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September 6, 2023

NCI CIRB  
Adult CIRB – Late Phase Emphasis

Re: CIRB Approval Pending Modification of Amendment Review of Update #07 of Alliance A071702

Dear NCI CIRB,

Please see the attached revised protocol and consent submission for Alliance A071702: *“A phase II study of checkpoint blockade immunotherapy in patients with somatically hypermutated recurrent WHO grade 4 glioma.”* We would like to thank the CIRB Reviewers for the review of the protocol and informed consent documents dated 09/05/2023. The Study Team’s response to each stipulation are included in bold text, with hyperlinks to each section of the protocol and consent containing each revision.

Please let us know what further information we may provide.

Sincerely,

Priya Kumthekar, MD  
Executive Officer  
Alliance for Clinical Trials in Oncology

#	Section	Stipulations
1.	<a href="#">ICF</a>	<p>Page 10, under “Possible side effects of Nivolumab” under the heading “Rare and Serious” replace 4th bullet with the following:</p> <p>“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”</p> <p><b><u>PI Response:</u> In the 4<sup>th</sup> bullet of the 1<sup>st</sup> bulleted list under the “Rare, and Serious” heading, the phrase “flu-like symptoms” has been added.</b></p>
2.	<a href="#">ICF</a>	<p>Page 10, under “Possible side effects of Nivolumab” under the heading “Rare and Serious” 2nd set of bullets – replace 6th bullet, with the following:</p> <p>“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)”</p> <p><b><u>PI Response:</u> In the 6<sup>th</sup> bullet of the 2<sup>nd</sup> bulleted list under the “Rare, and Serious” heading, the word “seizure” has been added.</b></p>

## ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

### PROTOCOL UPDATE TO ALLIANCE A071702

#### A PHASE II STUDY OF CHECKPOINT BLOCKADE IMMUNOTHERAPY IN PATIENTS WITH SOMATICALLY HYPERMUTATED RECURRENT WHO GRADE 4 GLIOMA

<input checked="" type="checkbox"/> <b>Update:</b>  <input type="checkbox"/> Eligibility changes  <input type="checkbox"/> Therapy / Dose Modifications / Study Calendar changes  <input checked="" type="checkbox"/> Informed Consent changes  <input type="checkbox"/> Scientific / Statistical Considerations changes  <input type="checkbox"/> Data Submission / Forms changes  <input type="checkbox"/> Editorial / Administrative changes  <input checked="" type="checkbox"/> Other: Updated CAEPR and Risk List for Nivolumab	<input type="checkbox"/> <b>Status Change:</b>  <input type="checkbox"/> Activation  <input type="checkbox"/> Closure  <input type="checkbox"/> Suspension / temporary closure  <input type="checkbox"/> Reactivation
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*The changes included in this update to A071702 have been made in response to an RRA from Dr. Howard Streicher ([streicherh@ctep.nci.nih.gov](mailto:streicherh@ctep.nci.nih.gov)). This Action Letter is posted on the A071702 study page on the CTSU website. A revised CAEPR for nivolumab with the new risk has been added to the protocol. Therefore, the model consent form has been revised to incorporate the new risk, consistent with the NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.*

*No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.*

*Reconsent is required by Alliance for patients currently on active nivolumab treatment, and patients who have been consented but are not yet receiving protocol treatment. Please follow the CIRB policy regarding notifying patients of new information contained in this update. For this requested amendment, patient enrollment may continue before the CIRB reviews and approves the changes.*

#### **UPDATES TO THE PROTOCOL:**

##### **Section 9.4.2 (Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 748726))**

The CAEPR for nivolumab has been updated from Version 2.4 (December 2, 2020) to Version 2.5 (June 10, 2023). Changes from Version 2.4 to Version 2.5 include the following:

- Added New Risk:
  - Rare but Serious: Blood and lymphatic system disorders - Other (lymphatic dysfunction)

