IRB Approved
Consent Release Date: 02/04/2021
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Fred Hutchinson Cancer Research Center
Seattle Cancer Center Alliance
University of Washington

Consent to take part in a research study:

ImmunoRad: Stratified Phase II Trial of Image Guided Hypofractionated Radiotherapy with concurrent Nelfinavir and Immunotherapy in Advanced Melanoma, Lung Cancer, and Renal Cell Carcinoma

Principal Investigator: Ramesh Rengan, MD PhD. University of Washington; Fred Hutchinson Cancer Research Center.

Emergency number (24 hours): 206-598-3300

Ask to speak to the resident on call

Your Study Doctor: _____ Phone Number: _____

We would like you to join this research study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. 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 explanation.

You are being invited to participate in a research study because you have metastatic melanoma or skin cancer, non-small cell lung cancer, or renal cell carcinoma that has spread to another part of your body and your cancer doctor has recommended treatment with an anti-PD1/PDL1 immunotherapy: Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), or Atezolizumab (Tecentriq®). Secondly, you have a tumor that can be benefited by radiation. We plan to enroll a maximum of 120 people at the University of Washington/Seattle Cancer Care Alliance.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

You do not have to be in this study. You are free to say yes or no, or to drop out after joining. There is no penalty or loss of benefits if you say no. Whatever you decide, your regular medical care will not change.

Why is this study being done?

Nelfinavir (brand name Viracept®) is a protease inhibitor and is approved in the United States and Canada for the treatment of HIV. Studies have suggested that protease inhibitors such as Nelfinavir may be effective against cancer. Nelfinavir appears to inhibit the regulation of cellular

processes vital for cancer and its spread. Nelfinavir has also been shown to have radiosensitizing properties, which causes radiation to be more effective.

Stereotactic body radiotherapy (SBRT) is a form of radiation treatment that uses a tightly focused radiation beam in order to deliver radiation to your tumor as accurately as possible. We are doing this study to evaluate whether the use of radiation with Nelfinavir given with PD1/PDL1 inhibitor immunotherapy that your doctor has recommended for you can improve the control of cancer and prevent further spread.

What will happen if I take part in this research study?

Before you begin the study

To make sure that you are not at increased risk for side effects and are eligible to receive treatment with SBRT+Nelfinavir +PD1/PDL1 inhibitor, your study doctor will need to evaluate your health.

These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor. These procedures include:

- Medical history and physical examination
- Urine or serum pregnancy test (for females of childbearing potential)
- A scan to evaluate your tumor. This may be CT, PET/CT, MRI or another type of scan.
- Laboratory tests for
  - Blood counts
  - Blood chemistry

For research purposes, about four tablespoons of blood will be drawn from one of your veins to conduct laboratory tests to make sure that you are able to participate and to provide additional information about how the drug may act in your body.

During the study

Once your study doctor ensures that you are not at increased risk for side effects and are eligible to receive the study treatment, you can begin the study therapy.

Upon entry into the study, you will begin taking Nelfinavir, 1250 mg (two 625 mg pills) taken twice a day. You will take this drug during the first 3 months of the study. We will tell you when you start and stop taking the drug. You will be asked to keep a drug diary to make sure you are taking the drug as well as keeping track of how you are feeling.

After one to two weeks of starting Nelfinavir, you will begin your PD1/PDL1 inhibitor infusions. This is medicine administered by intravenous (IV) infusion, meaning the drug is given by inserting a needle into a vein in your arm. A pump will be used to ensure the correct amount of medicine is given. This treatment will be given every two to three weeks with the treatment lasting from 30 minutes to 1 hour.

Radiation will be given after the 1st infusion and before the 3rd infusion of PD1/PDL1 inhibitor. You will receive three doses of Stereotactic Body Radiotherapy (SBRT) to a single tumor. Treatments can be delivered consecutively or several days apart.

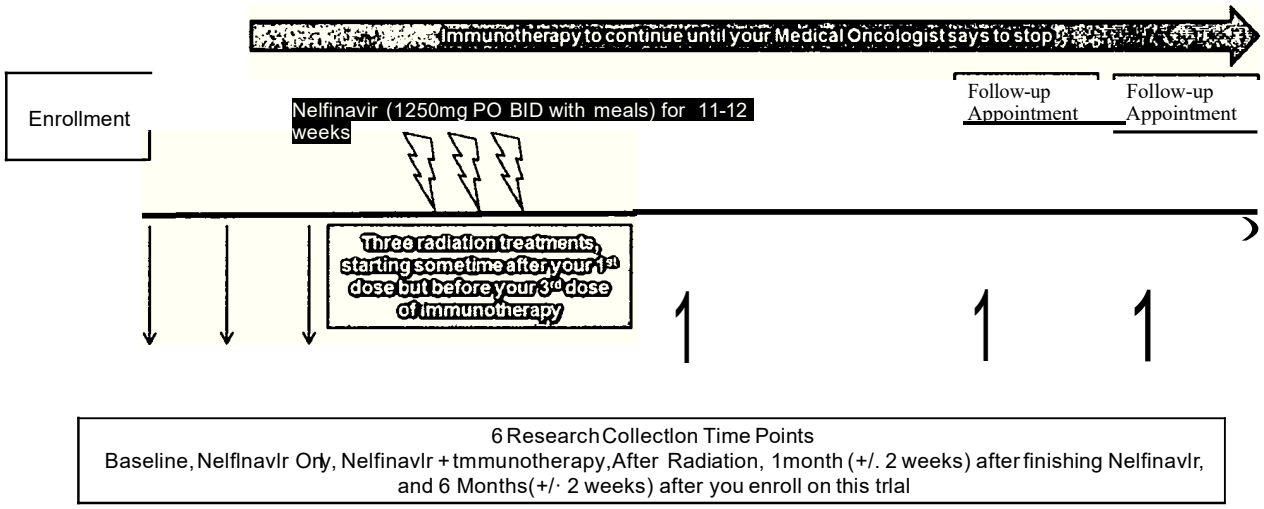
We will also be collecting your blood at specific time-points for markers of immune response. These are called correlative studies, and are specifically done for research purposes. This blood will be taken at the same time you have routine lab work, thus you will not have extra lab draws

6 Collection Timepoints:

- Baseline / Before you start treatment
- After 1-2 weeks on Nelfinavir only
- After 1st dose of PD1/PDL1 Immunotherapy
- After Radiation Treatment
- 1-month (+/-2 weeks) Follow-up Visit (after last dose of Nelfinavir)
- 6-months (+/- 2 weeks) Follow-up Visit (from when you start the trial)

We will collect 9 tubes of blood, or about 5-6 tablespoons each collection. This blood will be stored for processing when the study has been completed. These samples will not have your name on them and will only have a study number. You will not receive results of these tests.

Another way to find out what will happen to you during this research study is to read the chart below:



Follow-Up Appointments

1 month (+/- 2 weeks) after the last day you take nelfinavir

- Physical exam with vital signs
- Research Blood Draw
- CT Scans

6 months (+/- 2 weeks) after you start on the trial

- Physical exam with vital signs
- Research blood draw
- CT scan(s)

Follow-up (long term)

The study team would like to keep in contact with you for up to 2 years after you stop taking the study drug. This may be done by regularly scheduled office visits, or by a phone call.

How long will I be in the study?

If you choose to participate in this study, you will take the nelfinavir pills twice a day for 11-12 weeks, depending on how long you are taking it prior to initiating your PD1/PDL1 immunotherapy treatment. The follow-up appointment 6 months after you stop taking the nelfinavir will mark the end of the study period. However, you will continue your PD1/PDL1 immunotherapy treatment schedule until it is no longer helping you or you can no longer tolerate it. Based

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on discussions between you and your study doctor, you may discontinue for other reasons including your decision to stop being treated

Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first. 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. Your decision will not affect your future relationship with the University of Washington. If you leave the study, your test results and information cannot be removed from the study records.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen using these treatments together. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.
This form lists side effects of individual treatments.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks of PD1/PDL1 Immunotherapy
Anti-PD1/PDL 1 immunotherapy agents are known to cause several side effects listed below. This information has been summarized from cancer subjects in other clinical trials using PD1/PDL1 immunotherapy.

Likely side effects (20% or more of patients)

- Feeling tired
- Pain in muscles, bones, and joints
- Diarrhea
- Weakness
- Shortness of breath
- Decreased appetite
- Upper respiratory tract infection
- Rash
- Itchy skin
- Nausea
- Cough
- Constipation
- Back pain
- Fever

Less common (10% or more of patients)

- Irregular heartbeat
- Eye disorders
- Infusion-related reactions (while getting treatment)
- Numbing
- Dizziness
- Changes that show up in blood tests (white blood cells, metabolic, liver)
- Chills
- Weight gain
- Vomiting

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 (endocrine/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

Risks of Radiation/ Radiotherapy

In this study you will receive radiotherapy. Radiotherapy is a standard treatment for cancer. The total dose of radiation you will receive on this trial is 24 Gy (gray or "Gy" is the unit of radiation dose measured in terms of how your tissue absorbs energy). This dose will be divided into 3 days of treatment. The most common side effects of radiotherapy are listed below. The side effects of radiation are either early (which occur during radiation and usually go away after the completion of radiation) or late (which occur several weeks, months or years after the completion of radiation). You can further discuss these risks with your study doctor.

