For Protocol Consent Amendment 1 to: **NRG-HN007,** An Open-Label, Phase III Study of Platinum-Gemcitabine With or Without Nivolumab in the First-Line Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma

NCI/Local Protocol #: NRG-HN007

NCI Protocol Version Date: February 16, 2021

Section	**Change**
Global	• The protocol version date was updated in the document header. • Formatting was corrected as needed.
What exams, tests, and procedures are involved in this study?	The following paragraph was removed as it was a duplicate: *"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."*

What risks can I expect from taking part in this study?	The risk profile for nivolumab was updated to reflect the revised CAEPR as follows:
	• Added New Risk:
	  • Rare: 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
	• Provided Further Clarification:
	  • 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 is now reported as 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 urination; dizziness or fainting.
	  • A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss is now reported as 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 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) is now reported as 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) The risk profiles for cisplatin and carboplatin were updated per the current risk profiles on the CTEP website, which are consistent with the current package inserts.
Optional sample collections for known laboratory studies and/or storage for possible future studies?	The third bullet under “Known future studies” was updated to clarify ctDNA collection for Asia sites.

Research Study Informed Consent Document

NCI Protocol NRG-HN007

Study Title for Participants: Testing the addition of an anti-cancer immune therapy drug (nivolumab) to the usual chemotherapy treatment (cisplatin or carboplatin with gemcitabine) for recurrent or metastatic nasopharyngeal cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: NRG-HN007, "An Open Label, Phase III Study of Platinum-Gemcitabine With or Without Nivolumab in the First-Line Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma"
(NCT #04458909)

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 nasopharyngeal carcinoma (NPC) that has recurred or spread outside of your nasopharynx.

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?

This study is being done to answer the following question:

Will adding the immune therapy drug nivolumab to the standard chemotherapy extend your life?

We are doing this study because we want to find out if this approach is the same or better than the usual approach for your type of cancer. The usual approach is defined as care most people get for NPC that has come back or spread.

What is the usual approach to my recurrent or metastatic NPC?

The usual approach for patients who are not in a study is treatment with chemotherapy, such as the combination of cisplatin (or carboplatin if you cannot get cisplatin) and gemcitabine. You may get carboplatin if you have kidney problems, hearing loss, or other medical conditions that make it unsafe to give you cisplatin. For patients who get the usual approach for this cancer, about 56 out of 100 are alive after 2 years. For some patients with recurrence of NPC at locations limited to certain parts of their head and neck areas, the use of surgery or a second course of radiotherapy may be used.

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 cisplatin (or carboplatin if you cannot get cisplatin) and gemcitabine chemotherapy for up to 18 weeks;

OR

You will get cisplatin (or carboplatin), gemcitabine, and nivolumab for up to 18 weeks, followed by nivolumab alone for up to 2 years.

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 4 months after treatment for 2 years, then every 6 months for 3 years, then once 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 the study approach may not be as good as the usual approach for your recurrent or metastatic NPC at improving how long you live.

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 nivolumab is effective in shrinking your type of cancer. It is not possible to know now if the study approach will extend your life compared to the usual approach with your recurrent or metastatic NPC. 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. 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?

The purpose of this study is to compare the usual chemotherapy, cisplatin (or carboplatin) and gemcitabine alone to the usual chemotherapy plus an immune therapy drug, nivolumab. The addition of nivolumab to the usual treatment could help to shrink your tumor. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the study approach increases the average life span of patients by 6 months or more compared to the usual approach.

This immunotherapy drug, nivolumab, is already approved by the FDA for use in some head and neck cancers (but not the type you have). But, most of the time it is not used until chemotherapy or targeted therapy stops working. There will be about 316 people taking part in this study.

What are the study groups?

This study has 2 study groups.

- **Group 1**

  If you are in this group, you will get the immune therapy study drug called nivolumab plus the usual chemotherapy drugs used to treat this type of cancer: cisplatin (or carboplatin) and gemcitabine.

  You will get cisplatin (or carboplatin) through a vein (also called IV or intravenous), on the day 1 of each cycle. You will get gemcitabine through a vein on day 1 and 8 of each cycle. You will receive 6 cycles and each cycle is 21 days.

  You will also get nivolumab through a vein on day 1 of each cycle. You may receive nivolumab for up to 2 years.

  There will be about 158 people in this group.

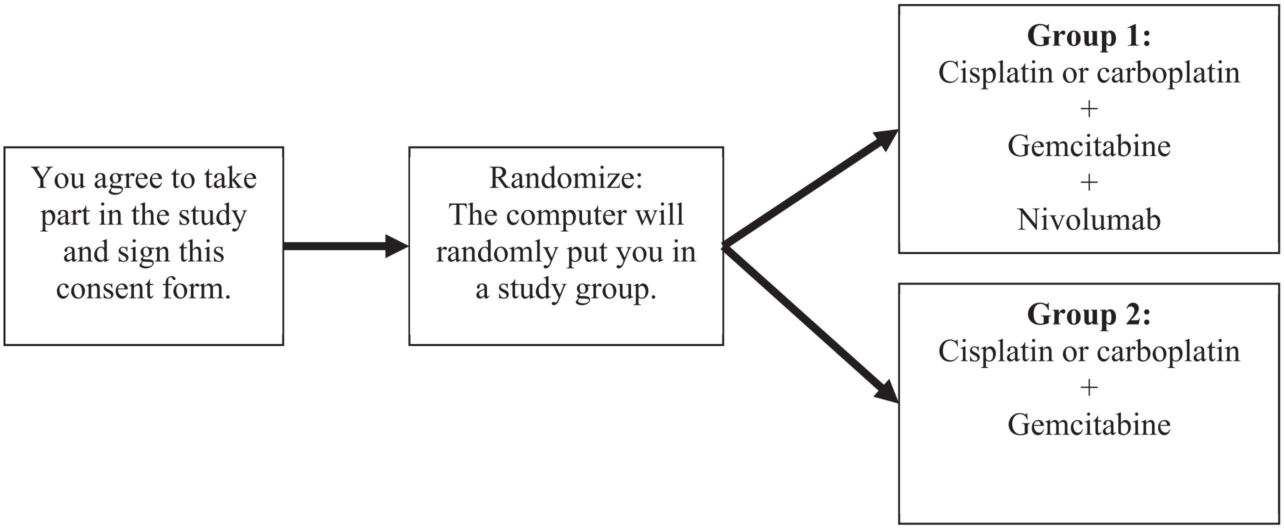
- **Group 2**

  If you are in this group, you will get the usual chemotherapy drugs used to treat this type of cancer: cisplatin (or carboplatin) and gemcitabine. You will get cisplatin (or carboplatin) through a vein (also called IV or intravenous), on day 1 of each cycle. You will get gemcitabine through a vein on day 1 and 8 of each cycle. You will receive 6 cycles and each cycle is 21 days.

  There will be about 158 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 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



What exams, tests, and procedures are involved in this study? (16-FEB-2021)

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.

- 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, Spanish, French (Canada), Chinese (traditional or Mandarin), or Korean, you will be asked to fill out 2 forms with questions about your ability to swallow and your physical and emotional well-being.

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 the forms at 4 times:

- Before you start treatment
- At week 18
- At year 1
- At year 2

Each form will take about 5 to 10 minutes to complete for a total of 10 to 20 minutes to complete the forms each time. The forms will ask about things like swallowing, hearing, pain, and daily activity level. You don’t have to answer any question that makes you feel uncomfortable.

If you speak and understand English or Spanish, you will have the option of completing the questionnaires by paper or by an electronic device (See *Section Below). If you speak and understand French (Canada), Chinese (simplified or traditional), or Korean, but not English or Spanish, you will complete the forms by paper.

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 4 times and each time it will take about 5 to 10 minutes to complete. All questionnaires will be completed:

- Before you start treatment
- At week 18
- At year 1
- At year 2

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 or 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 (Canada), Chinese (simplified or traditional), or Korean, but not English or Spanish, you will complete the survey by paper.

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

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 on paper before treatment. 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

Optional Sample Collection

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? (16-FEB-2021)

General Risks

If you choose to take part in this study, there is a risk that the study approach may not be as good as the usual approach at extending your life for your cancer.

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 chemotherapy and immune therapy drugs 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. Female patients who receive gemcitabine must use birth control for 6 months after completion of study treatment. Male patients who receive gemcitabine must use birth control for 3 months after completion of study treatment. All patients who receive cisplatin or carboplatin 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.

Side Effect Risks

The chemotherapy and immunotherapy drugs 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.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new 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, carboplatin, and gemcitabine are listed in tables below. These drugs are part of the usual approach for treating this type of cancer:

Possible Side Effects of Cisplatin (Table Version Date: January 25, 2021)**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, pain and tingling of the fingers, toes, arms and/or legs, loss of balance

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Cisplatin, from 4 to 20 may have:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Diarrhea
- Change in taste
- Swelling and redness at the site of the medication injection
- 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, including leukemia, resulting from treatment of a prior cancer

Possible Side Effects of Carboplatin (Table Version Date: October 15, 2020)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, 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
- Vomiting, nausea
- Pain
- Hair loss

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Carboplatin, from 4 to 20 may have:

- Diarrhea, Constipation, belly pain
- Changes in taste
- Numbness and tingling in fingers and toes
- Weakness

RARE, AND SERIOUS

In 100 people receiving Carboplatin, 3 or fewer may have:

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Visual loss
- Difficulty hearing

Possible Side Effects of Gemcitabine (Table Version Date: October 17, 2019)

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:

- Infection, especially when white blood cell count is low
- Bruising, bleeding
- Anemia which may require a blood transfusion
- Blood in urine
- Nausea, vomiting
- Flu-like symptoms of muscle pain, fever, headache, chills and fatigue
- Muscle weakness
- Feeling of "pins and needles" in arms and legs

COMMON, SOME MAY BE SERIOUS

In 100 people receiving Gemcitabine, more than 20 and up to 100 may have:

- Numbness and tingling of the arms and legs
- Swelling of arms, legs
- Tiredness
- Difficulty sleeping
- Rash
- Hair loss

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Gemcitabine, from 4 to 20 may have:

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

RARE, AND SERIOUS

In 100 people receiving Gemcitabine, 3 or fewer may have:

- Brain damage, Posterior Reversible Encephalopathy syndrome, which may cause headache, seizure, blindness
- Blockage of the airway which may cause cough
- Blood clot
- Severe blood Infection
- Anemia, kidney problems which may require dialysis

Study Group 1 – Possible side effects of nivolumab are listed in table below. This is the immunotherapy study drug.

Risk Profile for Nivolumab (CAEPR Version 2.4, December 2, 2020)

Special precautions

Side effects of Nivolumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when Nivolumab 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 Nivolumab, more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving Nivolumab, 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

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:

- 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 urination; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving Nivolumab, 3 or fewer may have:

- 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
- 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 Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

Additional Drug Risks

The study drug, nivolumab 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.

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.
- If you are receiving cisplatin, carboplatin, or gemcitabine, tell your study doctor right away if you think that you have become pregnant during the study or within 6 months after your last dose.
- If you are receiving nivolumab, tell your study doctor right away if you think that you have become pregnant during the study or within 5 months after your last dose.

For men:

- Do not father a baby while taking part in this study.
- If you are receiving cisplatin or carboplatin, tell your study doctor right away if you think that your partner has become pregnant during the study or within 6 months after your last dose.
- If you are receiving gemcitabine, tell your study doctor right away if you think that your partner has become pregnant during the study or within 3 months after your last dose.
- If you are receiving nivolumab, tell your study doctor right away if you think that your partner has become pregnant during the study or within 7 months after your last dose.

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 function and organ function will be billed to your health care plan/insurance provider.

- The costs of cisplatin, carboplatin, and gemcitabine 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. 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.

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:

- The study sponsor 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, including the Cancer Trials Support Unit (CTSU).
- 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, right now 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 the study doctor __________________ *(insert name of study doctor[s])* at __________________ *(insert telephone number).*

For questions about your rights while in this study, call the ____________ *(*insert name of organization or center*)* Institutional Review Board at ___________ *(*insert telephone number*).*

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 (16-FEB-2021)

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.

Known future studies

If you choose to take part in this optional study, researchers will collect a sample of tissue and blood for research on biomarkers called PD-L1, Epstein-Barr virus (EBV) DNA, and circulating tumor DNA (ctDNA).

Listed below are procedures that will be done for research purposes only.

- Blood sample for EBV DNA (a marker of your cancer) at 5 time points: before treatment, on day 8 and 15 during cycle 1 of chemotherapy, then on day 1 and 8 of cycle 2 of chemotherapy.
- A portion of your archival tumor will be obtained for biomarker research related to your cancer.
- *[For participating centers in Asia add the following*]: a sample of blood (ctDNA) will be obtained before treatment, for biomarker and circulating DNA research related to your cancer.
- The result of these tests will not be made available to you because they are for research only and at this stage we do not know whether these tests may help with your treatment.

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. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use. 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 and 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 1 to 4 teaspoons of blood will be collected from a vein in your arm. A sample from the tissue that was collected at the time of your biopsy will be sent to the biobank.
2. 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.
3. 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.
4. 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, ____________ *(*insert name of study doctor for main trial*),* at ____________ *(*insert telephone number of study doctor for main trial*)*, who will let the biobank know. 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, _______________ *(*insert name of study doctor for main trial*),* at ______________ *(*insert telephone number of study doctor for main trial*).*

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

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory (*study or studies*) described above.

YES NO

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's name (printed) **Date**

____ / ________________

Participant's signature **Date of signature**

____ / ________________

Signature of person(s) conducting the informed consent discussion **Date of signature**

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 ePRO 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 ePRO app is already on the device, or if you are using the study team's device, you can skip this section.

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 ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO 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 ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* 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 study team.

There are two possible ways to register. Your study team 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 ePRO 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 ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO 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 ePRO 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 ePRO 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.

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.