Official Title:	Pembrolizumab and aMVAC chemotherapy as neoadjuvant therapy in non-urothelial histology muscle-invasive bladder cancer: a pilot trial
NCT Number:	NCT04383743
Document Type:	Informed Consent Form
Date of the Document:	3/13/2024

University of Washington
Fred Hutchinson Cancer Center

Consent to take part in a research study:

Pembrolizumab and aMVAC chemotherapy as neoadjuvant therapy in non-urothelial histology muscle-invasive bladder cancer: a pilot trial

[Short title: Pembro+aMVAC non-UC MIBC]

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Request oncology fellow on-call

Important things to know about this study.

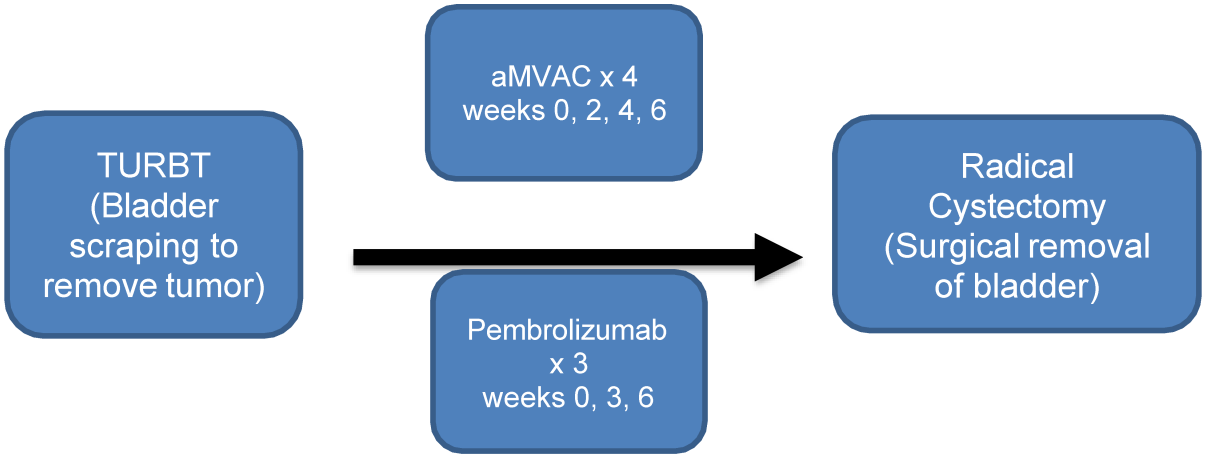
You are invited to participate in a research study. The purpose of this research is to see whether addition of the drug pembrolizumab (Keytruda) to standard preoperative chemotherapy (a combination of: **m**ethotrexate, **v**inblastine, doxorubicin/**A**driamycin and **c**isplatin – referred to as aMVAC) given before the surgical removal of your bladder and pelvic lymph nodes (known as radical cystectomy (RC) and pelvic lymph node dissection (PLND)) is effective in treating people who have non-urothelial bladder cancer.

People who agree to join the study will be asked to attend 8 visits over approximately 6 weeks. If you choose to be in this study, you will receive pembrolizumab every 3 weeks for 3 doses (weeks 0, 3, and 6) and aMVAC chemotherapy every 2 weeks for 4 doses (weeks 0, 2, 4, and 6). Both pembrolizumab and aMVAC chemotherapy will be given over the same 6-week period. Within 10 weeks of your final dose of aMVAC chemotherapy (week 6), you will undergo surgery to remove your bladder. The removal of your bladder is standard for patients with bladder cancer that has grown into the muscle layer of the bladder wall.

We do not know if pembrolizumab in combination with aMVAC chemotherapy will help cure or treat non-urothelial bladder cancer, and it could even make your condition/disease worse. Both treatments are used to treat urothelial bladder cancer. Pembrolizumab and aMVAC chemotherapy could cause side effects such as hair loss, tiredness, vomiting, and nausea, as described below in this form.

You do not have to join this study. You can choose to receive standard methods to treat your cancer instead of participating in this study. We will give you details about the purposes, procedures, risks, and possible benefits related to this study. We will explain other choices that you have. We will also give you any other information that you need in order to make a well-informed decision about joining this study.

Following is a more complete description of this study. Please read this description carefully. You can ask any questions to help you decide whether to join the study. You should not join this research study until all your questions are answered. Please take as much time as you need to make an informed decision. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your doctor for more information. If you join this study, we will give you a signed copy of this form to keep for future reference.



We invite you to join this research study.

We invite you to join this research study because you have non-urothelial bladder cancer. You are also being asked to take part in this research study because you are planning to undergo a surgical procedure called radical cystectomy to remove your bladder and a pelvic lymph node dissection. We hope to treat up to 17 people in this study.

Research is not the same as standard treatment or routine medical care. The purpose of a research study is to answer scientific questions that may inform standard routine practice in the future. You do not have to join the study. You are free to say "yes" or "no" or drop out after joining. If you say "no," you would have no penalty or loss of benefits. Whatever you decide, your regular medical care would not change.

Why are we doing this study?

We are doing this study to see whether the addition of pembrolizumab to aMVAC chemotherapy given before surgery is effective in treating people who have non-urothelial bladder cancer, and to examine the side effects, good and bad, associated with pembrolizumab and aMVAC chemotherapy.

The standard treatment for patients with non-urothelial bladder cancer that has grown into the bladder muscle includes receiving chemotherapy followed by surgery, going straight to surgery, or using a combination of radiation and chemotherapy.

We are studying whether the addition of pembrolizumab to aMVAC chemotherapy given before surgery improves the appearance of bladder tissue under the microscope at the time of surgery.

aMVAC chemotherapy is a combination of four chemotherapy medications (methotrexate, vinblastine, doxorubicin and cisplatin) that is regularly used for the treatment of bladder cancer.

Pembrolizumab, which is approved in the USA and some other countries, is available by prescription to treat several different cancers but may not be approved to treat your type of cancer. It works by helping your immune system to fight your cancer.

Pembrolizumab is an antibody that attaches to and blocks a molecule called PD-1. PD-1 is present on your immune system cells and it plays a role in shutting down or suppressing the body's ability to detect, attack, and destroy cancer cells.

Pembrolizumab has been shown to help patients with advanced (not removable by surgery) or metastatic (spread to other areas of the body) urothelial cancer (most common form of bladder cancer) live longer and better when used after chemotherapy is no longer working. Pembrolizumab is also used as first therapy in patients with advanced / metastatic urothelial cancer who cannot tolerate chemotherapy well. It is also used for treatment of earlier stage (superficial) bladder cancer in specific circumstances.

What research tests, procedures, and treatments are done in this study?

There are 3 phases to this study: Screening, Treatment, and Post-treatment. If you join this study, we would do these tests and procedures described below:

Screening Procedures

You will have the following tests and procedures to make sure you are eligible to be treated on this study; most of these tests are standard-of-care (routine) and are done regardless of whether or not you decide to be in this study. You will have these procedures within four weeks of starting therapy in this study:

- You will have Transurethral Resection of Bladder Tumor (TURBT) within 12 weeks of starting study treatment. TURBT is a standard surgical procedure that is used to diagnose bladder cancer (and see how deep it goes into the bladder wall) and remove cancer from the bladder. You may have already had this procedure.
- We will obtain your medical and surgical history.
- We will review all medications you are taking including over-the-counter medicines, vitamins, dietary and herbal supplements.
- We will do a detailed physical exam.
- We will obtain vital signs (temperature, pulse, and blood pressure), including your height and weight.
- We will evaluate how physically active you are.
- We will draw blood samples for screening tests. We will take about 1 tablespoon of blood. We will use your blood sample to test for the following:

  - complete blood count and chemistries
  - to check your thyroid function. The thyroid is a gland located beneath your voice box that helps regulate growth and metabolism.
  - to check your adrenal gland function. Your adrenal glands are located on top of each kidney and help regulate your metabolism, sugar levels and blood pressure. The adrenal glands also help regulate how you respond to stress.
  - blood (serum) pregnancy test for females of childbearing potential. The test must be negative before you can be entered in this study.
- We will collect a urine sample for analysis.
- We will do chest, abdomen and pelvic CT (Computed Tomography- type of x-ray using computers) scan with intravenous (IV) contrast, if possible, or MRI (Magnetic Resonance Imaging- takes pictures using magnetic rather than x-ray energy) to determine the extent of your disease.
- Other routine radiology studies may be needed to assess your cancer if recommended by your doctor.
- We will collect a sample of your tumor tissue during a standard/routine TURBT. If this was performed previously, we will request this tissue. This sample is required in order for you to take part in this study. A doctor well-trained in diagnosing cancer under the microscope will review the sample before you are registered to the study to make sure there is enough tumor in the sample. The tumor tissue sample will also be sent to a central lab. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research; this will not impact your treatment.
- We will collect a research blood sample: 10 mL (approximately 2 teaspoons) of blood will be drawn and stored for future research.
- We will collect urine and stool samples for future research.

Treatment Procedures

If you are eligible to be in this trial, you will start the study treatment. During the treatment period, you will be asked to come to the clinic to receive the study drugs (pembrolizumab and aMVAC chemotherapy). Before receiving each treatment, you will be seen and asked about any new problems that may have occurred since your last visit.

The aMVAC chemotherapy infusion will be given over approximately 2-4 hours and pembrolizumab will be given over approximately 30 minutes; you will also be given fluids for hydration. On week 0 and 6, you will receive pembrolizumab and aMVAC chemotherapy on the same day. Within 10 weeks after your last treatment (week 6), you will undergo surgery to remove your bladder and surrounding lymph nodes, which is usual standard care for patients with bladder cancer that grows into the muscle layer of the bladder wall. Your surgeon will go over your surgical procedure in more detail closer to the date of surgery.

During each of these treatment visits, you will have the following tests, procedures and assessments done:

- We will do a detailed physical exam.

- We will obtain vital signs (temperature, pulse, and blood pressure), including weight. These will also be done before and through your infusion.
- We will evaluate how physically active you are.
- We will draw blood samples for complete blood count and chemistries. We will draw about 1 tablespoon of blood.

Prior to First Two Pembrolizumab Doses (Weeks 0 and 3)

- We will monitor for any side effects – you should tell your study doctor immediately if you have new problems or changes, at any time when they occur. In addition to the assessment, tests and procedures above, we will collect additional study specimens as below:
  - We will collect additional blood samples for research: 40 mL (approximately 2¾ tablespoons) of blood will be drawn. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research.
  - We will collect urine samples for research: 30 mL (approximately 2 tablespoons) of urine will be collected and stored for future research.
  - We will collect samples of your stool (poop) that will be stored for future research.

Prior to Radical Cystectomy with Pelvic Lymph Node Dissection

- We will do a detailed physical exam.
- We will obtain vital signs (temperature, respirations, pulse, and blood pressure) including weight.
- We will evaluate how physically active you are.
- We will draw blood samples. We will draw about 1 tablespoon of blood. We will use your blood sample to test for the following:
  - complete blood count and chemistries
  - to check your thyroid function.
  - to check your adrenal gland function.
- We will do chest, abdomen and pelvic CT scan (with IV contrast if possible) or MRI to evaluate your disease. This is a standard practice routine test.
- We will collect blood samples for research: 40 mL (approximately 2¾ tablespoons) of blood will be drawn. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research.
- We will collect urine samples for research: 30 mL (approximately 2 tablespoons) of urine will be collected and stored for future research.
- We will review all medications you are taking including over-the-counter medicines, vitamins, dietary and herbal supplements.
- We will monitor for any side effects – you should tell your study doctor immediately if you have new problems or changes at any time, if they occur.

End of Treatment (approximately 30 days after radical cystectomy)

- We will do a detailed physical exam.

- We will obtain vital signs (temperature, respirations, pulse, and blood pressure) including weight.
- We will evaluate how physically active you are.
- We will take blood samples. We will take about 1 tablespoon of blood. We will use your blood sample to test for the following:
  - complete blood count and chemistries
  - to check your thyroid function.
  - to check your adrenal gland function
- We will collect research blood samples: 40 mL (approximately 2¾ tablespoons) of blood will be drawn. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research.
- We will collect research urine samples: 30 mL (approximately 2 tablespoons) of urine will be collected and stored for future research.
- We will review all medications you are taking including over-the-counter medicines, vitamins, dietary and herbal supplements.
- We will monitor for any side effects – you should tell your study doctor if you have new problems or changes immediately, at any time if they occur. You will be monitored for side effects for up to 90 days after your last dose of pembrolizumab and aMVAC chemotherapy.

