SUMMARY OF CHANGES – Consent Document Part 1

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 will happen if I decide to take part in Part 1 of this study?	3	Revised as follows: "If you decide to take part in this study, we will test your cancer to see if it has an elevated TMB using a procedure called molecular profiling. The test results will take about 3 weeks to receive."
2.	What are the risks and benefits of taking part in Part 1 of this study? Risks	3	Revised as follows: "Because Part 1 of this study may use some of this tissue for the ~~TMB test~~molecular profiling, there is a small risk that it could be used up."
3.	What is the purpose of Part 1 of this study?	4	Revised as follows: "The purpose of Part 1 of this study is to see if your cancer has an elevated TMB using a procedure called molecular profiling."
4.	What exams, tests, and procedures are involved in this study?	5	2nd paragraph, 1st bullet point, 1st sentence was revised as follows: "Your study doctor will need a sample of your tumor tissue to see if your cancer has an elevated TMB using a procedure called molecular profiling~~for the TMB test~~." 2nd paragraph, 1st bullet point, final two sentences were revised as follows: "Your sample will then be sent to a laboratory to be tested to see if your cancer has an elevated TMB using molecular profiling. ~~You and y~~Your study doctor will receive the ~~test~~molecular profiling results in about 3 weeks and will share ~~it~~the TMB result with you."
5.	What exams, tests, and procedures are involved in this study?	6	Final paragraph, 1st sentence was revised as follows: "At the end of this document you will also be asked if any samples leftover after completion of the ~~TMB test~~ molecular profiling may be stored for future studies if you do not take part in Part 2."
6.	What risks can I expect from taking part in this study? Genetic Testing Risks	6	1st paragraph, 1st sentence was revised as follows: "The genetic testing used in this study will test to see if your cancer has an elevated TMB."

#	Section	Page(s)	Change
7.	What are the costs of taking part in this study?	6	1st bullet point was revised as follows: "The ~~TMB test~~molecular profiling."
8.	Who will see my medical information?	8	4th paragraph, 8th bullet point was revised as follows: "Foundation Medicine Inc., which is the laboratory performing the ~~TMB test~~molecular profiling."
9.	Who will see my medical information?	8	5th paragraph was revised as follows: "When your information is shared with these organizations it will not identify who you are with the following exception: your sample sent to Foundation Medicine Inc. for ~~genetic TMB testing~~molecular profiling will include your initials, partial date of birth (month and year), and gender. The laboratory processing your sample before it is sent to Foundation Medicine Inc. will also have access to these identifiers. Additionally, your ~~TMB test~~molecular profiling results will be shared with your study doctor~~, who will include these results in your study records~~. The study doctor will only include the TMB result in your study records. Although your initials, partial date of birth, and gender will be removed from the TMB result~~s~~ placed in your study records, your genetic information will remain."
10.	Optional sample submission for known studies and/or storage of leftover samples for possible future studies: Storage of leftover samples for unknown future studies	10	4th paragraph, 1st sentence was revised as follows: "If you choose to take part in this optional study, any samples leftover after completion of the ~~TMB test~~molecular profiling in Part 1 of the main study will be stored for future studies."
11.	Optional sample submission for known studies and/or storage of leftover samples for possible future studies: What is involved in these optional studies?	11	5th paragraph, 1st sentence was revised as follows: "Any samples leftover after completion of the ~~TMB test~~molecular profiling in Part 1 of the main study will be sent to the biobank."

II. Administrative Changes:

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

Research Study Informed Consent Document
Part 1 – Molecular Profiling

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 and have cancer that has come back or has not responded to standard treatments.

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 divided into two parts: Part 1 and Part 2.

Part 1 of this study is being done to answer the following question:

- Does your cancer have an elevated biomarker called tumor mutation burden (TMB)?

TMB is the total amount of genetic changes or "mutations" found in tumor cells. Some studies in adults with cancer have shown that patients with a higher TMB are more likely to respond to immunotherapy drugs.

Participants who have an elevated TMB may be eligible to take part in the treatment portion of this study (Part 2) and get a combination of two immunotherapy drugs. Part 2 is explained in a separate document.

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 Part 1 of this study?

If you decide to take part in this study, we will test your cancer to see if it has an elevated TMB using a procedure called molecular profiling. The test results will take about 3 weeks to receive. If your TMB is elevated, you may then be eligible to take part in the treatment portion (Part 2) of this study. If there are other important genetic changes discovered while testing for TMB elevation, your doctor will discuss this with you outside of the study. You doctor will explain if there might be another treatment that might be better for you than the study drugs in Part 2.

What are the risks and benefits of taking part in Part 1 of 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. We want to make sure you know about a few key risks and benefits right now. We will give you more information later on in the consent form.

Risks

Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because Part 1 of this study may use some of this tissue for molecular profiling, there is a small risk that it could be used up.

Benefits

Part 1 of this study will not help you. It will test your cancer to see if it has an elevated TMB. If it is elevated, you may then be eligible to participate in the treatment portion (Part 2) of this study.

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.

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.
- 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.

