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| **Official Title:** | Nivolumab for Relapsed or Refractory Disease Post Chimeric Antigen Receptor T- cell Treatment in Patients with Hematologic Malignancies |
| **NCT Number**: | NCT04205409 |
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| **Date of the Document:** | October 4, 2021 |

University of Washington
Seattle Cancer Care Alliance
Fred Hutchinson Cancer Research Center

Consent to take part in a research study:

# RG1005491

**Nivolumab for Relapsed or Refractory Disease Post Chimeric Antigen Receptor T-cell Treatment in Patients with Hematologic Malignancies**

Principal Investigator: Andrew Cowan, MD
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Seattle, Washington 98109
206-606-7348

## UWMC Paging Operator
## Emergency number (24 hours): (206) 606-7348

Please ask for the operator to page the hematology/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 see how well Nivolumab works for patients with a hematologic malignancy that has come back or did not respond to CAR T therapy

People who agree to join the study will be asked to attend 2 visits every cycle over the course of their participation on the study. You will receive Nivolumab every cycle until you are no longer responding to treatment, you do not do well on the treatment or you and/or your doctor decide to stop treatment. Every cycle is 28 days. The study involves study visits with a doctor, blood draws, infusion visits and PET/CT scans.

We do not know if Nivolumab would help treat your cancer, and it could even make your condition/disease worse. Nivolumab could cause side effects such as fatigue, diarrhea, rash, fever and abdominal pain, 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 an 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 you want to help you decide whether to join the study. 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 a Hematologic Malignancy. This study will treat patients with different types of cancers including Non-Hodgkin Lymphoma (NHL), Chronic Lymphocyctic Leukemia (CLL), and Multiple Myeloma (MM). Up to 20 people will join this study.

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 the study. You are free to say "yes" or "no", or to 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 examine how well nivolumab works for people who have a hematologic malignancy that came back or did not respond to CAR-T therapy.

We are studying Nivolumab. Nivolumab is an FDA approved drug to treat advanced stage lung cancer, kidney cancer, liver cancer, Classical Hodkin Lymphoma, and other types of cancers. This drug is not FDA approved to treat NHL, CLL or MM after they have received CAR-T therapy.

In this study, we want to learn what effects, good or bad, that Nivolumab has on people with Hematologic Malignancies that did not respond, or their cancer came back after they received CAR-T cell treatment. If you join this study, we would give you Nivolumab and watch carefully for any side effects.

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

If you join this study, we would do these tests and procedures:

| Required Studies | Screening | Cycle 1 Day 1 | Cycle 1 Day 8 | Cycle 1 Day 15 | Cycle 1 Day 22 | Cycle 2 Day 1 | Cycle 2 Day 22 | Cycles 3-6 Day 1 | Cycle 7 + Day 1 | Post Therapy | Long-term Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Medical history | X | | | | | | | | | | |
| Clinic Visit | X | X | | | | X | | X | X | X | |
| Follow Up Visits | | | | | | | | | | | X |
| **Labs/Testing** | | | | | | | | | | | |
| Routine Laboratory Tests | X | X | X | X | X | X | | X | X | X | |
| Optional Research Blood Draw | X | X | X | X | X | X | | X | | | |
| Bone marrow studies (MM or CLL only) | X | | | | | | | X | | | |
| PET/CT Scans | X | | | | | | X | X | X | X | |
| Archival Tumor Biopsy | X | | | | | | | | | | |
| Urinalysis (MM only) | X | | | | | | | | | | |
| Pregnancy test (blood or urine) | X | | | | | | | | | | |
| **Drug Administration** | | | | | | | | | | | |
| Nivolumab Infusion | | X | | | | X | | X | X | | |

- **Medical history.** You will be asked questions about your medical history. This includes ongoing conditions you have and drugs you are taking.
- **Clinic Visit:** You will have clinic visits with a health care provider. We want to see how you are doing. Your visits will include a physical exam where we will assess your overall health status and measure your vital signs. This includes blood pressure, heart rate, temperature, and breathing rate. Your weight and height will also be recorded. You will also be asked how easily you perform daily activities. We will also ask you questions about your symptoms and side effects at each visit. We will also ask you about what other medications you may be taking.
- **Routine laboratory tests.** Blood samples will be taken for routine tests. About 2 – 3 teaspoons of blood will be taken, and your blood will be tested for levels for certain components to see if it is safe for you to receive treatment. A little over a teaspoon of blood may additionally be taken to perform tests which will give more information about your cancer, if clinically appropriate.
- **Optional Research Blood Draw**: We will request 1-2 teaspoons of blood that we will use for research tests. These results will not be reported in your medical record.
- **Optional Archival Tissue**: We will ask for a sample of archival tissue from a previous biopsy for future research purposes. Archival tissue is a piece of the tissue that was collected from a past biopsy you had. You will not need to have another biopsy for this. You may say 'yes' or 'no' to this at the end of this form.
- **Bone marrow testing (Multiple Myeloma and Chronic Lymphocytic Leukemia patients only)** Bone marrow aspiration and biopsy should be done to see if your cancer has spread to the bone marrow. For the bone marrow aspirate, a sample of bone marrow cells is taken by a needle inserted into a bone in your body. For biopsy, a small piece of bone is removed. These tests are done under local anesthesia.
- **Pregnancy test.** If you are a female who could become pregnant, you will have a pregnancy test. Either a blood or urine sample will be taken for this test.
- **Computed tomography (CT) scans.** CT is a medical x-ray imaging method. It provides 3-dimensional pictures of the body and organs by sections. CT scans of the chest, abdomen, and pelvis will be done. If it is clinically appropriate, a CT scan of the neck will be done.
- **Positron emission tomography (PET) scan.** If your doctor thinks this is clinically appropriate, PET will be done. PET is another imaging technique. It produces a 3-dimensional picture of processes going on at the cellular level in the body.
- **Urinanalysis (Multiple Myeloma patients only):** You may be asked to provide a urine sample for this study to test for your cancer.

**Screening**

- Medical History
- Clinic Visit
- Routine Lab Tests

- Optional Research Blood Draw
- Bone Marrow testing (if applicable)
- PET/CT Scans
- Urinanalysis (MM only)
- Pregnancy Test

**Cycle 1**

- Days 1
    - Clinic Visit
    - Routine Lab Tests
    - Optional Research Blood Draw
    - Nivolumab infusion
- Days 8, 15, 22
    - Routine Lab Tests
    - Optional Research Blood Draw

**Cycle 2**

- Day 1
    - Clinic Visit
    - Routine Lab Tests
    - Optional Research Blood Draw
    - Nivolumab infusion

- Day 22
    - Computed tomography (CT) scans
    - Positron emission tomography (PET) scan

**Cycles 3-6**

- Day 1
    - Clinic Visit
    - Routine Lab Tests
    - Optional Research Blood Draw
    - Nivolumab infusion
    - Computed tomography (CT) scans
    - Positron emission tomography (PET) scan

**Cycles 7 and beyond**

- Day 1
    - Clinic Visit
    - Routine Lab Tests
    - Nivolumab infusion
    - Computed tomography (CT) scans

**Post Therapy**

- Clinic Visit
- Routine Lab Tests
- Computed tomography (CT) scans
- Positron emission tomography (PET) scan

Long Term Follow Up

After you have finished taking Nivolumab, you would enter the **follow-up** part of the study. We would do these tests and procedures:

- Clinic visit

## How long would you stay in this study?

If you join this study, you would stay in this study until you no longer wish to participate or the study ends.

You would receive Nivolumab until you have side effects that require you to end the study, your disease gets worse or you decide on your own to not participate in the study anymore. After that, you would have a follow-up exam in the clinic about 100 days after you receive your last dose or before you start a new anti-cancer drug.

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.

**Long-term follow-up** means keeping track of someone's medical condition for a long time. If you join this study, we would contact you to see how you are doing. We would also ask your doctor to send a copy of your medical records. This information will help us learn about the long-term effects of Nivolumab.

You do not have to be in long-term follow-up. You could say "yes" or "no". Either way, you could still join this study. If you drop out of the study, you would be asked if we could call you until you do not want us to follow you anymore or until the study closes, whichever occurs first.

If you choose not to join long-term follow-up, you would not be contacted regularly, and we would not ask your doctor to send medical records, but we might still need to contact you for some other reason.

**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. Nivolumab could cause side effects we do not know about yet. We carefully watch everyone in the study for side effects.

If you join this study, we would tell you if we discover new side effects that could affect you.

Side effects may be mild or very serious. Medicines could be given to help lessen side effects. Many side effects go away soon after you stop taking Nivolumab. In some cases, side effects can last a long time or never go away.

<u>The most common side effects of Nivolumab are (≥5% of patients):</u>

- Fatigue
- Skin reactions: including rash, itching, hives, redness and dry skin
- Diarrhea
- Nausea
- Abdominal pain
- Decreased appetite
- Low red blood cells
- Fever
- Joint pain or stiffness

<u>Less common side effects of Nivolumab are (2-4% of patients):</u>

- Bowel inflammation
- Liver function blood test abnormalities
- Loss of color (pigment) from areas of skin
- Dry mouth
- Vomiting
- Weight loss
- Thyroid gland abnormalities
- Blood chemistry abnormalities, including low blood phosphate, magnesium and potassium levels
- High blood uric acid level
- Lung inflammation (pneumonitis – see details below)
- Cough
- Dizziness
- Headache
- Low white blood cells
- Chills
- Muscle soreness, weakness, stiffness, spasms or paralysis
- Pain in arms or legs
- Tingling, burning or numbness in hands and feet
- Shortness of breath
- Abnormal taste
- Flushing
- High or low blood pressure
- Allergic reaction during or between study drug infusions
- Increased sensitivity of skin to sunlight
- Constipation
- Difficulty swallowing
- Heartburn
- Low blood platelets (may increase risk of bleeding)

Rare but potentially serious side effects of Nivolumab are (<2% of patients):

- Low blood oxygen level
- Acute lung injury or failure
- Collection of fluid around the lungs
- Inflammation of the appendix
- Increase in inflammatory blood proteins (i.e. lipase)
- Adrenal gland abnormalities
- Pituitary gland abnormalities
- Thyroid gland abnormalities
- Changes in vision (including decreased or blurry vision), inflammation of the eye or bleeding into the eye
- Liver inflammation
- Acute kidney injury or failure
- Abnormal blood cell production
- Inflammation of the mouth and lining of the digestive tract
- Swelling of the face, arms or legs
- Inflammation of the pancreas
- Collection of fluid around the heart
- Increased blood sugar
- Dehydration
- Infections: including sepsis, lung infections and skin infections
- Decreased movement of the intestines
- Disorientation
- Swelling of the optic disc
- Inflammation of the optic nerve
- Inflammation or loss of the lining of the brain and spinal cord
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes and internal organ involvement (including liver, kidney and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]
- Myasthenia gravis, a nerve disease that may cause weakness of the eye, face, breathing and swallowing muscles.
    - One death in a patient who received Nivolumab combined with Ipilimumab was considered due to myasthenia gravis and severe infection (sepsis)
- Abnormal brain function due to brain inflammation (encephalitis), potentially life-threatening or fatal
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn, has occurred in patients who received Nivolumab treatment
- Muscle fiber released into the blood stream which could damage your

kidney (Rhabdomyolysis) and chronic muscle inflammation with muscle weakness (polymyositis) has been reported in one patient. Muscle tissue under the skin (fascia) becomes swollen and thick (eosinophilic fasciitis). This can affect your hands, arms, legs and feet and they can swell quickly.

- Red blood cells are destroyed and removed from the bloodstream before their normal lifespan is over (hemolytic anemia)
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Tumor bleeding (hemorrhage) or tumor flare
- Chest discomfort
- Disease of the heart muscle (cardiomyopathy)
- Heart palpitations
- Seizure
- Inflammation of the heart or its lining
- Gait disturbance and personality change

**Radiation risks**

Some of the tests that you will have in this research study will expose you to radiation. 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. For comparison, the estimated radiation dose from each of these tests is listed below. The risk to your health from this level of radiation exposure is too low to be detectable and may be nonexistent.

- 18 FDG-PET: 19 mSv
- CT-Chest: 7 mSv
- CT-Abdomen: 8 mSv
- CT-pelvis: 6 mSv
- CT-neck: 3 mSv

**Reproductive risks**

Chemotherapy and radiation treatments could cause sterility (unable to have children).

Taking Nivolumab 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 and could not donate eggs from the time this form is signed until at least 5 months after the last dose of Nivolumab. 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.

**Nivolumab risks for Multiple Myeloma Patients**

Previous clinical trials that have used PD-1/PD-L1 inhibitors such as Nivolumab in combination with other anti-cancer drugs for patients with Multiple Myeloma have shown an increased rate of side effects that may cause an increased risk of death compared to patients who did not receive a PD-1/PD-L1 inhibitor. These Multiple Myeloma patients receiving PD-1/PD-L1 inhibitors in combination with other anti-cancer drugs had worse overall survival compared to patients who do not receive them.

**Future stem cell transplantation risks**

There is an increased risk of death related to complications for patients who undergo an allogeneic stem cell transplantation after receiving Nivolumab. This should be taken into consideration for patients who are considering undergoing this in the future.

**What are the benefits?**

Although the study may not benefit you directly, we hope the information we learn will help people with hematologic malignancies in the future.

We do not know if this study would help you. We are testing Nivolumab to see its effects on people with hematologic malignancies. You might get better if you receive Nivolumab, but your condition could stay the same or even get worse. We hope the information from this study will help other people with hematologic malignancies 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.

Enrollment in this study may exclude you from 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.
- Bristol-Myers Squibb (financial supporter) and their agents.
- Institutional Review Boards (IRB), including the Fred Hutchinson Cancer Research Center IRB. An IRB is a group that reviews the study to protect the rights and welfare of research participants.
- Fred Hutchinson Cancer Research Center, University of Washington, and Seattle Cancer Care Alliance
- Office for Human Research Protections, Food and Drug Administration, and other regulatory agencies as required.

We will do our best to keep personal information 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 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.

**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 have some extra costs. Your insurance company might 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.
- Paying for the people who will administer Nivolumab
- Cost of people and equipment to give Nivolumab. There is no charge for Nivolumab itself.
- 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 the services done per standard of care in this study.

You would **not** be billed for:

- The cost of Nivolumab

**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. Cowan, MD at 206-606-7348. 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 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, we do not expect any test results that would affect your care, so we do not plan to return results to you.

**We invite you to donate tissue samples for other research.**

If you join this study, you would not have to donate archival tissue for future research. You would be free to say "yes" or "no." Regular medical care would not change if you say "no."

If you donate tissue, it would be stored in a secure location. If we want to use your tissue for other research or share it with other scientists for research, an ethics review committee (IRB) would review the request. The IRB would decide if we need to ask you for permission to do the research.

Your donated tissue would be used only for research. This research could be done by for-profit companies. Researchers would not report their results to you or your doctors. The research results would not be included in medical records. The results would not affect your medical care.

Research with tissue might help develop new products. If these products make money, there is no plan to share the money with the participants who donate the tissue.

If you donate tissue for research, you could withdraw the donation at any time by calling Dr. Cowan at 206-606-7348. You would have no penalty for withdrawing the donation, and regular medical care would not change. We could not return donated tissue, but we might be able to destroy the donated tissue. We could not destroy tissue if it is stored or shared without any label saying who donated it. In this case, it could still be used for research.

**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 of stopping Nivolumab. 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 the follow-up part of the 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.

**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.
- Prevent pregnancy.
- Tell us about side effects.

**For more information**

If you have questions or concerns about this study, you can 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) | 206-606-7348 (Dr. Andrew Cowan, MD) |
| If you get sick or hurt in this study | 206-606-7348 (Dr. Cowan, MD) |
| Your rights as a research participant | 206-667-5900 or email irodirector@fredhutch.org (Director of Institutional Review Office, Fred Hutchinson Cancer Research Center)<br><br>206-543-0098 (Human Subjects Division, University of Washington) |
| Your bills and health insurance coverage | 206-606-1377 (Patient Financial Services, Seattle Cancer Care Alliance) |

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# Emergency number (24 hours): (206) 606-7348

Please ask for the operator to page the hematology/oncology fellow on call

**Optional Research Blood and Archival Tissue**

Read each question and think about your choice. When you decide on each question, please circle **YES** or **NO**.

| |
|---|
| Do you agree to donate extra blood for future research testing?<br><br>(circle one)<br>**YES** **NO** |

| |
|---|
| Do you agree to donate your archival tissue for future research testing?<br><br>(circle one)<br>**YES** **NO** |

**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.

| Printed Name | Signature | Date |
|---|---|---|

If you served as an interpreter or impartial witness during the consent process, sign below to indicate you attest to the accuracy of the presentation and the participant's apparent understanding of and willingness to participate in the research.

Impartial 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 |
|---|---|---|

Copies to: Participant
Medical Records
Research File