Likely side effects (20% or more of patients)

- Tiredness for no apparent reason, which is temporary
  The skin in the treatment area may become reddened and/or dry, and hair in the treatment area may fall out and may not grow back
- Scar tissue formation at the site of radiation that could affect the functioning of the lungs *(If you receive radiation to the Lung)*
- Tanning of the skin; leather-like feeling (If you receive radiation to a Subcutaneous Tumor)

Less Common but serious side effects (Less than 20% of patients)

- A common effect of this treatment in previous studies was eventual collapse of a portion of the treated lung. This collapse generally affects a limited portion of the lung, but the collapse appears to be permanent. Efforts will be made to reduce this risk and limit its effect. If collapse of a portion of the treated lung occurs, you will have shortness of breath at rest or during exercise, may need to receive oxygen, and/or may have chest wall pain. A few patients may need oxygen therapy permanently. A collapse of a portion of the lung may be life threatening.
- Fracturing *(If you receive radiation to the Bone)*
- Scar tissue formation at the site of radiation that could affect surrounding organ function *(If you receive radiation to the liver)*

Rare (Less than 2%) but serious side effects

- small or large bowel obstruction
- bladder spasms
- risk of damage to bones resulting in fracture
- development of second tumors

Risks of Nelfinavir (Viracept®)

There are many other medicines that can interact with nelfinavir. Tell your doctor about all medications you use. This includes prescription, over-the-counter, vitamin, and herbal products. Do not start a new medication without telling your doctor. The most reported side effect of nelfinavir is diarrhea, occurring in 20% or less of patients.

Rare but serious (2% or less of patients) side effects of Nelfinavir include:

- Hematologic changes that show up in blood tests including decreased lymphocytes, neutrophils, platelets and hemoglobin
- Metabolic changes including abnormal liver function tests and high blood sugar that show up in blood tests
- Stomach bleeding and problems with digestive system

Combined Therapy Risks

The effects of combining nelfinavir, radiation, and your PD1/PDL1 immunotherapy are not fully studied.

Likely side effects (20% or more of patients)

- With this particular combination, we have seen a higher percentage of patients who experienced immune-mediated hepatitis (liver inflammation) compared to Nelfinavir or PD1/PDL1 immunotherapy alone. Cases of immune-mediated hepatitis have responded to therapy.

In addition, we know that PD1/PDL1 immunotherapy will ramp up your body's ability to fight against the cancer, which may leave you feeling like you have the flu.

- Fever
- Chills
- Weakness
- Dizziness
- Nausea or Vomiting
- Muscle or Join Aches
- Fatigue
- Headache
- Trouble Breathing
- Low or High Blood Pressure
- Swelling and Weight Gain (fluid retention)
- Heart Palpitations
- Sinus Congestion
- Diarrhea
- Risk of infection

Reproductive risks

The study drugs and SBRT may cause serious harm to unborn children or children who are breast-feeding. These effects could also harm the mother. It is also possible that harmful side effects that are not yet known could happen to both the mother and unborn or breast-feeding child. If you are currently pregnant, it is important that you inform the investigator because you will not be able participate in the study. If you are able to become pregnant, you will have either a urine or serum pregnancy test before entry into the study.
You are asked to use a medically accepted method of birth control such as prescribed pill or intrauterine implant while you participate in the study. You should not become pregnant while you are taking part in this study. If you do become pregnant, you must tell the investigator and consult an obstetrician or maternal-fetal specialist.

If you are a man, you must use a means of birth control (such as condoms, abstinence, vasectomy) while you are taking part in this study because the effect of treatment on your sperm or upon the development of an unborn child is not known.

Other Risks
The risks of blood drawing and intravenous injection include bruising, bleeding and infection, and rarely, nerve damage. Problems and side effects that are not known to the doctors at this time could also occur and could include life-threatening events. You will be told of any changes in the way the study is conducted and of any new risks that might be found.

If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time. or even at different times. may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

What are the benefits?

We do not know if SBRT with concurrent Nelfinavir and PD1/PDL1 inhibitor immunotherapy will help treat your cancer. You may or may not receive any personal benefits from being in this study. Benefit to you may be in the form of improved survival. Others may benefit by knowledge gained from this study. We may be able to tell in the future, just who may benefit the most from the combination of radiation and PD1/PDL1 inhibitor immunotherapy for cancer.