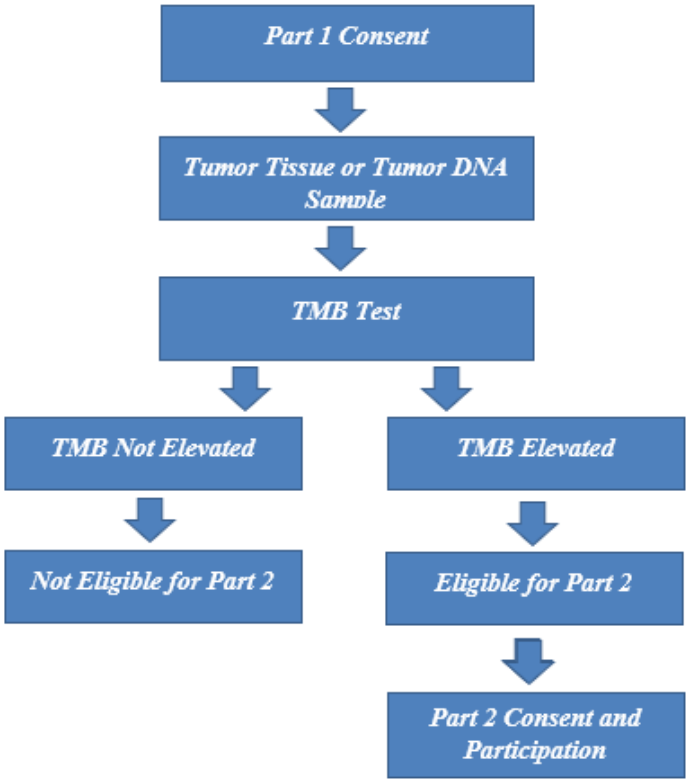
What is the purpose of Part 1 of this study?

The purpose of Part 1 of this study is to see if your cancer has an elevated TMB using a procedure called molecular profiling. There will be up to about 40 people taking part in Part 1 of this study and up to about 26 people taking part in the treatment portion (Part 2).

What are the study groups?

All participants in Part 1 of this study will have their TMB level tested. If it is elevated, you may then be eligible to take part in the treatment portion (Part 2) of this study. If we find that it is not elevated, then your doctor will discuss other options for your care.

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



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

Before you begin Part 1 of this 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.

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.

- Your study doctor will need a sample of your tumor tissue to see if your cancer has an elevated TMB using a procedure called molecular profiling. 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 are going to have a biopsy or surgery for usual care within the next month, your study doctor may obtain a sample of your tissue from this procedure. If tissue is not available but your hospital kept a sample of your DNA that was previously taken from your tumor tissue, your study doctor may obtain some of this DNA sample instead. Your sample will then be sent to a laboratory to be tested to see if your cancer has an elevated TMB using molecular profiling. Your study doctor will receive the molecular profiling results in about 3 weeks and will share the TMB result with you.
- Participants who have an elevated TMB may then be eligible to take part in the treatment portion (Part 2) of this study. Part 2 is explained in a separate document.

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 the molecular profiling may be stored for future studies if you do not take part in Part 2. Storing samples for future studies is called "biobanking". Biobanking your leftover samples is optional. You may also request to have any leftover samples returned to your study doctor if you do not take part in Part 2. (Please note that if you take part in Part 2, any leftover samples will be used for Part 2 research tests.)

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

General Risks

Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because Part 1 of this study may use some of this tissue, there is a small risk that it could be used up.

Genetic Testing Risks

The genetic testing used in this study will test to see if your cancer has an elevated TMB. This change may also be in your normal tissue and passed down through your family. For example, genetic changes may be passed down to your children in the same way that eye and hair color are passed down.

Since this study is only testing tumor tissue, we will not know if a genetic change in your tumor is also in your normal tissue. If you want to find out if the change is in your normal tissue, then you will need to get other tests done outside of this study.

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.

What are the costs of taking part in this study?

Part 1 of this study includes only tests and procedures done for research purposes. You and/or your insurance provider will not have to pay for tests and procedures done for research purposes only or that are covered by the study. This includes:

- The molecular profiling.
- If you agree to the optional tissue sample submission and/or biobanking, the tests for these studies.

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 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 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).
- Foundation Medicine Inc., which is the laboratory performing the molecular profiling.
- The Hospital for Sick Children and other cancer centers and laboratories performing the research tests required by the study.

When your information is shared with these organizations it will not identify who you are with the following exception: your sample sent to Foundation Medicine Inc. for molecular profiling will include your initials, partial date of birth (month and year), and gender. The laboratory processing your sample before it is sent to Foundation Medicine Inc. will also have access to these identifiers. Additionally, your molecular profiling results will be shared with your study doctor. The study doctor will only include the TMB result in your study records. Although your initials, partial date of birth, and gender will be removed from the TMB result placed in your study records, your genetic information will remain.

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 Part 1 of 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.

Storage of leftover samples for unknown future studies
If you choose to take part in this optional study, any samples leftover after completion of the molecular profiling in Part 1 of the main study will be stored for future studies. However, this will only be done if you do not take part in Part 2. If you take part in Part 2, any leftover samples will be used for Part 2 research tests. 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 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 Part 1 of 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 samples leftover after completion of the molecular profiling in Part 1 of the main study will be sent to the biobank. However, this will only be done if you do not take part in Part 2. If you take part in Part 2, any leftover samples will be used for Part 2 research tests.
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 Part 1 of 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 if I do not take part in Part 2, my leftover 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)