Title: **An Open Label, Randomized Study of Neoadjuvant Nivolumab and Chemotherapy, With or Without Sub-ablative Stereotactic Body Radiation Therapy, for Resectable Stage IIA to IIIB Non-small Cell Lung Cancer**

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PKEY INFORMATION FOR AN OPEN LABEL, RANDOMIZED STUDY OF NEOADJUVANT NIVOLUMAB AND CHEMOTHERAPY, WITH OR WITHOUT SUB-ABLATIVE STEREOTACTIC BODY RADIATION THERAPY, FOR RESECTABLE STAGE IIA TO IIIB NON-SMALL CELL LUNG CANCER

We are asking you to be a subject in a research study looking at the addition of low dose stereotactic radiation therapy improves response to chemotherapy and immunotherapy prior to surgery for lung cancer. Low dose stereotactic body radiation therapy uses imaging and focused beams of radiation to target a tumor. It can be used before surgery to try to shrink a lung tumor or to turn on the immune system. This page is designed to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By performing this study, we hope to learn whether chemotherapy and immunotherapy combined with low dose SBRT leads to better outcomes and increases the cure rate of lung cancer patients. Your participation in this research will last about 5 years as we continue to monitor you, but the low dose stereotactic radiation therapy therapy is only given for the first few weeks prior to surgery. The purpose of this research is to gather information on the safety and effectiveness of the combination of nivolumab (a type of immunotherapy), chemotherapy, and low dose stereotactic radiation therapy together.

WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?
Studies have shown that for patients who need chemotherapy prior to lung cancer surgery, giving an immunotherapy drug called nivolumab with the chemotherapy leads to improved surgical outcomes and survival. Research also suggests that adding low dose SBRT to the immunotherapy may further stimulate the body's own immune system to fight and kill the cancer. This trial allows volunteers the opportunity to receive low dose SBRT in addition to the standard of care of chemotherapy and nivolumab (that you would have received if you are not participating in this research study).

WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?
Immunotherapy and chemotherapy drugs can cause side effects that could delay surgery or rarely even require other treatment. It is not yet known which patients are best treated with immunotherapy and chemotherapy before surgery. Radiation can also have side effects.

DO YOU HAVE TO TAKE PART IN THE STUDY?
If you decide to take part in the study, it should be because you really want to be in it. You will not lose any services, benefits or rights or access to care you would normally have if you choose not to.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Dr. Brendon Stiles. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is: 1250 Waters Place 7th floor, Bronx, NY 10461, Phone: 718-920-5732.

If you have any questions, suggestions or concerns about your rights as a subject in this research, contact staff in the Einstein Institutional Review Board between the business hours of 9am and 5pm EST, Monday-Friday at 718-430-2253 or irb@einsteinmed.edu

ALBERT EINSTEIN COLLEGE OF MEDICINE
MONTEFIORE MEDICAL CENTER

DOCUMENTATION OF INFORMED CONSENT AND HIPAA AUTHORIZATION

Introduction

You are being asked to participate in a research study called **an open label, randomized study of neoadjuvant nivolumab and chemotherapy, with or without sub-ablative stereotactic body radiation therapy, for resectable stage IIA to IIIB non-small cell lung cancer**. Your participation is voluntary -- it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits or your access to care.

The researcher in charge of this project is called the "Principal Investigator." His name is Dr. Brendon Stiles. You can reach Dr. Stiles at:
Office Address: 1250 Waters Place, 7th floor
City, State Zip: Bronx, New York 10461
Telephone #: 718-920-5732
For questions about the research study, or if you believe you have an injury, contact the Principal Investigator or the IRB.

The Institutional Review Board (IRB) of the Albert Einstein College of Medicine and Montefiore Medical Center has approved this research study. The IRB # is in the stamp in the upper right hand corner. If you have questions regarding your rights as a research subject you may contact the IRB office at 718-430-2253, by e-mail at irb@einsteinmed.edu, or by mail:

Einstein IRB
Albert Einstein College of Medicine
1300 Morris Park Ave., Belfer Bldg #1002
Bronx, New York 10461

Support for this research study is provided by **Bristol Myers Squibb and Department of Oncology at Montefiore Medical Center**

Disclosure of Financial Interests

Bristol Myers Squibb, is providing funds to Montefiore Medical Center on a per subject basis for conducting this research study.

Dr. Stiles is serving as a paid consultant on the Advisory Board for Bristol Myers Squibb.

Why is this study being done?

The goal of this study is to determine whether the addition of low dose radiation therapy given before surgery increases your tumor's response to chemotherapy and immunotherapy. We are also performing this study to better understand which patients' tumors will respond to preoperative therapy and to understand how radiation therapy changes the immune responses.

We also want to find out if adding low dose radiation therapy to nivolumab and chemotherapy is safe without causing too many side effects.

The U.S. Food and Drug Administration (FDA) has approved nivolumab for stage IV lung cancers and for patients with many other types of cancer. Radiation therapy is also an approved treatment for lung cancer.

Why am I being asked to participate?

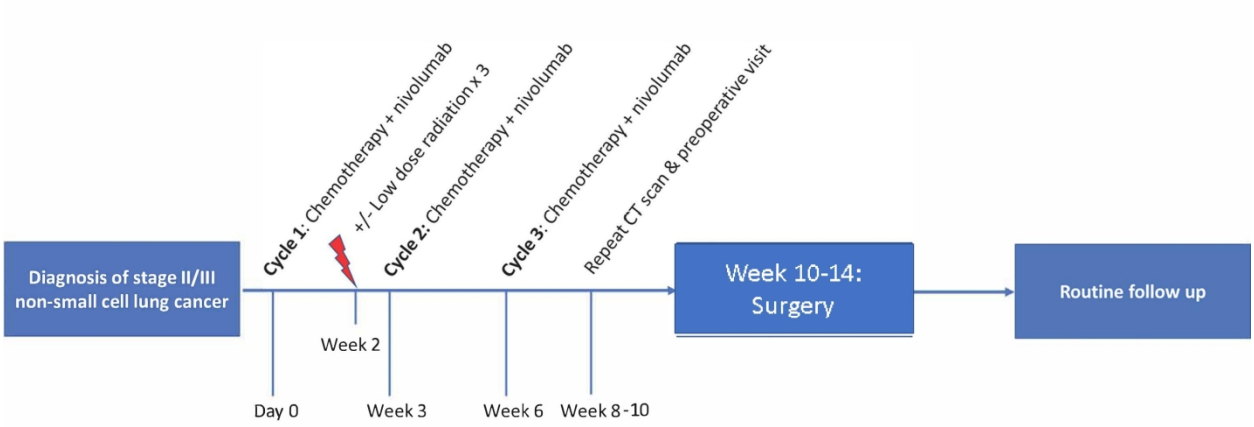
You are being asked to participate in this study because you have lung cancer that will require surgery, chemotherapy, and possibly immunotherapy. These drugs can either be given before or after surgery. Previous studies show that the drugs are better tolerated and more often completed in the before surgery. They can sometimes also be given for a shorter duration when given before as opposed to after surgery. There is some evidence that giving immunotherapy with chemotherapy prior to surgery may increase the chances of having a minimally invasive operation and of requiring removal of your whole lung. This may lead to better outcomes and quality of life.

How many people will take part in the research study?

You will be one of about **52** people who will be participating in this study.

How long will I take part in this research?

The study involves chemotherapy and immunotherapy given during the 6 weeks prior to surgery. This is now a standard approach approved by the FDA for patients with stage II and II lung cancer. Participation in this study will not add any extra time to this treatment. Following the 6 weeks of preoperative therapy, patients have surgery 4-8 weeks later. After recovery from surgery, patients will be followed according to standard of care with clinic visits and chest x-ray or CT scans at 2 weeks, 3 months, 6 months, 12 months, 18 months, 24 months and then yearly. The results of this research study will be recorded for approximately 5 years. During this time, we will ask you to make 15 follow-up study visits to Montefiore Medical Center, which is standard for patients following surgery for lung cancer.



What will happen if I participate in the study?

The screening visit will take about one hour. During this visit, we will do some tests and procedures to see if you eligible to be given the study drugs in this research study. Most of these are standard tests, meaning they would be done even if you were not in the study. The

study doctor will review the results of these tests and procedures. If you aren't eligible, the study doctor will tell you why. At this visit we will:

- Ask you about your medical history
- Give you a physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates)
- Draw blood samples (about one tablespoon) for routine tests and for HIV, Hepatitis A, B and C, and thyroid function. You will be required to sign a separate HIV testing consent form. If you test positive for HIV or Hepatitis B or C you will be told and information about counseling services will be provided. Your study doctor is required to report the positive results to the state or local health department.
- Test your urine for pregnancy, if you are a female able to become pregnant.
- Positron Emission Tomography (PET)/Computed tomography (CT) scans will be done to assess the size of your tumor.
- Electrocardiogram (ECG): This test will be performed to evaluate your heart's electrical activity. This test is not part of your standard care.
- You will have a consultation with a surgeon to confirm that your tumor can be removed by surgery
- We will also determine whether further biopsies are necessary. A sample of your lung biopsy that has been done will be used for the research. Depending upon the PET scan results, new biopsies may need to be obtained from lymph nodes or other sites in the body.
- Give you some questionnaires to fill out about your general health and well-being, quality of life, mental health, emotional health, mood, and memory

If you are eligible for the study, we will assign you by chance (like a coin toss) to the group of patients receiving low dose radiation therapy, chemotherapy, and nivolumab or the group receiving just chemotherapy and nivolumab. You and the study doctor cannot choose your study group. You will have equal (50-50) chance of being assigned to the low dose radiation group.

Patients who are assigned to the group receiving low dose radiation therapy, chemotherapy and nivolumab will receive 3 treatments of radiation therapy and 3 treatments of combined chemotherapy and nivolumab. This treatment course will last for 6 weeks prior to surgery.

Patients who are assigned to the group receiving chemotherapy and nivolumab will receive 3 treatments of combined chemotherapy and nivolumab. This treatment course will also last for 6 weeks prior to surgery.

Visit #2 will take about one hour. This visit we will:

- Check your vital signs
- Ask you about side effects or health problems since your last visit
- Draw a blood sample for routine testing(about two tablespoons of blood)
- Give you some questionnaires to fill out

Follow up visits after surgery:
Patients will be followed per routine care for all patients undergoing lung cancer resection. They will have a postoperative visit with a chest x-ray 2 weeks after discharge and again at 3 months. At both of these visits, blood will also be drawn. Patients will then have follow-up visits with CT scans of the chest at 6 months, 12 months, 18 months, 24 months, and then yearly until year 5. Blood may be drawn at these visits as well.

A description of this clinical trial will be available on 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.

As part of this study we will also review your medical records and put the information we collect in our research records.

Will there be testing for HIV?

Yes, HIV testing will be done during this research study. The following is important information about HIV, HIV testing, and your test results:

- HIV causes AIDS and can be spread through sexual activity, sharing needles, by pregnant women to their fetuses, and through breastfeeding infants.
- There is treatment for HIV that can help you stay healthy.
- People with HIV or AIDS should adopt practices to protect people in their lives from becoming infected with HIV.
- HIV testing is voluntary and can be done anonymously at a public testing center. However, testing is required if you would like to be in this research study.
- The law protects the confidentiality of HIV related test results.
- The law prohibits discrimination based on your HIV status and services are available to address any discrimination.
- If as a result of participation in this study you are INITIALLY diagnosed with HIV, the results must be reported to the New York State Department of Health for contact tracing purposes.
- If as a result of participation in this study you are diagnosed with HIV, you will be given HIV counseling or a referral for HIV counseling.

Genetic Testing

The tissue from the core biopsies and from your lung surgery will be stored for future studies. These studies may include genetic testing.
A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:
• Health insurance companies and group health plans may not request your genetic information that we get from this research.
• Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
• Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Genes are made up of DNA, and have the information needed to build and operate the human body. The information obtained from these tests will include genetic information about you. To protect your identity, we will give your specimen(s) a code number. Genetic factors are inherited and are passed down in families. Since genetic information is shared by family members, the information from these tests may apply to your family members, as well.

Genome Sequencing

Nearly every cell in the human body (from your skin to your blood to your saliva) contains a complete set of your DNA. This set of DNA, or operating instructions for everything from your hair color to your predisposition to disease, is known as your genome. Researchers will be mapping out your genome and then searching that genome for mutations (changes) or additions. These changes and additions can be inherited from your parents or can occur randomly.

However, the genetic testing in this study is not standard genetic testing or meant to evaluate your health. It is only for research, and you will not receive the results. Researchers must study samples from many people over many years before they know if the results have meaning. In the rare event that we discover something that may help you prevent or treat a serious illness, we may try to locate you and offer you the information.

Specimen Banking (Future Use and Storage)

We will store your specimens and information about you in a "biobank", which is a library of information and specimens (tissue and blood) from many studies. These specimens and information can be linked to you. In the future, researchers can apply for permission to use the specimens and information for new studies to prevent, diagnose or treat disease, including genetic research. If you agree to the future use, some of your de-identified genetic and health information (not linked to you) may be placed into one or more scientific databases. These may include databases maintained by the federal government. Your specimens and information may be kept for a long time, perhaps longer than 50 years. You may remove your consent for future research at any time by contacting the Principal Investigator named on the first page of the consent or the Institutional Review Board office at 718-430-2237. If you do, we will destroy remaining specimens and information but if these were already shared with other researchers, we cannot get them back.

You can choose not to participate in the biobank and still be part of the main study and this will not affect your treatment at this facility**.**

INITIAL ONE (1) OF THE FOLLOWING OPTIONS
_____ I consent to have my specimens and information about me used for future research studies.
_____ I do NOT consent to have my specimens and information about me used for future research studies. Information about me will be kept as long as required by regulations and institutional policy, but will not be used for future studies.

INITIAL YOUR CHOICE BELOW
_____ I consent to be contacted in the future to learn about:
_____ New research protocols that I may wish to join.
_____ General information about research findings.
_____ I do not want to be contacted at all.

Will I be paid for being in this research study?

You will not be offered compensation for participating in this study but you will receive $50 during each cycle of presurgical therapy (total 3 cycles) toward your study related expenses such as travel and parking. If you leave the study early, you will be reimbursed only for the cycles of therapy you completed. You will receive a Greenphire debit card at the first visit. The

card will be uploaded with the reimbursement amount within 2-3 days of each study visit. You can use the debit card like cash.

Tax law may require the payer (e.g. research institution or third party) to report the amount of payment you receive from that payer to the Internal Revenue Service (IRS) or other agencies, as applicable. Generally, this reporting would take place if you receive $600 or more from the payer in a calendar year. You would be responsible for paying the taxes on the payment you received from the study.
Some researchers may develop tests, treatments or products that are worth money. You will not receive payment of any kind for your specimens and information or for any tests, treatments, products or other things of value that may result from the research.

Will it cost me anything to participate in this study?

Taking part in this study will not involve added costs to you. The nivolumab will be given free of charge by the study sponsor (Bristol Myers Squibb). You and/or your insurance company will have to pay for any costs that are part of your regular medical care.

What will happen if I am injured because I took part in this study?

If you are injured as a result of this research, only immediate, essential, short-term medical treatment as determined by the participating hospital, will be available for the injury without charge to you personally.

- No monetary compensation will be offered.
- You are not waiving any of your legal rights by signing this informed consent document.
- If additional treatment is required as a result of a physical injury related to the research, necessary medical treatment will be provided to you and billed to your insurance company or to you as part of your medical expenses.

Immediately report any discomforts, problems or injuries you experience during the course of your participation in the study to Dr. Brendon Stiles at 718-920-5732.

What else do I have to do?

- You must tell the research study doctor about any past and present diseases or allergies you are aware of and about all medications you are taking including “over-the-counter” remedies and nutritional supplements or herbs.
- If you do not feel well at any time, call your doctor or the research study doctor immediately.
- ***Drugs may cause a reaction that, if not treated promptly, could be life-threatening. It is important that you report all symptoms, reactions and other complaints to the research study doctor.***
- If you think you have become pregnant, contact your research study doctor immediately.
- If any other doctor recommends that you take any medicine, please inform him/her that you are taking part in a research study. You should give the other doctor the research study doctor’s name and phone number.
- You may carry out all your normal daily activities.

Confidentiality

The researchers and study staff follow federal and state laws to protect your privacy. This part of the consent form tells you what information about you may be used and shared in the research described in this form. You do not have to sign this form but, if you do not, you may not participate in the research.

The health information that we may use or disclose for the research described in this form includes information from your entire medical record, such as your name, phone number, email, medical diagnoses, dates, test results, social security number, medical record numbers, etc.

Your information and research records will be kept confidential. Your study information will be kept as long as they are useful for the research described in this form.

The only people who can see your research records are:

- Researchers and other individuals who work with the researchers
- Organizations and institutions involved in this research, Bristol Myers Squibb
- Groups that review research such as Institutional Review Boards, the Office for Human Research Protections, the US Food and Drug Administration.

The purposes of these uses and disclosures are to (1) conduct the study and (2) make sure the study is being done correctly. The information covered under this form may no longer be protected by federal privacy laws (such as HIPAA) once disclosed, and those persons who receive your health information may share your information with others without your additional permission. All of these groups have been asked to keep your information confidential.

Medical information collected during the research, such as test results, may be entered into your Montefiore electronic medical record and will be available to clinicians and other staff at Montefiore who provide care to you.

To maintain the integrity of this research study, you generally will not have access to your research-related personal health information. If it is necessary for your care, your research-related health information will be provided to you or your physician.

Blood Draw

Rarely, the vein where we inserted the needle will become sore or red. Sometimes, a temporary harmless “black and blue” may develop. Very rarely, fainting may occur.

Radiation Risks

Common side effects:

- Difficulty, pain, or burning sensation when swallowing, which often is temporary
- Tiredness, which is temporary
- Tanning, redness of skin, and hair loss within the treatment area, which is temporary
- Skin in treatment area may remain permanently dry, and chest hair may not grow back
- Scarring in the lung, which sometimes causes collapse of the lung
- Fluid collection in the lung sac

Less common side effects:

- Cough and some difficulty in breathing (or shortness of breath) due to lung inflammation
- or scarring, which may be severe at times
- Irritation of the heart sac
- Irritation of the heart muscle
- Injury to the tube that carries food to your stomach
- Injury to the tube that carries oxygen to your lungs
- Bleeding from injury to the large blood vessels

Uncommon and rare side effects:

- Inflammation of the spinal cord
- A second cancer caused by the radiation you receive

Risks of Nivolumab

Nivolumab is FDA approved in this preoperative setting and may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. They may be life threatening or lead to death. You should tell your doctor or nurse right away about any possible side effects you experience.

Common side effects:

- Abdominal pain
- Abnormalities in various organ function blood lab test results that may indicate damage to organs such as liver, bone, pancreas, and kidneys
- Allergic reactions. The symptoms may include, but are not limited to fever, rash, pain, and swelling
- Chills
- Constipation
- Cough
- Decreased appetite
- Dizziness or vertigo (feeling off balance which can lead to dizziness)
- Dry mouth
- Dry skin
- Fever
- Headache
- Increased blood sugar, a lab test result or diabetes, a disease that results in too much sugar in the blood
- Inflammation of the colon which may cause diarrhea, blood in stools, severe belly pain
- Loss of color (pigment) from areas of skin
- Low platelet counts, which increases the risks of bruising, nose bleeds, and bleeding from the gums, and serious bleeding.
- Low red blood cell counts , which may make you feel weak, tired, short of breath, or result in heart failure
- Lung inflammation, which may cause difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, fever, low blood oxygen levels, or fatigue
- Nausea
- Pain in the muscles, bones, ligaments, tendons, and nerves
- Swelling, including face, arms, and legs

- Abnormal thyroid gland function (either increased or decreased), which may result in tremors, mood swings, difficulty sleeping, hypersensitivity to heat or cold, weakness, weight loss or weight gain, and fatigue
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting

Less common side effects:

- Diarrhea
- Feeling tired or lack of energy
- Skin itching
- Rashes

Uncommon side effects:

- A common viral / bacterial infection that affects the nose, throat, and airways (upper respiratory tract infection)
- A condition in which not enough oxygen passes from your lungs into your blood or when your lungs cannot properly remove carbon dioxide (respiratory failure)
- A skin disorder that's considered to be an allergic reaction to medicine or an infection. Symptoms may include symmetrical, red, raised skin areas that can appear all over the body, more noticeable on the fingers and toes. These patches often look like "targets" (dark circles with purple-grey centers)
- Blistering of the skin or mouth
- Decreased secretion of hormones produced by adrenal glands, which may cause weakness, diarrhea, nausea, vomiting, loss of appetite, and low blood pressure
- Inflammation of the eyes, which may cause visual disturbances, double vision, blurred vision.
- Inflammation of the kidneys may cause blood in urine, reduced frequency of urination
- Inflammation of the lining of bronchial tubes, which carry air to and from the lungs which may cause cough, production of mucus, shortness of breath, fever.
- Inflammation of the liver, which may cause abdominal pain, swelling and loss of appetite
- Inflammation of the muscles, which may result in pain throughout the body
- Inflammation of the pancreas, which may cause abdominal pain
- Inflammation of the pituitary gland – which may cause excessive thirst and urination, weight loss, and loss of libido
- Inflammation of the stomach, which may cause abdominal pain and loss of appetite.
- Inflammation of the thyroid gland which may cause pain, difficulty swallowing, hoarseness
- Kidney function failure, kidney disease which may cause decrease in the amount of urine, blood in urine, ankle swelling.
- Low blood pressure
- Low white blood cell counts, which increases the risk of certain serious infections
- Trouble falling and/or staying asleep (insomnia)
-

Rare side effects:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing
- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause blurred vision, ringing in the ears, changes in hair or hair loss

- Swelling of the bowels

Nivolumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

The following events have been identified during post-approval use of nivolumab. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

- A condition that occurs when donor bone marrow or stem cells attack the recipient (graft-versus-host-disease)
- A disease that may affect several parts of the body, including the eyes, ears, nervous system, and skin. The symptoms may include eye swelling, pain and/or blurred vision; hearing loss, ringing in the ears; and /or loss of skin color (Vogt-Koyanagi-Harada (VKH) disease)
- Solid organ transplant rejection

Risks of chemotherapy: These risks are well understood and are described in the attached appendix.

Additional information on lung inflammation (pneumonitis): Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest X-rays and/or CT scans.

Please inform your study doctor or nurse AT ONCE if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;

- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest X-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Additional information on transplant risks: Complications, including fatal events, have occurred in patients who received allogeneic hematopoietic stem cell transplantation (HSCT) before or after nivolumab.

Complications, including rejection, have also been reported in patients who have received an organ or tissue transplant. Treatment with nivolumab may increase the risk of rejection of the organ or tissue transplant.

Biopsy Risks

- Bleeding
- Pain
- Collapsed lung with the need for treatment and hospitalization
- Infection

Risks to Women Who Are or May Become Pregnant

The effects of chemotherapy and radiation on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding or sharing breast milk

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a hysterectomy. All other female subjects must have a negative pregnancy test before starting the study drug.

Acceptable birth control methods for use in this study are:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)

- Intrauterine device (IUD)
- Abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, we will stop giving you nivolumab. The study doctor will ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Allergic Reaction to Study Drug
Any drug can cause an allergic reaction which could be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you are having trouble breathing, call 911 immediately.

Therapeutic Radiation Risks

You will be receiving additional radiation as part of the study treatment from Stereotactic Body Radiation Therapy (SBRT). The research is studying whether this is effective or not. We do not know what long term risks may be the result of this additional radiation.
it is important to know the risks involved with this treatment. Your study doctor will explain how this treatment is given and any risks or side effects associated with SBRT. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. s**Many** side effects go away shortly after the radiation therapy is stopped, but in some cases side effects can be serious or long lasting or permanent. You should tell your doctors immediately if you have any symptoms of chest pain, shortness of breath, cough, or fever, or others described below.
Commonly experienced side effects (affects between 1 in 10 and 1 in 100 patients) include fatigue, loss of appetite, skin redness and dryness, shortness of breath, cough, fever, difficulty swallowing (due to inflammation of the esophagus), and chest wall discomfort / pain. These side effects generally occur during and for a few weeks after SBRT treatment.

Inflammation of the lungs may also occur with SBRT treatment. In some cases this may require a course of steroid therapy.

Additionally, the part of the lung receiving radiation may eventually collapse. This generally affects a limited portion of the treated lung, but could be permanent. Efforts will be made to reduce this risk and limit its effect. If collapse occurs, you may have shortness of breath at rest or with exercise, or may require oxygen therapy.

Uncommon / rare but serious side effects can also occur including:

- Irritation of the lining around the heart, which can cause chest pain, shortness of breath, and irregular or rapid heartbeat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart; rarely, this can cause a heart attack, heart failure, and/or death.
- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Narrowing of the esophagus (tube to the stomach)
- Irritation of the large blood vessels surrounding the heart; rarely, this can cause bleeding (coughing up blood) and/or death.

- Lung scarring (fibrosis) requiring the use of oxygen

New Findings
If we learn any significant new findings during the study that might influence your decision to participate, we will contact you and explain them.

Unknown Risks
We have described all the risks we know. However, because this is research, there a possibility that you will have a reaction that we do not know about yet and is not expected.

Are there any risks to me?
A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of privacy means having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your privacy – see the Confidentiality section above for details.

Questionnaire
You may feel uncomfortable answering questions about your health. You can choose not to answer questions that make you feel uncomfortable.

Are there possible benefits to me?

There is no guarantee that you will benefit from being a subject in this study. While doctors hope that the combination of chemotherapy, immunotherapy, and low dose radiotherapy will be more useful against cancer compared to the usual treatment, there is no proof of this yet. The information from this study may help doctors learn more about the effectiveness of this approach as a treatment for cancer. This information could help future cancer patients.

What choices do I have other than participating in this study?

You can refuse to participate in the study. If you decide not to participate, the medical care providers at this facility will still give you all of the standard care (that you would have received if you were not participating in this study)and treatment that is appropriate for you. This would generally consist of chemotherapy alone followed by surgical resection of your tumor. For some patients who are not eligible for or refuse surgery, chemotherapy is often combined with full dose radiation for treatment.

Are there any consequences to me if I decide to stop participating in this study?

No. If you decide to take part, you are free to stop participating at any time without giving a reason. This will not affect your care and you will continue to be treated at this facility. However, some of the information may have already been entered into the study and that will not be removed. The researchers and the sponsor may continue to use and share the information they have already collected.

To revoke (take back) your consent and authorization, you must contact the Principal Investigator in writing at the address on page 1 of this form. However, you may first call or speak to the Principal Investigator and he will stop collecting new information about you. If you take back your consent and authorization, you will not be allowed to continue to participate in this research study.

Can the study end my participation early?

Your participation could end if the investigator, the study sponsor, the U.S. Food and Drug Administration, or the committee that oversees this study to safeguard subjects' rights stops the study earlier than expected.

CONSENT TO PARTICIPATE

I have read the consent form and I understand that it is up to me whether or not I participate. I know enough about the purpose, methods, risks and benefits of the research study to decide that I want to take part in it. I understand that I am not waiving any of my legal rights by signing this informed consent document. I will be given a signed copy of this consent form.

Printed name of participant	Signature of participant	Date
Printed name of the person conducting the consent process		Date

Appendix:
Chemotherapy Risks (Standard)

Carboplatin

Most common

- Low platelet counts , which increases the risks of bruising, nose bleeds, and bleeding from the gums.
- Low red blood cell counts which may make you feel weak ,tired, short of breath, or result in heart failure.
- Nausea
- Vomiting
- Abdominal pain
-
- Abnormalities in various organ function blood lab test results that may indicate damage to organs such as liver and kidneys
- General pain and increase in sensitivity
- Hearing disturbances
- Blood electrolyte disturbances
- Flu-like syndrome

Less common

- Low white blood cell counts which mayincrease the risk for infection.
- Diarrhea
- Constipation
- Sores, ulcers, or white patches in the mouth and throat
- Pain, burning, or tingling in the hands or feet
- Hair loss
-
-
- Loss in ability to taste food
-
- Sudden changes in vision, including color vision
- Shortness of breath with everyday activity or when lying flat
- Ringing in ears and difficulty hearing
- Allergic reaction (rash, itching, skin redness and swelling, shortness of breath, and low blood pressure)

Cisplatin

Most common

- Abnormalities in various organ function blood lab test results that may indicate damage to organs such as kidneys.
- Low white blood cell counts which may increase the risk for infection
- Low red blood cell counts which may make you feel weak ,tired, short of breath, or result in heart failure.
- Low platelet counts, which increases the risks of bruising, nose bleeds, and bleeding from the gums.
- Nausea

- Vomiting
- Loss of appetite
- Inflammation may occur in the area of the injection after administration,

Less common

- Cough or hoarseness accompanied by fever or chills
- Dizziness or faintness (during or shortly after a dose)
- Fast heartbeat (during or shortly after a dose)
- Fever or chills
- Lower back or side pain
- Painful or difficult urination
- Pinpoint red spots on skin
- Swelling of face (during or shortly after a dose)
- Unusual bleeding or bruising
- Wheezing (during or shortly after a dose)
- Joint pain
- Loss of balance
- Ringing in ears
- Swelling of feet or lower legs
- Trouble in hearing
- Unusual tiredness or weakness
- Convulsions (seizures)
- Loss of reflexes
- Loss of taste
- Numbness or tingling in fingers or toes
- Trouble in walking
- Agitation or confusion
- Blurred vision
- Change in ability to see colors (especially blue or yellow)
- Muscle cramps
- Sores, ulcers, or white patches in mouth and on lips

Pemetrexed

Most common

- Tiredness
- Nausea and vomiting
- Loss of appetite
- Skin Rash
- Anemia
- Low red blood cell counts which may make you feel weak ,tired, short of breath, or result in heart failure
- Diarrhea

Less common

- Low white blood cell counts which may increase the risk for infection Redness of sores in your mouth, throat, or lips
- Infection

- Numbness, tingling, or loss of sensation in the hands and feet
- liver toxicity which may cause yellowing of the skin, abdominal pain, dark colored urine.
- Swelling of hands, ankles, feet, or lower legs
- Hyperpigmentation (darker patches on skin)
- Infectious and non-infectious disorders of the skin

Paclitaxel

Most common

- Low white blood cell counts which may increase the risk for infectionLow red blood cell counts which may make you feel weak ,tired, short of breath, or result in heart failure
- Low platelet counts, which increases the risks of bruising, nose bleeds, and bleeding from the gums.
- Infections: if you have a fever (temperature above 100.4°F) or other sign of infection, tell your healthcare provider right away
- Numbness, tingling, or pain in the hands and feet
- Muscle and joint pain
- Nausea and vomiting
- Diarrhea
- Sores, ulcers, or white patches inside your mouth or on your lips
- Hair loss
- Hypersensitivity reaction including trouble breathing, sudden swelling of your face, lips, tongue, throat, or trouble swallowing; hives (raised bumps) or rash
- Abnormal ECG

Liver toxicity which may cause yellowing of the skin, abdominal pain, dark colored urine
Less common

- Slow heart rate
- Low blood pressure
- Swelling of your hands, face, or feet
- Bleeding events
- Irritation at the injection site

Tumor lysis syndrome (when a large number of tumor cells die within a short period of time and release their contents into the blood stream) has been identified during post-approval use of paclitaxel. Because reports are voluntary from a population of unknown size, an estimate of frequency cannot be made.

Docetaxel

Most common

- Infections
- Low white blood cell counts which may increase the risk for infection.
- Low red blood cell counts which may make you feel weak ,tired, short of breath, or result in heart failure
- Low platelet counts, which increases the risks of bruising, nose bleeds, and bleeding from the gums.
- Allergic reactions
- Changes in your sense of taste
- Shortness of breath

- Constipation
- Decreased appetite
- Changes in your fingernails or toenails
- Swelling of your hands, face, or feet
- Feeling weak or tired
- Joint and muscle pain
- Nausea and vomiting
- Diarrhea
- Mouth or lip sores
- Hair loss
- Redness of the eye
- Excess tearing
- Skin reactions at the site of docetaxel injection administration such as increased skin pigmentation, redness, tenderness, swelling, warmth or dryness of the skin, and tissue damage if docetaxel injection leaks out of the vein into the tissues.

Gemcitabine

Most common

- Flu-like symptoms of muscle pain, fever, headache, chills and fatigue
- Nausea, vomiting
- Rash
- Hair loss
- Infection, especially when white blood cell count is low which may increase the risk for infection
- Bruising, bleeding
- Anemia which may require a blood transfusion
- Muscle weakness
- Blood in urine
- Feeling of "pins and needles" in arms and legs
- Numbness and tingling of the arms and legs
- Tiredness
- Difficulty sleeping
- Swelling of arms, legs

Less common

- Swelling and redness of the area of radiation
- Blisters on the skin
- Diarrhea, constipation
- Sores in mouth which may cause difficulty swallowing
- Liver damage which may cause yellowing of eyes and skin, swelling
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of
- breath, swelling of the face or throat
- Scarring of the lungs
- Shortness of breath
- Fluid in the organs which may cause low blood pressure, shortness of breath, swelling of
- ankles
- Brain damage, Reversible Posterior Leukoencephalopathy Syndrome, which may cause

headache, seizure, blindness