<u>Radical Cystectomy with Pelvic Lymph Node Dissection (within 10 weeks after last dose of study treatment)</u>

- This surgery is standard of care, regardless of the study. Tumor tissue for research will be obtained at the time of your radical cystectomy procedure. The tumor tissue sample will be sent to a central lab. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research.

Post-Treatment Procedures (Follow-Up)

Once you are no longer receiving study medication, or if you withdraw from the study at any time, we will follow-up to see how you are doing and ask about any other anti-cancer therapies you may have taken or are taking (either during a routine clinic visit or in a phone call). This will occur approximately every 3-6 months for at least 2 years after your cystectomy or until the study closes (around 3 years). Afterwards, you will continue to be monitored at regular intervals to make sure that the cancer does not come back.

Additionally, if your cancer comes back, we would like to obtain:

- Blood samples for research: 40 mL (approximately 2¾ tablespoons) of blood will be drawn. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research.
- Urine samples for research: 30 mL (approximately 2 tablespoons) of urine will be collected and stored for future research.
- Stool samples for research that will be stored for future research
- Tumor tissue for research: Tumor tissue obtained after your treatment (by biopsy, fine needle aspirates (FNA), etc.) as part of your normal medical care under the

guidance of your doctor. Some of the sample will be used to check how your immune system is reacting and the rest will be stored for future research.

How long would you stay in this study?

If you join this study, you would receive pembrolizumab and aMVAC chemotherapy for approximately 6 weeks followed by surgery within 10 weeks of your last treatment date. After that, you would have a return visit about one month after your surgery to mark the end of treatment. You will then have follow-up exams or phone calls every 3-6 months (either a routine clinic visit or phone call) for at least 2 years after your cystectomy or until the study closes (approximately 3 years) to check on your health and about any other anti-cancer therapies you may have taken or are taking.

Doctors could take you out of this study at any time. This would happen if:

- They think it is in your best interest not to continue in the study.
- You are not able or willing to follow study procedures.
- The whole study is stopped.

If you withdraw from the study for any reason, previously collected information would remain in the study records and would be included in the analysis of results. This information could not be removed from the study records.

Mandatory tissue/blood/urine/stool samples for research

Your tumor tissue sample from the standard/routine TURBT (mentioned above) are required in order for you to take part in this research study. Tumor tissue samples will also be obtained at the time of your standard/routine radical cystectomy.

Additionally, we would like to receive samples of tumor tissue obtained after your treatment (by biopsy, fine needle aspirates [FNA], etc.) if the cancer comes back as part of your normal medical care under the guidance of your doctor.

You must also be willing to provide research blood, urine, and stool samples to participate in this research study.

Your samples will be sent to the central laboratory using a unique identifier and not linked to your medical record number, which protects your identity. The samples will be kept until they are used up. We will store samples for future research studies to help better understand bladder cancer and the immune system, and to develop future studies and new therapies.

What are the side effects (risks)?

In this part of the consent form, we describe the side effects we expect from the tests and treatments in this study. Pembrolizumab and/or aMVAC (methotrexate, vinblastine, doxorubicin and cisplatin) could cause side effects that we do not know about yet. We carefully watch everyone in the study for side effects.

You may experience all, some, or none of the side effects described below. Side effects may be mild or very serious. Medicines could be given to help lessen side effects. Some side effects may not show up until several weeks after treatment is given. Many side effects may go away soon after you stop taking the medications. In some cases, side effects can last a long time or never go away. There is also a risk of death.