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".

Your other choices may include the following:

- Getting treatment or care for your cancer without being in a study (according to the discretion of your treating oncologist). This could include standard therapies that may include radiation, chemotherapy, other targeted therapies or even immunotherapies that may be FDA approved.
- Taking part in another study.
- Receiving no treatment at this time.
- Getting comfort care (also called palliative care). This type of care addresses pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly.

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:

- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB and/or the University of Washington IRB. An IRB is a group of people who review the research study to protect your rights as a research participant.
- Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance.

- US National Institutes of Health, National Cancer Institute, Office for Human Research Protections, and other agencies as required.
- Food and Drug Administration (FDA)

These people are interested in study data, not your personal information. Personal information is information that can identify you. It may include your name, date of birth, social security number, phone number or other information.

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

Federal regulations and the policies of the University of Washington (UW Medicine) and the Seattle Cancer Care Alliance (SCCA) require that certain information about your participation in this research be made a part of your permanent medical record. If you do not already have a medical record at UW Medicine or SCCA, one will be created for you even if your only connection with them is as a research subject.

The information in your permanent medical record will include:

- Name of the study
- Name of the group or company that is paying for the research.
- The number the group or company assigned to this study.
- The name of the researcher.
- The name of the study coordinator.
- Contact phone number for the study.
- Contact email address for the study.
- Emergency phone number for the study.
- Expected start and end dates for your time in the study.
- Whether this study includes healthy volunteers.

Information about your participation in this study such as the title of the study and the names of the researchers involved in the study will be made a part of your permanent medical record. If you authorize others to see your medical record, they will find out about your participation in this study.

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.

IRB Approved
Consent Release Date: 02/04/2021

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.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for most of the costs of treating your cancer in this study, including the costs of radiation and immunotherapy PD1/PDL 1 inhibtors). This is because PD1/PDL1 immunotherapy and radiation are administered per standard of care. Study related procedures that are part of standard monitoring for patients will be billed to you and/or your insurance company. 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.

The research blood draws, Nelfinavir (Viracept®), and the optional biopsy will be paid for with funds from the study. Neither your insurance company nor you will be responsible for costs associated with the optional biopsy, nelfinavir (Viracept®), and the research blood draws.

Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. Please be aware that if your health insurance will not cover your treatment with radiation, you have the option to pay out of pocket. If neither your insurance company nor you agree to pay for this treatment, you will not be able to participate in this research study. However you will be able to receive the standard radiation treatment. Coverage and costs for standard radiation treatment may vary based on your insurance coverage.

You will not be paid for taking part in this study. The data collected during this study could be used to develop products. If these new products make money, there is no plan to share the money with you.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/learninqabout/payinqfor/how-insurance-companies-decide. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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.

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the study doctor about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

For all other medical problems or illness related to this research, immediately contact the study doctor, Dr. Ramesh Rengan. He 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.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. If you choose to tell your doctor why you are leaving the study, your reasons for leaving may be kept as part of the study record. You and the doctor could talk about the follow-up care (i.e. when you would be able to start a new treatment) and testing that would help the most.

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.
- Take study medications as directed and bring your completed pill diaries to your next visit
- Prevent pregnancy.
- Tell us about your current medications and let us know before you start any new ones.
- Tell us about side effects.

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)	206-598-4110 (Dr. Ramesh Rengan)
If you get sick or hurt in this study	206-598-4110 (Dr. Ramesh Rengan)
Your rights as a research participant	206-667-4867 (Karen Hansen, 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	The financial services department at the medical center where you will be treated.
Seattle Cancer Care Alliance University of Washington Medical Center	Patient Financial Services 206-606-6226 (phone) 1st Floor Seattle Cancer Care Alliance (in-person) 825 Eastlake Ave. E Seattle, WA 98109 Patient Financial Services 206-598-1950 (phone) UW Tower (in-person) 4333 Brooklyn Avenue NE Seattle, WA 98195

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

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. The surgeon would biopsy tissue from a site of disease that was not a target of radiation. 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 generate 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 sometime in the follow-up period, after your radiation and nelfinavir are complete. 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?

YES **NO** **Initials:**_____ **Date:**_____

Signature
If you have read this form (or had it read to you), asked any questions you might have, and agree to participate, please sign:

_____ _____
Research Participant Signature Date

_____
Research Participant 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

Current version date: 04/09/2019

Copies to: Patient, Study Chart, Patient's Medical Record