- Added footnote 3 in column: “Rare but Serious (<3%), under Eye Disorders,” “Eye disorders - Other (Vogt-Koyanagi-Harada)<sup>3</sup>.”
- Clarified Risk in column: “Rare but Serious (<3%), under Hepatobiliary Disorders,” “Hepatobiliary disorders - Other (Immune-~~mediated-related~~ hepatitis).”
- Clarified Risk in column: “Rare but Serious (<3%), under Immune System Disorders,” “Immune system disorders - Other (sarcoid granuloma, sarcoidosis)<sup>3</sup>.”
- Clarified Risk description in column: “Specific Protocol Exceptions to Expedited Reporting (SPEER), under Investigations,” “CD4 lymphocytes decreased (Gr 4).”
- Clarified Risk in column: “Rare but Serious (<3%), under Renal and Urinary Disorders,” “Renal and urinary disorders - Other (Immune-~~mediated-related~~ nephritis).”
- Clarified Risk in column: “Rare but Serious (<3%), under Respiratory, Thoracic and Mediastinal Disorders,” “Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))<sup>3</sup>.”
- Note: there were no changes in the footnotes from CAEPR Version 2.4 to Version 2.5.

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## **UPDATES TO THE CONSENT FORM:**

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

The tables under the “Possible Side Effects of Nivolumab” heading have been updated per CAEPR Version 2.5 with the following risk list changes:

- Added New Risk:
  - o Rare: Swelling of arms and legs which may cause a feeling of heaviness and tightness
- Clarified Risk: “Rare, and Serious,” “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.”
- Clarified Risk: “Rare, and Serious,” “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).”

**A replacement protocol and model consent forms have been issued.**

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**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**

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## **Research Study Informed Consent Document**

**Study Title for Participants:** A study testing the effect of immunotherapy for people with recurrent glioma with elevated mutational burden

**Official Study Title for Internet Search on <http://www.ClinicalTrials.gov>:** A Phase II Study of Checkpoint Blockade Immunotherapy in Patients with Somatically Hypermutated Recurrent WHO Grade 4 Glioma (NCT04145115)

### **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.

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

We are asking you to take part in this research study because you have a glioblastoma which has recurred (come back) or gotten bigger after your initial treatment.

#### **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: Can we lower the chance of your recurrent glioblastoma with elevated mutational burden from growing or spreading by adding immunotherapy drugs after the initial therapy failed? For this study, "high mutational burden" is defined as at least 10 mutations on the FoundationOne CDx test described in more detail below.

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your recurrent glioblastoma with elevated mutational burden. The usual approach is defined as care most people get for recurrent glioblastoma with elevated mutational burden.

### **What is the usual approach to my recurrent glioblastoma?**

The usual approach for patients who are not in a study is treatment with either repeat surgery or a different type of chemotherapy. There is not one single standard of care for recurrent glioblastoma. Sometimes combinations of these are used and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more

### **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 get nivolumab and ipilimumab together for four doses over three months, and then nivolumab alone as long as your tumor is controlled. You will be on nivolumab until your cancer gets worse, or the side effects become too severe.

After you finish your study treatment, your doctor will continue to follow your condition every 3 months for 3 years and watch you for side effects.

### **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 drugs may not be as good as the usual approach for your cancer at shrinking or stabilizing your cancer.

There is also a risk that you could have side effects from the study drugs. 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:

- Rash
- Fatigue
- Nausea
- Muscle pain
- Back pain
- Abdominal pain
- Joint pain
- Inflammation
- Diarrhea
- Headache
- Fever
- Dizziness
- Cough
- Shortness of breath
- Constipation
- Decreased appetite
- Itchy skin

### **Benefits**

This combination of immunotherapy medications has been shown to shrink or stabilize tumors that have a high number of mutations in their DNA in many types of cancer. That is why we need to perform testing on your tissue sample to see if it has a higher number of mutations than normal. It is unlikely that it will work in everyone with your type of cancer or help you live longer. This study may help the study doctors learn things that may help other 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 drugs so that there is not a sudden unsafe change. 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 (the Alliance). 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 test the good and bad effects of the combination of immunotherapy drugs called nivolumab and ipilimumab, which could shrink your brain tumor, but it could also cause side effects that are described in the risks section below. The study doctors hope to learn if the study drugs will lead to a stability or reduction in the size of your tumor.

Nivolumab and Ipilimumab have already been approved by the FDA to treat other cancers.

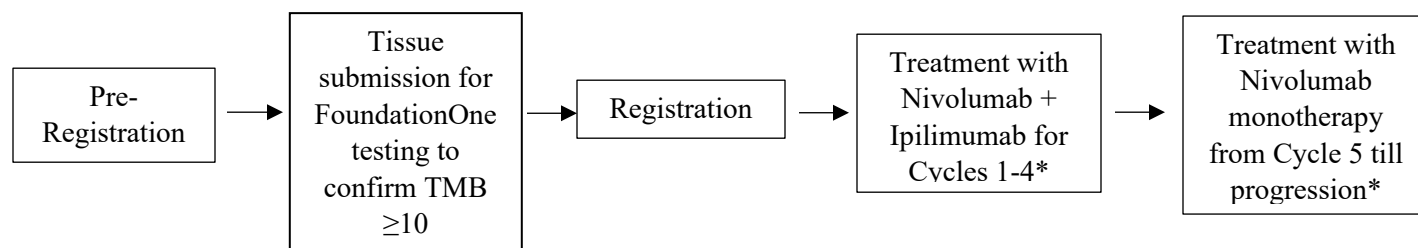
There will be about 37 people taking part in this study. Up to 185 people will be screened to evaluate participation.

## **What are the study groups?**

This study has a screening step. The purpose of this step is to test your tumor to find out if it has a higher than normal number of mutations. If it does, and you meet all the study requirements, then you will receive study treatment. If we find that your tumor sample does not have a higher than normal number of mutations that are needed for this study, then your doctor will discuss other options for your care. The screening test to determine the number of mutations in your tumor is FDA approved for other cancers.

In this study, if your tumor has a higher number of mutations, you will receive a combination of nivolumab and ipilimumab every three weeks for four cycles and then you will receive nivolumab alone every four weeks as long as you keep responding to it and do not experience any serious side effects. During dual therapy (nivolumab + ipilimumab), one cycle is three weeks long. During treatment with nivolumab alone, one cycle is four weeks long. Both drugs will be administered via intravenous infusion on the first day of every cycle, with nivolumab taking 30 minutes and ipilimumab taking 30 minutes. If your tumor starts to grow while receiving the medication, we will stop treating you with it.





\* During Cycles 1-4, one cycle is defined as 3 weeks. Beginning at Cycle 5, one cycle is defined as 4 weeks.

## 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:

- Blood counts done at screening and every other cycle for the duration of treatment.
- Brain MRI done at screening and every 8 weeks
- Physical exams done at screening and every cycle for the duration of treatment.

This study will use genetic tests that may identify changes in the genes in the DNA isolated from your tumor. Your genes carry information about you and your family, from the color of your eyes to health conditions for which you may be at risk, such as certain kinds of cancer. Some of these changes only occur in the tumor. The test we use, called FoundationOne CDx, looks at 324 genes that are often altered in cancers. The test also reports a value called “tumor mutational burden”, or “TMB”. This number tells us the relative number of mutations in your tumor. If your tumor has at least 10 mutations, then you may be eligible for this study. Finding these changes would not affect your treatment in this study. However, they could affect your health in other ways. If there are changes found that could cause health problems, then your study doctor will discuss your options with you.

Your study doctor will need to use some of the tissue left over from your biopsy or surgery if the tumor that has come back. This sample is a required part of the study. You and your study doctor will get the results of this testing.

## 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 study drugs may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing 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 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 for three months after you have completed the study.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

## **Genetic Testing Risks**

As part of this study, we are also studying a genetic test. The test is designed to find out if your tumor has the genetic mutations that are needed for this study. If it does, we will assign you to a study group based on the genetic changes in your tumor.

Because this genetic test is still being studied, there is a risk that the test results may be wrong. If the test results are wrong, you may be included in this study even though it may not offer the best treatment option for you. Or, you may not be included in this study even though it may offer a good treatment option for you.

## **Side Effect Risks**

The 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.

There is also a risk that you could have other side effects from the study drugs.

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 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 study drugs to treat this type of cancer. This 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.

### Possible Side Effects of Ipilimumab (MDX-010) (CAEPR Version 2.10, March 29, 2019)

<p><b>Special precautions</b></p> <p>Side effects of ipilimumab (MDX-010) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab (MDX-010) is used in combination with BMS-936558 (nivolumab). <b>Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.</b></p>
<p style="text-align: center;"><b>COMMON, SOME MAY BE SERIOUS</b></p> <p>In 100 people receiving ipilimumab (MDX-010), more than 20 and up to 100 may have:</p> <ul style="list-style-type: none"> <li>• Diarrhea, nausea</li> <li>• Tiredness</li> </ul> <p>Ipilimumab (MDX-010) 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:</p> <ul style="list-style-type: none"> <li>• Skin: itching; rash, blisters including inside the mouth (can be severe); hives</li> </ul>

<p style="text-align: center;"><b>OCCASIONAL, SOME MAY BE SERIOUS</b></p> <p>In 100 people receiving ipilimumab (MDX-010), from 4 to 20 may have:</p> <ul style="list-style-type: none"> <li>• Abnormal heartbeat</li> <li>• Hearing loss</li> <li>• Swelling and redness of the eye</li> <li>• Pain</li> <li>• Difficulty swallowing, eating</li> <li>• Constipation, vomiting</li> <li>• Weight loss, loss of appetite</li> <li>• Fever</li> </ul>
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- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab (MDX-010) 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). 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
- 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.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- 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.
- 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 ipilimumab (MDX-010), 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Confusion

Ipilimumab (MDX-010) 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:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body

- 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), 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 ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck

### Possible Side Effects of Nivolumab (CAEPR Version 2.5, June 10, 2023)

#### 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:

- Swelling of arms and legs which may cause a feeling of heaviness and tightness
- 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 flu-like symptoms, 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, 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 Nivolumab therapy, since the risk and severity of transplant-associated complications may be increased.

### **Additional Drug Risks**

Although these study drugs could interact with other drugs or food types, no significant interactions have yet been identified. It is important to let your doctor know if you begin a new medication while on study.

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. Contraception use must continue for 5 months from the last dose of study drug for women of childbearing potential.

**For men:** Do not father a baby while taking part in this study. Contraception use must continue for 7 months from the last dose of study drug for men involved with women of childbearing potential.

**For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within three months after your last dose of study drug.

### **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.
- the costs of getting the nivolumab and ipilimumab 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. These include:

- The FoundationOne CDx test to determine your mutation number. This central test will be run by Foundation Medicine and will be paid for by the study sponsor.

You or your insurance provider will not have to pay for the nivolumab or ipilimumab 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.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research
- Foundation Medicine

The laboratory at Foundation Medicine will do the FoundationOne CDx testing on the tissue. They will need information to verify that the tissue they are testing is yours and not other patients'. This information will include your date of birth and your gender. Your contact information will not be shared with Foundation Medicine.

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 and your doctor will receive the results of the FoundationOne test that is performed to determine eligibility. You and your doctor 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, and email address if appropriate\*).

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 your condition 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 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.

### **Known future studies**

These research studies 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.

If you choose to take part in this optional study, researchers will collect blood and tissue for research to study how the immune system interacts with your cancer. Additional leftover tumor tissue from your surgery will be used for comprehensive genomic (DNA sequencing) and transcriptomic (RNA sequencing) testing to examine the changes in all genes in the cancer DNA as well as the resulting changes in what genes are expressed. The type and amount of inflammation in the tumor will also be examined. Furthermore, blood samples will be collected to perform genomic testing on normal blood cells (germline testing) to assess for the presence of potential cancer predisposing genes as well as to measure levels of inflammatory markers in the blood.

### **Unknown future studies**

If you choose to take part in this optional study, stool will be collected and stored. Any leftover blood and tissue samples from the above optional study and some related health information will be stored. Storing samples for future studies is called "biobanking." The biobank is being run by the Alliance 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.

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.

Right now, we don't know what research may be done in the future using your stool 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.

### **What is involved in this optional sample collection?**

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

1. A sample of tissue will be collected from a previous surgery or biopsy. No new surgery or biopsy is required. Blood samples will be collected from a vein your arm prior to protocol treatment, twice while on treatment, and at progression. A single stool sample will be collected before you begin treatment.
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?**

- 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 blood and/or tissue samples and related health information may be used for the laboratory studies described above.

YES

NO

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to learn about results from these studies.

YES

NO

**Samples for unknown future studies:**

I agree that my stool samples may be collected, and I agree that my stool samples and related health information may be kept in a biobank for use in future health research.

YES

NO

I agree that my leftover 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 signature**

Date of signature

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

Date of signature