots. Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting.
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy.
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs
- Inflammation of the brain with confusion and fever. This may also include disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness

Potential Risk or Discomfort from Research Procedures

Blood Draws

The insertion of the needle to draw blood is painful; however, the discomfort is usually brief. For most people, needle punctures to get blood samples do not cause any serious problems; however, they may cause bleeding, bruising, discomfort, infections, dizziness, or fainting.

CT Scans

If you take part in this research, you will have one or more medical imaging studies which use radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may not have received or will receive from other tests. The CT scan that you will receive in this study will expose you to low amounts of radiation. Every day, people are naturally exposed to low levels of radiation that come from the sun and the environment. This type of radiation is called "background radiation." No one knows for sure whether exposure to low amounts of radiation is harmful for your body. However, scientists believe that being exposed to too much radiation can cause harmful side effects, including causing a new cancer. The amount of radiation that scientists think can cause harmful side effects equals more than 15 times the amount of extra radiation you would receive from being in this study. Also, scientists believe the number of people who would be at risk for developing a second cancer from being exposed to large amounts of radiation to be about 1 out of every 1,000.

Bone Scan

A bone scan is a test that helps diagnose and track bone disease. A bone scan will be done when you first start the study. For a bone scan, you will receive an injection of a tracer into a vein in your arm. You will need to lie still on a table while a machine with an arm-like device supporting the camera passes over your body to record the pattern of the tracer being absorbed by your bones. This is painless. A scan of your entire skeleton will take up to 60 minutes. You may find the injection and the need to lie still during the scanning procedure mildly uncomfortable. The risk of an allergic reaction to the tracer is extremely rare.

Biopsies

Risks associated with biopsies include pain, redness, swelling, low blood pressure, excessive bleeding, bruising, or draining at the needle site, abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site. Two to 3% of patients require hospitalization after a tumor biopsy. Rarely, an infection can occur. You will sign a separate consent form before the biopsy is taken. This will be a standard surgical consent form from the institution where the biopsy procedure takes place.

Risks specifically associated with lung biopsy are pneumothorax (collapse of lung), air embolus (air in a blood vessel), hemopericardium (blood around the heart), and lung torsion (twisting that interrupts the blood supply to the lung).

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks

You should not get pregnant, breastfeed, or father a baby while in this study. The CPI therapy used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What happens to the information collected for the research?

Your information or samples that are collected as part of this research will not be used or distributed for future research studies, even if all of your identifiers are removed.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

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

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?

Your involvement in this research study is voluntary and you will not be paid for your participation.

You and/or your health plan/insurance company will need to pay for some or all of the costs of treating your cancer in this study (i.e., medical history, review of medications, physical exams, performance status, routine blood tests, pregnancy test, x-rays and/or scans for tumor measurement). Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

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

If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at (216) 444-2924.

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Moshe C. Ornstein, MD MA and the research study staff at Cleveland Clinic and/or University Hospitals for the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition.

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses and disclosures at any time by writing to:

Moshe C. Ornstein, MD MA
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, you can ask the Principal Investigator and/or research staff at at 216-444-9567.

<u>Emergency or after-hours contact information</u>

If you are a Cleveland Clinic patient, you should contact the page operator at [redacted] or toll free at [redacted], and ask for the oncologist (cancer doctor) that is on call.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB 216-444-.

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Signature

Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Signature of Participant	Date	Printed Name of Participant

I have discussed the information contained in this document with the participant and it is my opinion that the participant understands the risks, benefits, alternatives and procedures involved with this research study.

Signature of Person Obtaining Consent	Date

Printed Name of Person Obtaining Consent