If you join this study, we would tell you if we discover new side effects that could affect you. Risks and side effects that are related to standard routine treatment aMVAC chemotherapy regimen given in this study may include:

Methotrexate

Common side effects *(greater than 20 out of 100 will experience)* include:

- Nausea, vomiting, loss of appetite
- Increased risk of sunburn, rash
- Hair loss

Less common side effects *(4 to 20 out of 100 will experience)* include:

- Fluid around heart
- Seizure
- Internal bleeding which may cause belly pain, black tarry stool, blood in vomit
- Blood clot which may cause swelling, pain, shortness of breath
- Severe skin rash with blisters and peeling which can involve mouth and other parts of the body
- A new cancer resulting from treatment of a prior cancer
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia (low red blood cell count) which may cause tiredness, or may require transfusion
- Hepatitis or damage to the liver which may cause yellowing of eyes and skin, swelling
- Scarring of the liver
- Kidney damage which may require dialysis
- Sores in mouth which may cause difficulty swallowing
- Diarrhea
- Confusion

Rare and serious side effects *(3 or less out of 100 will experience)* include:

- Scarring of the lungs which may cause shortness of breath
- Dizziness

Vinblastine

Common side effects *(greater than 20 out of 100 will experience)* include:

- High blood pressure which may cause headaches, dizziness, blurred vision
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Pain
- Mouth sores

- Tiredness

Less common side effects *(4 to 20 out of 100 will experience)* include:

- Stroke, which may cause paralysis, weakness
- Damage to the lungs which may cause shortness of breath
- Nausea, vomiting, loss of appetite, constipation
- Abnormal menstrual period in women
- Confusion
- Numbness and tingling in fingers and toes
- Pain or redness at site of infusion
- Hair loss

Rare and serious side effects *(3 or less out of 100 will experience)* include:

- Damage to hearing which may be permanent
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Headache

<u>Doxorubicin</u>

Common side effects *(greater than 20 out of 100 will experience)* include:

- Vomiting
- Red colored urine, saliva, or sweat
- Hair loss

Less common side effects *(4 to 20 out of 100 will experience)* include:

- Heart failure or heart attack which may cause shortness of breath, swelling of ankles, cough or tiredness which may occur years after the dose
- Abnormal heartbeat
- Cancer of the bone marrow (leukemia) caused by chemotherapy
- Damage to the lungs which may cause shortness of breath when combined with radiation
- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia (low red blood cell count) which may cause tiredness, or may require transfusion
- Hepatitis or damage to the liver which may cause yellowing of eyes and skin, swelling
- Kidney damage which may require dialysis
- Sores in the mouth or throat
- Belly pain
- Nausea, diarrhea
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Damage to the skin which may cause pain
- Swelling and redness at the site of the medication injection or area of previous radiation

- Loss of nails
- Darkening of the nail beds or skin or hands and feet

Rare and serious side effects *(3 or less out of 100 will experience)* include:

- Severe blood infection

<u>Cisplatin</u>

Common side effects *(greater than 20 out of 100 will experience)* include:

- Nausea, vomiting
- Infection, especially when white blood cell count is low
- Anemia (low red blood cell count) which may cause tiredness, or may require blood transfusions
- Bruising, bleeding
- Kidney damage which may cause swelling, may require dialysis
- Hearing loss including ringing in ears

Less common side effects *(4 to 20 out of 100 will experience)* include:

- Hair loss
- Change in taste
- Diarrhea
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Confusion
- Difficulty with balance
- Numbness and tingling of the arms and legs
- Blurred vision or changes in ability to see colors (especially blue or yellow)

Rare and serious side effects *(3 or less out of 100 will experience)* include:

- Cancer of bone marrow caused by chemotherapy later in life
- Seizure

<u>Pembrolizumab</u>

Pembrolizumab can cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e., causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Risks and side effects that are related to treatment with pembrolizumab given in this study may include:

Very Common side effects *(greater than 20 out of 100 will experience)* include:

- Itching of the skin
- Loose or watery stools
- Cough

Common side effects *(5 to 20 out of 100 will experience)* include:

- Pain in back
- Rash
- Joint pain
- Fever
- Pain in belly
- Loss of skin color
- Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism)
- Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

Uncommon side effects *(5 or less but at least 1 out of 100 will experience)* include:

- Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis)
- Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have 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 (colitis)
- 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 (Severe skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis)

Rare side effects *(1 or less out of 100 will experience)* include:

- 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 (Guillain-Barré syndrome)
- Inflammation of the muscles, so you may feel weak or have pain in your muscles (myositis)
- 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 have vomiting that gets worse when you eat (pancreatitis)

- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- 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, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- 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 (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and bellyaches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- 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 (nephritis)
- 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 (myocarditis)
- 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 (thyroiditis)
- A condition that may make you feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- 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 (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue.
- Low levels of parathyroid hormone (a hormone made by 4 tiny glands in your neck) which may result in low blood calcium and cause muscle cramps or spasms; fatigue or weakness; numbness, tingling, or burning in your fingertips, toes, or lips (hypoparathyroidism).
- Inflammation of the stomach (gastritis). You may have pain in your belly, feel

full, or sick to your stomach. You may also experience nausea, vomiting, or loss of appetite.
- Low number of red blood cells (cells that carry oxygen) due to destruction of red blood cells (hemolytic anemia). You may feel weak, tired, lightheaded, short of breath, or have a fast heartbeat. You may also experience difficulty with physical exercise, pale or yellow skin, dark urine, or fever.
- Not enough pancreatic enzymes (proteins that break down food) that leads to poor digestion of food (exocrine pancreatic insufficiency). You may have bloating, gas, discomfort in your belly, diarrhea, abnormal stool that is oily, or weight loss.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).
- Optic Neuritis: Inflammation or swelling of the nerve fibers of the eye which send visual information from your eye to your brain. This health condition often has a sudden onset of vision loss, loss of color vision, pain when moving your eyes, and/or loss of peripheral vision. It may affect one or both eyes at the same time.

This form lists side effects of *individual* drugs. Other side effects could occur when we use these drugs *together*.

Drug interactions
Pembrolizumab or pembrolizumab and aMVAC taken in combination with other medicines may be associated with other risks that are unknown at this time. If any physician other than your study doctor prescribes medication for any other condition or you are taking over-the counter medications, vitamins, dietary or herbal supplements, you must inform the study staff.

You may not take certain medications or receive certain medical treatments without the permission of the study staff during the study therapy with pembrolizumab and aMVAC. This includes other anti-cancer treatments, other medications that can suppress your immune system (such as prednisone) and live vaccines. Ask your medical team about any new medication or supplements.

Other risks and discomforts
The risks of having blood drawn and/or inserting the needle in your vein include fainting, bleeding, bruising at the place on your arm where the blood was drawn or needle inserted, pain, swelling, and rarely can cause infection or nerve damage. However, blood work is standard during chemotherapy regardless of the study.

Radiation risks
Some of the tests that you will have in this research study will expose you to radiation; however, these tests would occur anyway as standard of care regardless of the study. Everyone receives a small amount of radiation every day called "background radiation." This radiation is natural and comes from space, air, water, soil, and the food you eat.

Each year you are exposed to about 3 milliSieverts (mSv) of this background radiation. A milliSievert is a unit of radiation dose.

There is minimal risk to your health from the amount of radiation you will receive in this study (these tests would occur anyway as standard of care regardless of the study). The usual lifetime risk of getting cancer is 42%. For every 10 mSv you receive, your risk may increase 0.1%. If you have more procedures that expose you to radiation, your risk will go up. For comparison, the estimated radiation dose from each of these tests is listed below:

- CT chest: 7 mSv
- CT abdomen: 8 mSv
- CT pelvis: 6 mSv

Reproductive risks
Chemotherapy could cause sterility (unable to have children). Taking the study drugs (aMVAC and pembrolizumab during pregnancy may involve unknown risks to an embryo fetus (unborn baby) or nursing infant. Therefore, you could not join this study if you are pregnant, if you are planning to become pregnant during treatment and within 6 months after the last dose of study treatment, or if you are breast feeding.

If you join this study, you would have to use an effective method of birth control from the time this form is signed until at least 6 months after the last dose of aMVAC or pembrolizumab. If you are already using a method of birth control, you would have to check with the study doctor or a member of the study staff to make sure it is acceptable.

If you became pregnant after joining this study, you would have to notify the study doctor immediately. Participation in this study would end, and you would receive counseling and follow up throughout the pregnancy and for some time after the child is born.

The effects of the study drugs (aMVAC and pembrolizumab) on fathering a child are also unknown. Men who join this study must also agree to use one or more forms of effective and acceptable birth control from the time this form is signed until at least 6 months after last dose of aMVAC or pembrolizumab.

Tumor Biopsy
TURBT is standard routine care and may be repeated as clinically indicated, for example, to ensure that there is adequate information for the diagnosis, to assess the extent/depth of the cancer, and to ensure there is adequate tumor content in the sample. There are no other biopsies to be done only for research purposes in this study.

What are the benefits?

We do not know if aMVAC chemotherapy with pembrolizumab would help cure or treat your cancer. We are testing the combination of aMVAC with pembrolizumab to see its effects on people with non-urothelial bladder cancer. You might get better if you receive aMVAC and pembrolizumab, but your condition could stay the same or even get worse. We hope the information from this study will help other people with non-urothelial bladder cancer in the future.

You have other choices besides this study.

You do not have to join this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no".

You have other choices for treatment. Each of these choices has risks and benefits. You should talk to your doctor or healthcare provider about these choices.

Other choices include:

- Standard therapy which may include other FDA-approved available therapies for your cancer, such as cisplatin-based chemotherapy with aMVAC or gemcitabine and cisplatin followed by radical cystectomy (surgery to remove your bladder)
- Radical cystectomy without systemic therapy
- TURBT, chemotherapy with radiation.
- Taking part in another research study.
- Surveillance with TURBTs or close observation with no therapy, also called "watch and wait" approach if you don't want treatment at this time after talking it over with your doctor.
- No therapy with care to help you feel more comfortable if you don't want any treatment at all despite discussion with your doctor.

Enrollment in this study may exclude you from most other research studies.

Protecting Privacy as an Individual and the Confidentiality of Personal Information

If you join this study, some people or organizations might need to look at your medical records and research records for quality assurance or data analysis. They include:

- Researchers involved with this study.
- Merck Sharp & Dohme Corp. (the funder of the study) and their agents.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer Center and University of Washington.
- US National Institutes of Health, National Cancer Institute, Office for Human Research Protections, Food and Drug Administration, and other regulatory agencies as required.

We will do our best to keep personal information strictly confidential, but we cannot guarantee total confidentiality. Personal information may be given out if required by law.

For example, workplace safety rules may require health workers to contact you about lab tests. Or a court may order study information to be disclosed. Such cases are very rare.

We will not use personal information in any reports about this study, such as journal articles or presentations at scientific meetings.

If you join this study, information about your participation would be made part of your permanent medical record. This information would include a copy of this consent form. If an insurance company or employer or anyone else were authorized to see your medical record, they would see a copy of this consent form.

How is my genetic information protected?

A federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect genetic information about people who join research studies.

GINA restricts access to genetic information so that it cannot be used for health insurance coverage decisions. GINA prevent health insurance companies or group health plans from

- Asking for genetic information obtained in research studies, or
- Using genetic information when making decisions regarding your eligibility or premiums

GINA *does not* help or protect against genetic discrimination by companies that sell life, disability or long-term care insurance. However, there is no plan to have genetic information derived from study research procedure as part of your medical record.

Who is paying for the study?

We are receiving financial support from Merck Sharp & Dohme Corp.

Would we pay you if you join this study?

There is no payment for being in this study.

Would you have extra costs if you join this study?

If you join this study, you would potentially have some extra costs. Your insurance company usually pay these costs, but some insurance policies do not cover these costs. We could help find out whether your insurance company would cover these costs.

The extra costs are:

- Cost of tests that are given more often than usual.
- Cost of aMVAC chemotherapy. There is no charge for pembrolizumab itself.
- Cost of people and equipment to give aMVAC and pembrolizumab.
- Cost of standard doctor visits and lab tests.
- Cost of any other medical care needed because of this study.

If you join this study, you or your insurance company would have to pay for the costs of standard/routine treatment in this study.

You would **not** be billed for:

- Study drugs, pembrolizumab.
- Submission and storage of tumor samples obtained from TURBT or surgery
- Submission and storage of tumor samples obtained at time of your radical cystectomy and at any time during your follow-up
- Collection and storage of research blood samples
- Collection and storage of research urine samples
- Collection and storage of research stool samples

What if you get sick or hurt after you join this study?

For a life-threatening problem, call 911 right away or seek help immediately. Contact your study doctor when the medical emergency is over or as soon as you can.

For all other medical problems or illness related to this research, immediately contact Dr. Petros Grivas at 206.606.7416. They will treat you or refer you for treatment. You or your health insurance will have to pay for the treatment. There are no funds to pay you for a research-related injury, added medical costs, loss of a job, or other costs to you or your family. State or national law may give you rights to seek payment for some of these expenses. You do not waive any right to seek payment by signing this consent form.

You or your insurer will be billed for treatment of problems or complications that result from your condition or from standard clinical care.

You would not lose any legal right to seek payment for treatment if you sign this form.

What will my information and/or tissue samples be used for?

Your information and samples (such as blood, urine, stool and tumor tissue) will be used for the purposes of this study.

Your samples might help researchers develop new products or learn more about this cancer. This research will be done by scientists in our institutions but part of it could potentially be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your samples. During this study, if the researchers learn new information that may be important to your general health or your disease or condition, they will share that information with you.

Will my information and/or tissue samples ever be use for future research?

In addition, be aware that by agreeing to participate in this study, your information or samples could be used for future research studies or sent to other investigators for future research studies without additional consent from you. These future research studies will be reviewed by an oversight group known as an institutional review board if required by law. The information that identifies you will first be removed from your information or samples. If you do not want your information or samples to be used for future research studies without your consent, you should not participate in this study.

Your samples contain DNA and RNA. DNA and RNA make up the genes that serve as the "instruction book" for the cells in our bodies. By studying genes, researchers can

learn more about diseases, such as cancer. There are many different types of genetic tests. The testing on your samples might include genetic testing called whole genome sequencing. Whole genome sequencing looks at all the genetic information in your cells. This type of testing can provide very useful information to researchers. It can also present rare risks if the test results became known to others, for example you could have implications with family members or insurance companies, but this could be extremely rare. There is also a risk that these test results could be combined with other genetic information to identify you, but this could be extremely rare.

Your rights

- You do not have to join this study. You are free to say "yes" or "no".
- If you get sick or hurt in this study, you do not lose any of your legal rights to seek payment by signing this form.
- During the study, we might learn new information that you need to know. For example, some information may affect your health or well-being. Other information might make you change your mind about being in this study. If we learn these kinds of information, we would tell you.
- If you join this study, you would not have to stay in it. You could stop at any time (even before you start). Your regular medical care would not change. You would have no penalty for stopping, but it would be better not to join the study if you think that you would change your mind later.
- If you decide to drop out, we would want you to tell the study doctor. The doctor could tell you about the effects or stopping aMVAC chemotherapy and/or pembrolizumab. You and the doctor could talk about the follow-up care and testing that would help the most.
- Before you leave the study, the doctor might ask you to continue in on the same imaging schedule used while on treatment to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

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

Your responsibilities

If you join this study, you would have some responsibilities.

- Follow the schedule of all study visits and procedures.
- Prevent pregnancy and breastfeeding.
- Tell us about side effects, new problems, medications and changes.
- Attend scheduled study visits.

For more information

If you have questions or concerns about this study, you could talk to your doctor anytime.

Other people you could talk to are listed below.

If you have questions about:	**Call:**
This study (including complaints and requests for information)	206-606-7416 (Dr. Petros Grivas)
If you get sick or hurt in this study	206-606-7416 (Dr. Petros Grivas)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-598-8260 (UWMC Patient Financial Services)

Emergency number (24 hours): 206-598-6190

Signatures

Please sign below if you:

- have read this form (or had it read to you);
- had the opportunity to ask any questions you have;
- had the opportunity to discuss the research with the person obtaining consent; and
- agree to participate in this study.

Participant (age 18+):

Printed Name	Signature	Date

If you served as an interpreter or witness during the consent process, sign below to indicate you attest to the accuracy of the presentation to the participant and the apparent understanding of the research by the participant.

Witness or Interpreter:

Printed Name	Signature	Date

Researcher's statement

I have discussed the research study, including procedures and risks, with the person signing above. A copy of the signed consent form will be given to the participant.

Person obtaining consent signature:

Printed Name	Signature	Date

Protocol: AMVAC PEMBRO
Current version date: 20 DEC 2023
Previous version date: 05 DEC 2022
Copies to: