UNIVERSITY OF WASHINGTON

Consent to take part in a research study:

Phase II Trial of Neutron Radiotherapy with Concurrent Checkpoint Inhibitor Immunotherapy (pembrolizumab) in Patients with Advanced Urothelial Carcinoma

Principal Investigator: Jing Zeng, MD, Associate Professor
Department of Radiation Oncology
206-598-4100

Emergency number (24 hours): 206-598-6190 Ask for the Radiation Oncologist on-call.

We are asking you to be in a research study.

Research is not the same as treatment or medical care. The purpose of this study is to answer scientific questions. You do not have to be a part of this study. You are free to say yes or no, or to drop out any time after joining.

There is no penalty or loss of benefits if you say no. Whatever you decide, your regular medical care will not change.

Your study doctor will explain this research study to you. Research studies include only people who choose to take part. Please take your time to read this consent form, ask questions, and make your 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 study doctor for more information.

Why are we doing this study?

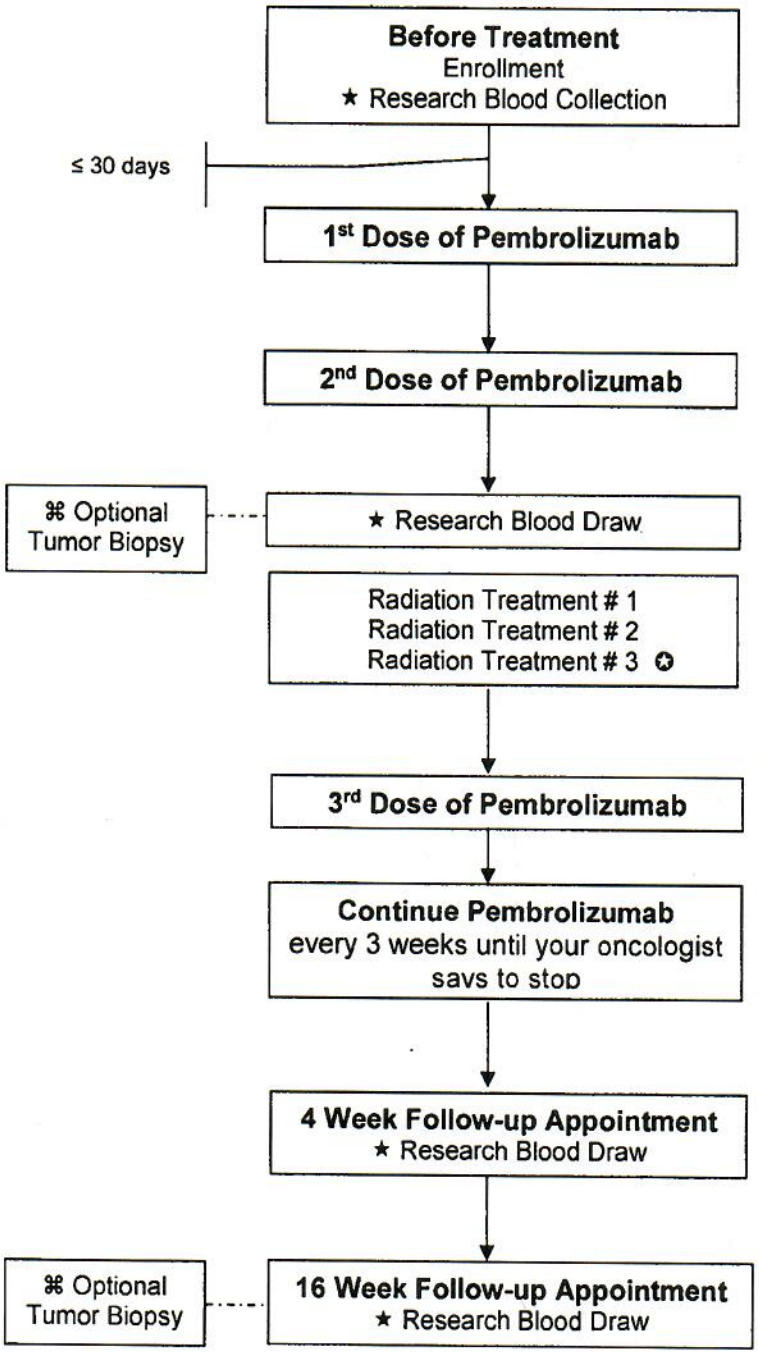
We are doing this study to learn more about whether radiation can improve response rates in patients receiving immunotherapy for their advanced bladder cancer. In this trial, we are testing radiation to a single tumor to act as a "vaccine" by stimulating an immune response.

You are being asked to join this study because you are beginning Pembrolizumab (Keytruda®), an immunotherapy. This kind of therapy blocks a protective system on cancer cells. You are also being asked to join this study because you can benefit from radiation using neutrons. Neutron radiation treatment has a higher effectiveness than standard radiation. We believe that neutron radiation will kill more cancer cells. We would like to study the effects of neutron radiation therapy on your immune system, good or bad, and whether it helps produce a larger healing effect for your bladder cancer.

Our goal is to enroll 20 patients in this study.

What will happen if I participate in this research study?

This research study makes no change to your existing treatment plan as recommended by your primary oncologist. Pembrolizumab and neutron radiation therapy are standard treatments recommended for your bladder cancer treatment. Your radiation oncologist may target one to three tumors. The area targeted with radiation treatment does not have to be an area that you are experiencing side effects from. The following diagram shows the flow of the study and how much time there is between the study events.



Symbol Key

★ 9 tubes of blood for research purposes

✪ 3 to 5 radiation doses occurring over 2 weeks' time

⌘ Optional research biopsy of radiated or non-radiated tumor

To make sure you are eligible for this clinical trial, your oncology team will review the following:

- medical history
- ability to do daily tasks
- blood draws
- CT scans

Research Blood Collection

We will be collecting your blood at specific timepoints for us to study changes in your body's immune response. We will try to collect blood during the times you would normally get blood drawn to minimize the amount of needle pricks you receive.

4 Collection Timepoints:

- Before you start pembrolizumab
- Right before radiation treatment
- 4-weeks after radiation treatment ends
- 16-weeks after radiation treatment ends

We will collect 9 tubes of blood, or about 5-6 tablespoons each collection. If we are not able to combine a research blood draw with a clinical blood draw, arrangements will have to be made to return to SCCA or UWMC for the research blood collection. Each blood draw visit would be 15 minutes or less. We will make every attempt to make this convenient for you.

Neutron Radiation Treatment

You will start radiation treatment after your second dose of pembrolizumab, or shortly after your 2nd research blood draw. You will have up to 3 cancerous spots radiated at the same time.

Visits

- Radiation treatment planning
- 1st radiation treatment
- 2nd radiation treatment
- 3rd radiation treatment

All radiation treatments must be completed within a 2-week period.

Your study doctor may spread out your treatment to 5 treatments if he/she is concerned for any side-effects you may experience. The daily amount of radiation you will receive will range between 1.5 – 2.8 gray units (radiation is measured in terms of how your tissue absorbs energy). Each radiation treatment will be a visit that is 30 minutes or less.

How long will I be in this study?

You will be considered enrolled on study after you review and sign the consent form. You will be on this study for approximately 22 weeks (5-6 months). After the study period, you will see with your medical oncologist at least every 3 months. Your study team may look at your records to see how you are doing.

Your doctors may take you off study earlier if:

- They think it is in your best medical interest not to continue in the study.
- Your conditions worsens
- New information becomes available and this information suggests the treatment may be ineffective or unsafe for you.
- The study is stopped early due to lack of funding or participation.

Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. If you decide to stop participating in the study, we encourage you to talk to the researcher and your doctor first. Your decision will not affect your future relationship with the University of Washington or Seattle Cancer Care Alliance.

If you leave the study for any reason, your test results and information previously collected cannot be removed from the study records. However, additional information will not be collected upon leave the study. Attempts will be made to obtain permission to record at least survival data up to 6 months post-treatment.

What are the risks (side effects) of the study?

The treatments available in this clinical trial are standard of care and the side-effects of each have been well studied.

Side effects associated with Pembrolizumab

- Most Common (> 20% of patients)
    - Tiredness
    - Bone and Muscle Pain
    - Decreased Appetite
    - Constipation
    - Rash
    - Diarrhea
- Common (≥ 10% of patients)
    - Drop in red blood cells
    - Nausea
    - Abdominal Pain
    - Changes that show up in blood tests
    - Vomiting
    - Weight Loss
    - Low Sodium
    - Joint Pain

- Cough
- Shortness of Breath
- Swelling
- Itching
- Fever

- Rare , but Serious (≥ 2% of patients)
  - Urinary Tract Infection
  - Blood in Urine
  - Kidney Damage
  - Infection in the lungs
  - Blood poisoning caused by infected urine
- Rare but serious immune-mediated reactions (3% or less of patients)

Conditions that occur when the immune system over-reacts or attacks itself:

- Immune-mediated pneumonitis (lung inflammation)
- Immune-mediated colitis (inner lining of colon inflammation)
- Immune-mediated hepatitis (liver inflammation)
- Immune-mediated endocrinopathies (hormone gland inflammation)
- Immune-mediated nephritis and renal dysfunction (kidney inflammation)
- Immune-mediated skin adverse reactions
- Other Immune-mediated reactions that will require high dose corticosteroids

Side effects associated with Neutron Radiation

Exact toxicity depends on the site of treatment and your radiation oncologist will discuss this with you.

- General
  - Fatigue
  - Itchy Skin
  - Hair loss inside radiation field
- Head and neck treatment
  - Dry mouth
  - Inflammation of membranes
  - Difficulty swallowing
  - Nausea
  - Tooth decay
- Chest treatment
  - Difficulty swallowing

- Nausea
- Lung damage causing shortness of breath, cough, or fever

- Abdomen treatment
  - Nausea/vomiting
  - Diarrhea
- Pelvis treatment
  - Diarrhea
  - Urinary irritation
  - Rectal irritation causing bleeding or urgency
  - Inability to have children

***Side effects associated with the research blood collection*:**

- Bruising or minor swelling at the site of needle injection
- Light headedness or dizziness
- Pressure from the rubber band around your upper arm to increase blood flow

Reproductive risks

Taking pembrolizumab and radiation 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, 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 4 months after the last dose of 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 about 6 months after the child is born.

Non-physical risks

If you join this study, non-physical risks are:

- You might not be able to work.
- Results of genetic tests might be released by accident. This risk is very low, because we keep personal information private. If these results became known, you could have problems with family members or insurance.

You have other choices besides this study

You do not have to enroll onto this study. You are free to say "yes" or "no". Your regular medical care would not change if you decide to say "no". If your doctor recommends pembrolizumab and/or neutron radiation, you can still receive those treatments as part of your regular care.

without being on this clinical trial. You should discuss with your doctor what is available to you. Enrollment in this study may exclude you from other research studies.

What are the benefits of this study?

There is no direct benefit to you for enrolling onto this study. We are testing whether using neutron radiation therapy will act as a vaccine when combined with immunotherapy. Information gained from your enrollment onto this study will help the research doctors explore the effect of neutron radiation therapy on patients receiving immunotherapy. Any possible knowledge gained may help future patients with bladder cancer.

Protecting your Privacy as an Individual and the Confidentiality of Your Personal Information

Some people or organizations may need to look at your research records for quality assurance or data analysis. They include:

- Researchers involved with this study
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center (FHCRC) IRB. An IRB is a group that reviews the study to protect your rights as a research participant.
- Fred Hutchinson Cancer Research Center, University of Washington Medical Center, and Seattle Cancer Care Alliance.
- US National Institutes of Health, National Cancer Institute, Office for Human Research Protections, and other agencies as required

We will do our best to keep your personal information confidential, but we cannot guarantee total confidentiality. Your personal information may be given out if required by law. For example, work place 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 rare.

We will not use your 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.

Will you pay me to be in this study?

There is no payment for being in this study.

How much will this study cost me?

Under normal circumstances you would have physician appointments and undergo similar lab and scan procedures as you would on this study. This is known as standard of care and therefore, you and/or your insurance company will be billed for any standard of care procedure. While on study you will be responsible for meeting your insurance plan co-pay/deductible requirements.

The tests that are exclusively done for the research will not be billed to you or your insurance company. These research tests include:

- Research blood collection (if not done during standard blood draws) and supplies
- Optional research biopsy

You may incur additional medical care costs associated with the medical management of side effects experienced while you are receiving pembrolizumab and radiation.

What if I get sick or hurt in 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 your study doctor. 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.

The costs of the treatment may be billed to you or your health just like other medical costs, or it may be covered by the UW's discretionary Human Subjects Assistance Program (HSAP), depending on a number of factors. The researcher may request HSAP coverage by following established procedures. If you wish to request HSAP coverage yourself, contact the researcher or the UW Human Subjects Division at hsdinfo@uw.edu or 206-543-0098. You may also call collect to the UW Human Subjects Division at 206-221-5940 if you do not otherwise have access to a telephone. Ask the researcher if you would like information about the limits and conditions of the HSAP. The UW does not normally provide any other form of compensation for injury. However, the law may allow you to seek payment for injury-related expenses if they are caused by malpractice or the fault of the researchers. You do not waive any right to seek payment by signing this consent form. [If appropriate, also add these two sentences] We will bill your health insurance for treating problems that result from your [insert name of disease or underlying condition] or from standard clinical care. If you have no health insurance or your insurance refuses to pay, we will bill you.

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

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

Your tissue samples might help researchers develop new products. This research could be done by for-profit companies. There is no plan to share with you any revenue generated from products developed using your tissue samples.

During this study, if the researchers learn new information that may be important to your general health or to you disease or condition, they will not share that information with you.

In addition, be aware that by agreeing to participate in this study, your information or tissue 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 tissue samples. If you do not want your information or tissue samples to be used for future research studies without your consent, you should not participate in this study.

Your tissue contains DNA. DNA makes 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 tissue samples [WILL OR MIGHT] include genetic testing called whole genome sequencing. Whole genome sequencing looks at all the known genes in your cells. This type of testing can provide useful information to researchers. It can also present risks if the test results became known to others, for example you could have problems with family members or insurance companies. There is also a risk that these test results could be combined with other genetic information to identify you.

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.

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 study visits and procedures.
- Takes study medications as directed.
- Prevent pregnancy.

- Tell us about side effects.

For More Information
If you have questions or concerns about this study, you may talk to your doctor anytime. Other people you can talk to are listed below.

If you have questions about:	Call:
This study (including complaints and requests for information)	206-598-4100 (Dr. Jing Zeng) 206-598-8239 (Anna Reyes, Research Coordinator)
If you get sick or hurt in this study the study)	206-598-4100 (Dr. Zeng)
Your rights as a research participant	206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center) 206-543-0098 (Human Subjects Division, University of Washington)
Your bills and health insurance coverage	206-606-6226 Seattle Cancer Care Alliance Financial Services 206-598-1950 UW Medical Center Financial Services

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

Tumor Biopsy (Optional)

The additional research biopsy part of this study is completely optional. You can still participate in the main part of this study without undergoing the research biopsy. It is important to understand that the results of this research biopsy are not designed specifically to help you. This is an opportunity for us to get more information regarding your type of cancer. Information from this research will not be included in your medical record. For those who give permission for the research tumor biopsy, the biopsy will be scheduled before you begin radiation treatment (between second and third dose of pembrolizumab) and 16-weeks after you end radiation treatment. There will be a separate procedure consent form that will outline the risks associated with the area planned for biopsy. You and your insurance company will not be charged for this research procedure.

Making Your Choice

Please think about your choice on whether to participate in this optional portion of the study. When you decide, please circle **YES** or **NO**. Please initial and date in the spaces provided.

Do you agree to donate your tumor tissue to study cancer?

Pre-Treatment **YES** **NO** Initials: _____ Date: _____

Post-Treatment **YES** **NO** Initials: _____ Date: _____

Subject's statement

This study has been explained to me. I volunteer to take part in this research. I have had a chance to ask questions. If I have questions later about the research, or if I have been harmed by participating in this study, I can contact one of the researchers listed on the first page of this consent form. If I have questions about my rights as a research subject, I can call the Human Subjects Division at (206) 543-0098 or call collect at (206) 221-5940. I give permission to the researchers to use my medical records as described in this consent form. I will receive a copy of this consent form.

Signature

_____ _____

Research Participant Signature Date

_____

Research Participant Printed Name

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/Interpreter Signature Date

_____

Witness/Interpreter Printed Name

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 Date

_____

Person Obtaining Consent Printed Name

Protocol: CCIRB 9940
Current version date: 4/30/18
Copies to: patient, patient's medical record, research record.