NCI Protocol NRG-HN005
Phase II Consent Form

Study Title for Participants: Testing less intensive radiation therapy with chemotherapy or immunotherapy to treat selected low-risk patients with HPV-positive oropharyngeal cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: NRG-HN005, "A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early-Stage, p16-Positive, Non-Smoking Associated Oropharyngeal Cancer" (NCT # 03952585)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

We are asking you to take part in this research study because you have low-risk, Human Papillomavirus (HPV) positive oropharyngeal cancer.

This study has two parts called phase II and phase III. After reading this consent form, you will be asked if you want to agree to take part in the first part of the study, phase II.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

The first part of this study is being done to answer the following question:
Does a reduced dose of radiation along with chemotherapy or immunotherapy result in the same length of time without your cancer getting worse as the usual approach?

We are doing this study because we want to find out if this approach is the same as or worse than the usual approach for your type of cancer. The usual approach is defined as the care most people get for HPV positive oropharyngeal cancer.

If the study approach is the same as the usual approach, the study will advance to the second part, the phase III, and you may be asked to participate in the second part of the study. If you are asked to participate in the second part of the study, at that time you will be asked to sign a different consent form for the phase III.

What is the usual approach to my low risk, HPV positive oropharyngeal cancer?

The usual approach for patients who are not in a study is treatment with radiation therapy and chemotherapy. For patients who get the usual approach for this cancer, about 88 out of 100 are free of cancer after 5 years.

What are my choices if I decide not to take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated for cancer.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will either get the usual dose of radiation over 6 weeks plus cisplatin chemotherapy, reduced-dose radiation over 6 weeks plus cisplatin chemotherapy, or reduced-dose radiation over 5 weeks plus nivolumab immunotherapy.

After you finish your treatment, your doctor and study team will watch you for side effects and continue to evaluate your disease. They will check you every 3 months for 2 years after treatment. Then they will check you every 6 months for 3 years. After that, they will check you every year for your lifetime unless your doctor thinks you need to be seen sooner.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that study approach may not be as good as the usual approach in shrinking or stabilizing your cancer and preventing your cancer from coming back.

There is also a risk that you could have side effects from the study approach. These side effects may be worse and may be different than you would get with the usual approach for your cancer. Some of the most common side effects that the study doctors know about are:

- Tiredness
- Nausea, vomiting
- Sores in the mouth and throat which may be painful especially with swallowing

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that this study approach could be effective in shrinking or stabilizing your type of cancer. It is not possible to know now if the study approach will control your cancer for the same amount of time compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. This may mean slowly stopping the study drug so that there is not a sudden unsafe change or risk in your health. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NRG Oncology). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

This study has two parts. The purpose of the first part of this study is to compare the usual treatment of a standard-dose radiation given over 6 weeks with cisplatin chemotherapy to a reduced-dose radiation given over either 6 weeks with cisplatin or 5 weeks with the immunotherapy drug, nivolumab. A lower dose of radiation as compared to the usual radiation treatment dose could be as effective in lengthening the time without your cancer getting worse.

Nivolumab with reduced-dose radiation may or may not be as effective in lengthening the time without your cancer getting worse. But, it could also cause side effects, which are described in the risks section below.

Nivolumab is approved by the FDA for use in patients with recurrent or metastatic head and neck cancer whose disease has progressed after receiving chemotherapy, but it is not approved for use in your type of head and neck cancer.

This study will help the study doctors find out if this different approach is the same or worse than the usual approach. To decide if it is the same, the study doctors will be looking to see if the study approach maintains the length of time without cancer getting worse compared to the usual approach.

There will be about 399 people taking part in this study.

What are the study groups?

This study has 3 study groups.

- **Group 1**

  If you are in this group, you will get the usual radiation dose and chemotherapy (cisplatin) used to treat this type of cancer. You will receive 6 radiation treatments a week for 6 weeks. You will get cisplatin through a vein (also called IV or intravenous) every 3 weeks (on days 1 and 22 of radiation).

  There will be about 133 people in this group.

- **Group 2**

  If you are in this group, you will get the reduced radiation dose and chemotherapy (cisplatin). You will receive the reduced dose of 5 radiation treatments a week for 6 weeks. You will get cisplatin through a vein (also called IV or intravenous) every 3 weeks (on days 1 and 22 of radiation).

  There will be about 133 people in this group.

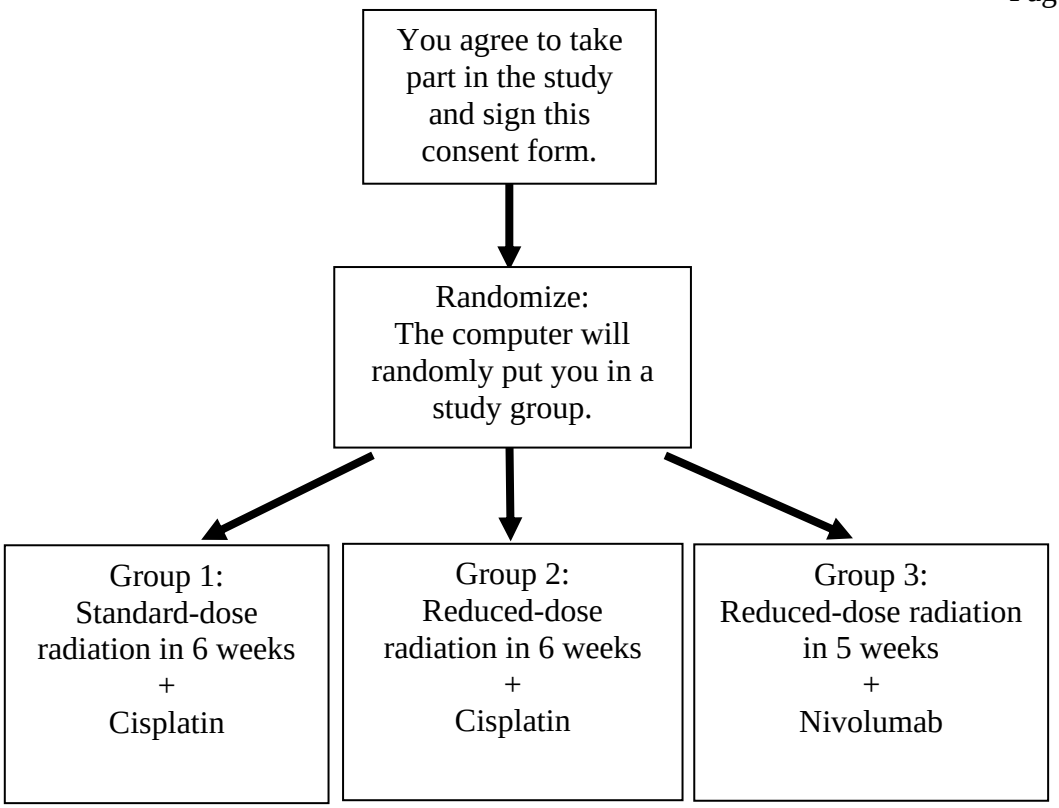
- **Group 3**

  If you are in this group, you will get the reduced radiation dose and the immunotherapy drug (nivolumab). You will receive the reduced dose of 6 radiation treatments a week for 5 weeks. You will get nivolumab through a vein (also called IV or intravenous) every 2 weeks for 6 cycles (each cycle lasts 14 days). You will start nivolumab 1 week before radiation and it will continue for a total of 12 weeks.

  There will be about 133 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization". It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1, Group 2, or Group 3.

Another way to find out what will happen to you during this study is to read the chart below. Start reading from the top to the bottom, following the lines and arrows.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health, but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Six blood tests to monitor thyroid function and organ function if you are receiving nivolumab (before each dose of nivolumab)

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only.

Quality of Life (QOL)

If you speak and understand English, you will be asked to fill out 4 forms with questions about your ability to swallow, your physical and emotional well-being. If you speak Spanish or French, you will be asked to fill out 3 forms because 1 form is not available in your language. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

You will be asked to fill out this form at 6 times:

- Before you start treatment
- At the end of radiation (at weeks 5 or 6)
- At 3, 6, 12, and 24 months from the end of radiation

Each form will take about 7 to 10 minutes to complete for a total of 25 to 30 minutes to complete the forms each time. The forms will ask about things like swallow, hearing, pain, and daily activity level. You don't have to answer any question that makes you feel uncomfortable.

You will have the option of completing the questionnaires by paper or by an electronic device (See *Section Below).

Symptoms Survey

You will be asked to answer questions about your symptoms and side effects, as well as your physical and emotional wellbeing. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

You will be asked to fill out this symptoms survey 6 times and each time it will take about 5 to 10 minutes to complete.

- Before starting treatment
- At week 2 of radiation
- At completion of radiation therapy (at weeks 5 or 6)
- At 3, 6, 12, and 24 months from the end of radiation

Since this is a research survey, the responses you provide will not be shared with your doctor. If you are having any severe symptoms, health issues or other concerns, please be sure to discuss these with your doctor or nurse right away.

At the end of the study, the answers you provided will be used to learn more about how cancer and cancer treatment affects patients, and it may help future patients.

If you speak and understand English and Spanish, you will have the option of completing the survey by paper or by an electronic device (See *Section Below). If you speak and understand French, but not English and Spanish, you will complete the survey by paper.

*<u>*Option for completing Quality of Life Questionnaires and Symptoms Survey with a personal electronic device*</u>

If you speak and understand English or Spanish, you will have the option of completing the questionnaires and survey by paper or by an electronic device. If you choose to complete the questionnaires and survey with an electronic device, you will enter your answers to the questionnaires and survey via a personal electronic device such as your smart phone or tablet. In some cases, a tablet may be provided to you at your health care institution. The use of your own electronic device on a cellular network may result in a nominal cost to your data plan. Regardless of the device you use, your answers and personal information will not be stored on the device. Your survey answers will be sent to the research database and will be kept private in the same way listed in the later section about who will see your medical records. Your e-mail address will only be used for this survey study and will not be used for mail or marketing purposes. NRG Oncology will not keep your e-mail address

If you need help using the survey application on your phone or tablet, ask for help at your study site. You don't have to answer any question that makes you feel uncomfortable. Someone may help you enter your answers in the device if you need.

All patients will complete the questionnaires and survey before treatment on paper. After that, you can choose to complete the remaining forms online or on paper. The choice is up to you. If you choose to complete questionnaires using an electronic device, see Appendix I of this document for more information.

Please circle your answers:

I choose to use the electronic software for completing the Quality of Life Questionnaires and Symptoms Survey. I agree to fill out the Quality of Life and Symptoms Survey forms electronically (after treatment has started).

YES NO

<u>Optional Sample Collection</u>
Optional blood draws and a sample of tumor tissue from your original biopsy will be stored in the Biobank and used for future studies. This will be discussed in the section on optional studies below.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the reduced-dose radiation therapy with cisplatin or nivolumab may not be as good as the standard-dose radiation therapy with cisplatin at shrinking or stabilizing your cancer and preventing your cancer from coming back.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The radiation, chemotherapy, and immunotherapy used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and after you complete study treatment. Patients who receive cisplatin must use birth control for 6 months after completion of study treatment. Female patients who receive nivolumab must use birth control for 5 months after completion of study treatment. Male patients who receive nivolumab must use birth control for 7 months after completion of study treatment.

Risks of Blood Draws

The most common risks related to drawing blood from your arm are brief pain and possibly a bruise. Rarely, an infection can occur.

Side Effect Risks

The radiation therapy, chemotherapy, and immunotherapy used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 and Group 2 – Possible side effects of cisplatin are listed in the tables below. This drug is part of the usual approach for treating this type of cancer:

Possible Side Effects of Cisplatin (Table Version Date: November 8, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require blood transfusions • Kidney damage which may cause swelling, may require dialysis • Hearing loss including ringing in the ears • Nausea, vomiting • Confusion • Numbness and tingling of the arms and legs

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cisplatin, from 4 to 20 may have:
• Diarrhea • Change in taste • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Hair loss

RARE, AND SERIOUS In 100 people receiving Cisplatin, 3 or fewer may have:
• Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness • Seizure • A new cancer resulting from treatment of a prior cancer

Study Group 3 – Possible side effects of nivolumab are listed in the tables below. This drug is part of the usual approach for treating this type of cancer:

Risk Profile for BMS-936558 (Nivolumab, MDX-1106) (CAEPR Version 2.3, June 18, 2018)

Special precautions Side effects of BMS-936558 (nivolumab, MDX-1106) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 (nivolumab, MDX-1106) is used in combination with ipilimumab. **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving BMS-936558 (nivolumab, MDX-1106), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving BMS-936558 (nivolumab, MDX-1106), from 4 to 20 may have:
• Anemia which may require blood transfusion • Swelling and redness of the eye • Pain • Diarrhea, nausea • Dry mouth • Fever • Swelling and redness at the site of the medication injection • Bruising, bleeding • Pain or swelling of the joints • Loss of appetite • Reaction during or following a drug infusion which may cause fever, chills, rash

BMS-936558 (nivolumab, MDX-1106) 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:

- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Skin: itching; rash, blisters including inside the mouth; loss of skin pigment
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving BMS-936558 (nivolumab, MDX-1106), 3 or fewer may have:

- Dry eyes
- Sores in the mouth which may cause difficulty swallowing

BMS-936558 (nivolumab, MDX-1106) 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, seizure, 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
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.

Additional Drug Risks

The study drug could interact with other drugs. Your study doctor will give you a clinical trial wallet card. Share this information with your health care providers and pharmacists.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

Possible Side Effects of Radiation Therapy

Study Group 1, Group 2, and Group 3 – Possible side effects of head and neck radiation are listed in the tables below. This is part of the usual approach for treating this type of cancer:

Possible Side Effects of Head and Neck Radiation

COMMON, SOME MAY BE SERIOUS In 100 people receiving head and neck radiation, more than 20 and up to 100 may have:
• Sores in the mouth and throat which may be painful especially with swallowing • Dry mouth, changes in taste, reduced sense of smell—may be permanent • Thick saliva • Hoarseness • Skin changes that may be permanent, swelling and redness of the skin in the area of radiation • Pain or pressure in the ear

COMMON, SOME MAY BE SERIOUS In 100 people receiving head and neck radiation, more than 20 and up to 100 may have:
• Tiredness • Weight loss • Permanent hair loss in the area of radiation (face, chin, neck) • Cavities, tooth decay; loss of teeth; tooth sensitivity

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving head and neck radiation, from 4 to 20 may have:
• Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine • Damage to the nerves of the shoulder and arm which may cause decreased movement and feeling • Ear infection • Hearing loss • Difficulty swallowing which may require a long term or permanent feeding tube

RARE, AND SERIOUS In 100 people receiving head and neck radiation, 3 or fewer may have:
• Breathing and swallowing problems that may require a surgical procedure to create an opening through the neck into the windpipe • Damage to the nerves in the head and neck that control sensation, expression, or other motor functions • Damage to the jawbone which may cause jaw pain and loosening of teeth • Damage to the voice box or nerves to the voice box which may cause hoarseness, shortness of breath, inability to speak • Damage to the skin, soft tissues, or other parts of the head and neck that may require a major operation to correct and, rarely, can be life threatening • Damage to the spinal cord which may cause permanent weakness

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study

- if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study.
For men: Do not father a baby while taking part in this study.
For both women and men receiving cisplatin: Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 6 months after your last dose of cisplatin.
For both women and men receiving nivolumab: Tell your study doctor right away if you think that you become pregnant during the study or within 5 months or your partner has become pregnant during the study or within 7 months after your last dose of nivolumab.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects. If you are receiving nivolumab, the extra blood tests to monitor thyroid and organ function will be billed to your health care plan/insurance provider.
- the costs of cisplatin drug and administration.
- the costs of getting nivolumab ready and giving it to you.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study.

You or your insurance provider will not have to pay for the nivolumab while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. Contact information for your study doctor is listed on the consent cover page. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

No funds have been set aside to compensate you in the event of injury.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- Montana Cancer Consortium
- NRG Oncology and any company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.

- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research, including the Imaging and Radiation Oncology Core (IROC).

In addition to storing data in the study database, data from studies that are publicly funded may also be shared broadly for future research with protections for your privacy. The goal of this data sharing is to make more research possible that may improve people's health. Your study records may be stored and shared for future use in public databases. However, your name and other personal information will not be used.

Some types of future research may include looking at your information and information from other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

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.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact information for your study doctor is listed on the consent cover page.

For questions about your rights while in this study, call the Operations Office of the National Cancer Institute (NCI) Central Institutional Review Board (CIRB) at 888-657-3711.

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading this optional study hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in this optional study is your choice. You can still take part in the main study even if you say "no" to this study. There is no penalty for saying "no." You and your insurance company will not be billed for this optional study. If you sign up for, but cannot complete this optional study for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for the following study.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, a sample of tissue from your previous biopsy and your blood will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by NRG Oncology and is supported by the NCI. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and

data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your tissue or blood samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes. If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced. This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About 2 tablespoons of blood will be collected from your vein:
    - Before you begin the study.
    - During radiation treatment.
    - After completion of all treatment.
2. A sample from the tissue that was collected at the time of your biopsy will be sent to the biobank.
3. Your sample will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
4. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
5. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.
- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?
You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?
There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?
If you decide you no longer want your samples to be used, you can call the study doctor, who will let the biobank know. Contact information for your study doctor is listed on the consent

cover page. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?
If you have questions about the use of your samples for research, contact the study doctor. Contact information for your study doctor is listed on the consent cover page.

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for unknown future studies:
I agree that my samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant Signature: _____

Date: _____

Signature of Person Obtaining Consent: _____

Date: _____

Time of consent: _____ (AM) (PM)
(Required for initial consent only)

Appendix I: Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App

If you are using your personal device, and you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the app available. Ensure that the correct version of the ePRO app is downloaded by the patient.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud app.
2. Tap the *App Store* icon.
3. Search for the appropriate Medidata Patient Cloud ePRO application and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud app
2. Tap the *Play Store* icon.
3. Search for the appropriate Medidata Patient Cloud ePRO application and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

APPENDIX II: PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #:
Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov