SUMMARY OF CHANGES – Consent Document Part 2

NCI Protocol #: PED-CITN-01
Local Protocol #: PED-CITN-01
Protocol Version Date: July 6 ,2021

Protocol Title: 3CI Study: Childhood Cancer Combination Immunotherapy. Phase 1b and Expansion Study of Nivolumab Combination Immunotherapy in Children, Adolescent and Young Adult (CAYA) Patients with Relapsed/Refractory Hypermutant Cancers

Informed Consent Version Date: July 6, 2021

I. Investigator-Initiated Changes:

#	Section	Page(s)	Change
1.	What risks can I expect from taking part in this study? General Risks	8	Updated pregnancy reporting requirements to reflect the guidelines included in the current investigator brochures for Ipilimumab (v24, dated March 23, 2021) and Nivolumab (v10, dated June 29, 2020 and Addendum 1, dated September 28, 2020).
2.	What are my responsibilities in this study?	13	Updated pregnancy reporting requirements to reflect the guidelines included in the current investigator brochures for Ipilimumab (v24, dated March 23, 2021) and Nivolumab (v10, dated June 29, 2020 and Addendum 1, dated September 28, 2020).
3.	What are the costs of taking part in this study?	14	Corrected to state the study does not cover the cost of getting the study drugs ready and giving them to the patient. The patient or their insurance may therefore be responsible for this cost.

II. Administrative Changes:

#	Section	Page(s)	Change
4.	Headers	All	Updated the protocol version date.

Research Study Informed Consent Document
Part 2 - Treatment and Correlative Exploratory Biology

Study Title for Participants: Testing the combination of two immunotherapy drugs (nivolumab and ipilimumab) in children, adolescent, and young adult patients with relapsed/refractory cancers that have an increased number of genetic changes

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:
PED-CITN-01 3CI Study: Childhood Cancer Combination Immunotherapy. Phase 1b and Expansion Study of Nivolumab Combination Immunotherapy in Children, Adolescent and Young Adult (CAYA) Patients with Relapsed/Refractory Hypermutant Cancers

Principal Investigator(s):
[Note to local Investigator: Contact information for principal investigator(s) should be listed here.]

Potential participants 18 years and older: *This is a consent form. It provides a summary of the information the research team will discuss with you. If you decide that you would like to take part in this research study, you would sign this form to confirm your decision. If you sign this form, you will receive a signed copy of this form for your records.*

Potential participants 14-17 years of age: *This form also serves as an assent form. That means that if you choose to take part in this research study, you would sign this form to confirm your choice. Your parent or guardian would also need to give their permission and sign this form for you to join the study. A separate assent will be available for children 12 to <14 years of age.*

Parents/Guardians of participants 1-17 years of age: *You have the option of having your child or teen join a research study. This is a parental permission form. It provides a summary of the information the research team will discuss with you. If you decide that your child can take part in this study, you would sign this form to confirm your decision. If you sign this form, you will receive a signed copy for your records. If you are serving as a legally authorized representative, a guardian, or are providing parental permission for a child in this study, the terms "participant", "you", and "your" refer to the person for whom you are providing consent or parental permission.*

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 (DHHS). We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer.

This study is being conducted by the Pediatric Cancer Immunotherapy Trials Network (CITN) and sponsored by NCI. The Pediatric CITN administrative coordinating center is located at the Fred Hutchinson Cancer Research Center (FHCRC) and works with researchers from several cancer centers and universities across the country.

We are asking you to take part in this study because you are between 12 months and 25 years of age, have cancer that has come back or has not responded to standard treatments, and have an elevated biomarker called tumor mutation burden (TMB). TMB is the total amount of genetic changes or "mutations" found in tumor cells.

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 questions:

- What are the side effects of treatment with a combination of nivolumab and ipilimumab and will this treatment shrink or stabilize relapsed/refractory cancers in children, adolescents, and young adults with an elevated TMB?

We are doing this study because we want to find out if the study drugs (nivolumab and ipilimumab) can be given safely and what the side effects are. We also want to see if the study drugs work in treating your cancer and, if so, how well.

"Relapsed" means cancer that reappears or grows again after a period of remission.

"Refractory" is used to describe cancer that does not respond to treatment (meaning the cancer cells continue to grow) or when response to treatment does not last very long.

What is the usual approach to my cancer?

The usual approach for patients who are not in a study is treatment with surgery, radiation, chemotherapy, or immunotherapy. Sometimes, combinations of these treatments are used. Your doctor can explain which treatment may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for a few months or longer.

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 the study drugs (nivolumab and ipilimumab) for about 2 years. If your disease gets worse or the side effects become too severe, we will stop giving the study drugs to you.

After you stop study treatment you will have an end-of-treatment visit within one week and a safety follow-up visit about one month later. After that you will complete follow-up visits every 12 weeks (3 months) for up to one year so that your study doctor can continue to follow your condition and watch you for side effects. You will return to the doctor's office for these follow-up visits. Some of the follow-up visits may be done by phone.

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 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 doctors know about are:

- Nivolumab: Tiredness, anemia, abnormal liver tests, rash, nausea.
- Ipilimumab: Diarrhea, nausea, tiredness, rash, itchiness, intestinal problems.
- Nivolumab and ipilimumab (together): Tiredness, rash, diarrhea, nausea, fever, muscle pain, itchiness, abdominal pain, vomiting, cough, joint pain, decreased appetite, difficulty breathing.

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

Benefits

Some studies in adults with cancer have shown that patients with a higher TMB are more likely to respond to immunotherapy drugs. There is also evidence in adult patients with cancer that the study drugs can shrink or stabilize cancer. However, we do not know if this will happen in pediatric patients. It is unlikely that the study drugs will work in everyone with your cancer type 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. 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 females: You become pregnant while getting study treatment.
- The study is stopped by the Institutional Review Board (IRB), Food and Drug Administration (FDA), Health Canada, or study sponsor (NCI). The study sponsor is the organization that 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 safety and effects of nivolumab in combination with ipilimumab in children, adolescents, and young adults with relapsed/refractory cancers and an elevated TMB.

Nivolumab in combination with ipilimumab is approved by the FDA for adult patients with several cancer types, but this may not include your cancer type. The combination of nivolumab and ipilimumab in pediatric patients is experimental, meaning that it is not FDA approved.

Outside of a few young adults included in other adult trials, there is little published data for the use of nivolumab in combination with ipilimumab in younger children.

There will be up to about 26 people taking part in this study.

What are the study groups?

There are two dose levels of the study treatment combination (nivolumab and ipilimumab), **Dose Level 1** and **Dose Level -1**.

The higher dose level, Dose Level 1, will be tested first in a group of about 6 people. If there are no serious side effects in this group during their first treatment cycle (Cycle 1), this dose level will be selected as the final dose level for the study. If there are serious side effects, Dose Level 1 will be stopped and the lower dose level, Dose Level -1, will be selected. Once the final dose level is determined, up to an additional 20 people will be enrolled in the study and all participants will be given the final dose level.

All participants will be told which dose level they will be receiving. Everyone will receive study treatment for up to 2 years if their cancer responds or does not worsen. Enrollment may be stopped if the study doctors learn that the study treatment is not effective.

Dose Level 1 Treatment Schedule:

- **Cycles 1-4:** The first 4 cycles each last 21 days. On the 1st day of each cycle (Day 1) you will get both nivolumab and ipilimumab by infusion (through a vein in your arm or through a central line, which is a tube placed in a large vein in your neck, chest, groin or arm).

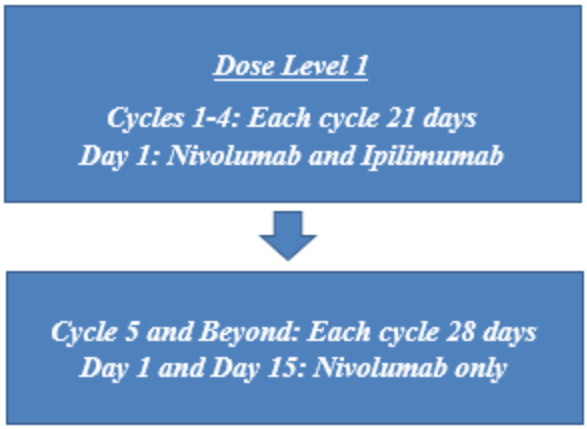
  Nivolumab will first be given over 30-40 minutes. After completion of nivolumab infusion you will be observed for at least 30 minutes. Ipilimumab will then be given over 30-40 minutes. Following your first treatment cycle (Cycle 1), your study doctor may increase the infusion times of both study drugs to up to 90 minutes if they decide it is better for your health.

  After completion of ipilimumab infusion you will be observed in the clinic for 2 hours. On Cycle 1 Day 1 (C1D1) this observation period may be extended to 24 hours, and you may be admitted to the hospital if medically necessary. Following C1D1 your study doctor may decrease the observation period if you did not previously have infusion-related side effects.

- **Cycle 5 and Beyond:** Starting with Cycle 5 the cycles each last 28 days. On the 1st and 15th day of each cycle (Day 1 and Day 15) you will get only nivolumab infusion.

  Nivolumab will be given over 30-40 minutes. Your study doctor may increase the infusion time to up to 90 minutes if they decide it is better for your health.

  After completion of nivolumab infusion you will be observed in the clinic for one hour. Your study doctor may decrease the observation period if you did not previously have infusion-related side effects.

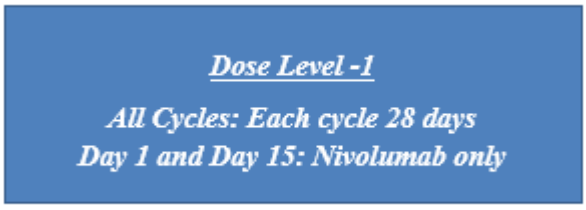


Dose Level -1 Treatment Schedule:

- **All Cycles:** Each cycle lasts 28 days. On the 1st and 15th day of each cycle (Day 1 and Day 15) you will get only nivolumab infusion.

  Nivolumab will be given over 30-40 minutes. Following your first treatment cycle (Cycle 1), your study doctor may increase the infusion time to up to 90 minutes if they decide it is better for your health.

  After completion of nivolumab infusion you will be observed in the clinic for 2 hours. On Cycle 1 Day 1 (C1D1) this observation period may be extended to 24 hours, and you may be admitted to the hospital if medically necessary. Following C1D1 your study doctor may decrease the observation period if you did not previously have infusion-related side effects.



You may not be able to get additional doses of the study drugs after you have completed the study. Nivolumab in combination ipilimumab is FDA approved for adult patients with several cancer types, but this may not include your cancer type. The combination of nivolumab and ipilimumab is not FDA approved in pediatric patients.

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. We call this "screening." 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.

- We will measure your tumor by looking at scans of your body (*e.g.,* CT, MRI, or x-ray) at the following timepoints: before your first infusion of study treatment; at the end of Cycles 2 and 4 or the middle of Cycle 2 and the end of Cycle 3 depending upon the dose level of the study treatment you are receiving; at the end of Cycle 6 and every third cycle thereafter (*i.e.,* end of Cycles 9, 12, 15, etc.); when you stop study treatment; and at each follow-up visit. Additional scans may be done as needed throughout the study. If you had scans done recently, they may not need to be repeated. If your tumor cannot be evaluated by scans, the medically appropriate evaluation will be done instead.
- If you have signs or symptoms of heart disease, cardiac tests will be done as needed throughout the study.

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

- Blood samples will be collected for required research tests at the following timepoints: before your first infusion of study treatment; before dosing for Cycle 2, 3, 5, 8, 11, 14, 17, 20, 23; at the time of initial response (when your cancer first shrinks, stabilizes, or worsens) and/or when you stop study treatment; and at one of the follow-up visits.
- Your study doctor will need a sample of your tumor tissue at the beginning of the study for research tests. If there is enough tissue left over from a biopsy or surgery you previously had for usual care, your study doctor may use some of this tissue. Or if you have a biopsy or surgery for usual care before your first infusion of study treatment, your study doctor may obtain tissue from this procedure. If you took part in Part 1 of this study and there is tissue remaining after completion of the TMB test, this leftover sample may also be used.
- Additionally, if you have a tumor biopsy or surgery for usual care after your first infusion of study treatment, your study doctor will obtain tissue from this procedure for research tests. If you have more than one tumor biopsy or surgery for usual care while taking part in this study, your study doctor will obtain tissue from each procedure.
- Your blood and tissue samples will be used for research tests, including genetic tests. Some of the genetic tests using your tissue sample(s) will involve sequencing of all or part of your DNA. This is called genomic sequencing. The research tests will help us understand how your body, especially your immune system, is responding to the study treatment. The tests will also help us learn more about how immunotherapy drugs can help patients with relapsed/refractory cancers. You and your study doctor will not get the results of this testing.

You can also choose to take part in an optional tissue sample submission. If you have a tumor biopsy or surgery for usual care while taking part in the study, a fresh tissue sample from this procedure may be submitted to researchers at the Hospital for Sick Children and used to create cell

lines and animal models. These cell lines and animal models will be used for research tests to help researchers understand more about cancers with elevated TMB. You and your study doctor will not get the results of these tests. The optional tissue sample submission is described further at the end of this document.

At the end of this document you will also be asked if any samples leftover after completion of this study may be stored for future studies. Storing samples for future studies is called "biobanking". Biobanking your leftover samples is optional.

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 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 study drugs 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. If you are a female who has started menstruating and are sexually active 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 3 months after your last dose of ipilimumab and 5 months after your last dose of nivolumab. Males will not be required to use contraceptive measures.

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

Genetic Testing Risks

Some of the genetic tests used in this study will test your tumor tissue and blood for genetic changes. These 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.

Genetic tests of normal tissue can reveal information about you and also about your relatives. Your study doctor will talk with you about what testing your normal tissue may mean for you and your family. He or she also may suggest that you talk with a genetics counselor to learn more. You or your insurance plan would have to pay for any genetic tests and visits to a genetic counselor done outside of this study.

Blood Draw Risks

The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.

Side Effect Risks

The study 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/study approach.

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 difficult 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 nivolumab and ipilimumab. 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 Nivolumab
(Table Version Date: December 2, 2020)

Special Precautions Side effects 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, seizure 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 and legs, 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.

Possible Side Effects of Ipilimumab
(Table Version Date: March 29, 2019)

Special Precautions
Side effects of ipilimumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab is used in combination with nivolumab. **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 ipilimumab, more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness

Ipilimumab 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:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS

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

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- 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 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 and legs, 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, 3 or fewer may have:

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

- Confusion

Ipilimumab 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 swelling 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.

Additional Drug Risks

The study drugs could interact with other drugs and could increase your side effects or may cause new side effects.

Rarely, there are problems getting enough supplies of the study drug(s). If that happens, the study 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; and
  - if you have been or are currently in another research study.

For females who have started menstruating and are sexually active: Do not breastfeed while getting study treatment. Do not become pregnant while getting study treatment and for 3 months after your last dose of ipilimumab and 5 months after your last dose of nivolumab. Tell your study doctor right away if you think that you have become pregnant during the study. **Males:** Will not be required to use contraceptive measures.

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.
- 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 research labs using blood samples collected at the following timepoints: before your first infusion of study treatment; before dosing for Cycle 2, 3, 5, 8, 11, 14, 17, 20, 23; at the time of initial response and/or when you stop study treatment; and at one of the follow-up visits.
- The research tests using tumor tissue samples obtained at the beginning of the study and each time you have a tumor biopsy or surgery for usual care during your participation in the study.
- The research tests for the optional tissue sample submission and/or biobanking, if you agree to this part of the study.

You or your insurance provider will not have to pay for nivolumab and ipilimumab while you take part in this study. However, the study does not cover the cost of getting the drugs ready and giving them to you, so you or your insurance company may have to pay for this.

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.

[Note to local Investigator: Please insert a description of any compensation for participation or reimbursement for expenses.]

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 sponsor 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 get 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.
- Health Canada and the groups it works with to review research.
- The Pediatric Cancer Immunotherapy Trials Network (CITN).
- Fred Hutchinson Cancer Research Center (FHCRC).
- The Hospital for Sick Children and other cancer centers and laboratories performing the research tests required by the study.

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

Circle your choice of "yes" or "no" for each of the following studies:

Optional sample submission for known studies and/or storage of leftover samples 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.

Submission of fresh tissue for known studies
If you choose to take part in this optional tissue sample submission, if you have a tumor biopsy or surgery for usual care while taking part in the main study, a fresh tissue sample from this procedure may be submitted to researchers at the Hospital for Sick Children and used to create cell lines and animal models. These cell lines and animal models will be used for research tests to help researchers understand more about cancers with elevated TMB. If you have more than one tumor biopsy or surgery for usual care while taking part in the main study, this may be done for each procedure.

Storage of leftover samples for unknown future studies
If you choose to take part in this optional study, any leftover blood and/or tissue samples from the main study will be stored for future studies. Storing samples for future studies is called "biobanking".

The biobank is being run by the Nationwide Children's Hospital in Columbus, Ohio, 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. Your

genomic sequence will also be stored in a secure NIH database for future use. 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.

We do not know what research may be done in the future using your blood and/or tissue 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.
- Future research studies may include genomic sequencing.
- You will not get reports or other information about any research that is done using your samples.

What is involved in these optional studies?

If you agree to take part in the **submission of fresh tissue for known studies**, here is what will happen next:

1. If you have a tumor biopsy or surgery for usual care while taking part in the main study, a fresh tissue sample from this procedure may be submitted to researchers at the Hospital for Sick Children.
2. Your sample will be used to create cell lines and animal models. These cell lines and animal models will be used for research tests to help researchers understand more about cancers with elevated TMB. Researchers performing these tests will not be given your name or contact information.

If you agree to take part in the **storage of leftover samples for unknown future studies**, here is what will happen next:

1. Any leftover blood and/or tissue samples from the main study will be sent to the biobank.
2. Your samples will be stored in the biobank. There is no limit on the length of time the biobank 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 these optional studies?

- 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 a tissue sample is submitted to the Hospital for Sick Children and/or the biobank for these optional studies, 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 samples 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 samples 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 these optional studies?

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 these optional studies?

There are no costs to you or your insurance. You will not be paid for taking part in these studies. 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 these optional studies?

If you decide you no longer want your samples to be used, you can call the study doctor, _____ (*insert name of study doctor[s]*) at _____ (*insert telephone number*), who will let the Hospital for Sick Children and/or the biobank know. Then, any samples that remain at the Hospital for Sick Children and/or 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 these optional studies?

If you have questions about the use of your samples for research, contact the study doctor, _____ (*insert name of study doctor[s]*) at _____ (*insert telephone number*).

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

Submission of fresh tissue for known studies:

- I agree that if I have a tumor biopsy or surgery for usual care while taking part in the main study, a fresh tissue sample from this procedure may be submitted to researchers at the Hospital for Sick Children and used to create cell lines and animal models for research tests.

  YES NO

Storage of leftover samples for unknown future studies:

- I agree that my leftover blood and/or tissue samples and related health information may be kept in a biobank for use in future health research.

  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 (print) (or parent/guardian if subject is under 18)	**Participant's signature** (or parent/guardian if subject is under 18)	**Date** (dd-MMM-yyyy)

Participants aged 14-17:

Your signature below indicates that you agree to be in this study.

Printed name of participant	**Signature of participant**	**Date** (dd-MMM-yyyy)

STUDY STAFF SIGNATURE

Study staff conducting consent discussion (print)	**Study staff signature**	**Date** (dd-MMM-yyyy)