SUMMARY OF CHANGES – Consent

NCI Protocol #: 9706
Local Protocol #: CIRB 15-0185
Protocol Version Date: 04/25/2023

Protocol Title: Randomized phase II study to assess the role of Nivolumab as single agent to eliminate minimal residual disease and maintain remission in acute myelogenous leukemia (AML) patients after chemotherapy (REMAIN TRIAL)

Informed Consent Version Date: 04/25/2023

#	Section	Page(s)	Change
1.	Document Header	All pages	Version date updated to 04/25/2023

Study Title for Study Participants: Testing Nivolumab to prevent disease from coming back after treatment in patients with acute myeloid leukemia (REMAIN TRIAL)

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol NCI 9706, Randomized phase II study to assess the role of Nivolumab as single agent to eliminate minimal residual disease and maintain remission in acute myelogenous leukemia (AML) patients after chemotherapy (REMAIN TRIAL), (NCT02275533)

Overview and Key Information

What am I being asked to do?

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

We are asking you to take part in this research study because you have acute myelogenous leukemia (AML) that is in remission after chemotherapy and you are at increased risk for the leukemia to come back.

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 lower the chance of your acute myelogenous leukemia (AML) from coming back. Since you are in remission after chemotherapy, we hope to reduce the chance of leukemia coming back, by treating you with a drug called Nivolumab.

The purpose of this study is to compare good and bad effects of using the drug Nivolumab compared to the usual approach of being closely followed but no treatment. Nivolumab could prevent your leukemia from coming back but it could also cause side effects. This study will allow the researchers to know whether this different approach is better, the same, or worse than the usual approach. To be better, the study approach should increase the time before leukemia comes back by 12 months compared to the usual approach. This study will use an experimental drug called Nivolumab which has now been approved by the US Food and Drug Administration (FDA) for melanoma and non-small cell lung cancer. There will be about 80 people to participate in this study.

If you are assigned to the "no treatment" group, you have the option to be treated with Nivolumab, if your disease comes back, while on the study.

What is the usual approach to my acute myeloid leukemia (AML)?

You are being asked to participate in this study because you have acute myelogenous leukemia (AML) that is in remission after chemotherapy and you are at increased risk for the leukemia to come back. People who are not in a study are usually followed closely by their doctor to watch for the return of their leukemia, and receive no treatment. For patients who receive the usual approach of being closely followed by their doctor, about 20 to 40 out of 100 are free of cancer at five years.

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

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated for cancer, but you may want to receive comfort care to relieve symptoms.

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

If you decide to take part in this study, you will either receive the study drug, Nivolumab in your vein every 2 weeks for 46 doses or you will not receive treatment.

If you are in the no treatment group, you will be monitored monthly for one year, then every 2 months for another year. If your leukemia comes back, you will have the option to be treated with Nivolumab every 2 weeks for 46 doses.

After you finish taking the study drug, your doctor will continue to watch you for side effects and follow your condition for another 2 years maximum. In addition, subjects who have completed two years of study treatment/ observation will be followed every 6 months for the first year after coming of treatment/observation, and yearly until death or recurrence.

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 drug, Nivolumab, may not be as good as the usual approach for your cancer and at preventing your cancer from coming back.

There is also a risk that you could have side effects from the Nivolumab. 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 of Nivolumab, that the study doctors know about are:

Potential allergic reactions:

Very rarely, allergic reactions may occur, 10 minutes to 4 hours after the infusion of study drug. Mild to

moderate swelling and itching at the infusion site can occur. Mild headache, flushing, dizziness, and nausea may also occur. Moderate symptoms include chest pain, shortness of breath, fever, and change in blood pressure. These symptoms can become more severe with partial obstruction of the airways, severe flushing, and joint stiffness. Delayed symptoms usually occur between 24 hours to 14 days after study drug dosing. The delayed symptoms include rash, flu-like symptoms, stiffness of the joints, pain in the joints, headache, and muscle pain.

Possible immune related side effects:
Nivolumab is a drug that acts by enhancing the function of your immune system and if referred to as immunotherapy. However, in rare cases, immunotherapy may result in an overreaction against your healthy tissues and organs; this is called an autoimmune reaction. This means that the study drug may cause your immune system to not only attack the cancer cells, but also normal healthy cells in your body, and potentially may cause an autoimmune disease.

Immune-related side effects that have been seen in subjects that received nivolumab dosing include the following:

- **Uveitis:** inflammation of the eyes that may cause eye redness, eye pain, sensitivity to light, blurred vision, decreased vision, and floating spots in your vision
- **Hypophysitis:** inflammation of the pituitary gland that may cause low blood sugar, dehydration, weakness, dizziness, and other symptoms
- **Hyperthyroidism:** overactive thyroid gland activity that may lead to fatigue, weakness, muscle aches, anxiety, weight loss, intolerance to heat, in addition to other symptoms
- **Hepatitis:** inflammation of the liver that may result in nausea, fatigue, abdominal pain, impart a yellowish hue to your skin or eyes, or darkness of your urine
- **Pancreatitis:** inflammation of the pancreas that may lead to high levels of lipase and that may be accompanied by nausea, vomiting, and abdominal pain
- **Colitis:** inflammation of the lining of the colon, sometimes associated with severe diarrhea
- **Arthritis:** painful swelling, inflammation and stiffness of the fingers, wrists, arms and legs

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

Benefits
It is not possible to know at this time if the Nivolumab approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

If I decide to take part in this study, can I stop later?
Yes. You can decide to stop at any time.

If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The 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.

The study doctor may take you out of the study:
- If your health changes and the study is no longer in your best interest

- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

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 Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor. The study sponsor is the organization who oversees the study.

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

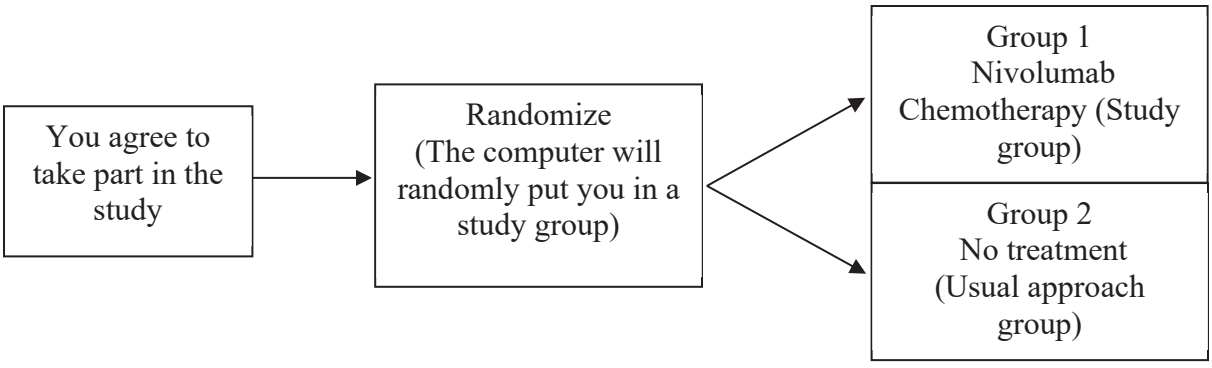
What is the purpose of this study?

The purpose of this study is to compare good and bad effects of using the drug Nivolumab compared to the usual approach of being closely followed but no treatment. Nivolumab could prevent your leukemia from coming back but it could also cause side effects.

What are the study groups?

This study has two study groups. Group 1 will receive the study drug, Nivolumab, and Group 2 will not receive any treatment. A computer will by chance assign you to treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

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



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

Before you start the study, you will have to have some screening procedures in order for the doctor to tell if you can participate in this study.

Most of the exams, tests, and procedures you will have are part of the usual approach for your leukemia. However, if you take part in this study, the analyses/processing of the research blood and bone marrow biopsy/aspiration samples are additional, and are not considered a part of usual care.

Before you begin the study:

These screening procedures include:

- An electrocardiogram (ECG) will be performed to measure the electrical activity of your heart if indicated.
- Urine or serum pregnancy test (only for women who can get pregnant)
- Approximately 1-2 teaspoons of blood will also be taken for HIV (the virus that causes AIDS) and hepatitis testing. Your study doctor will tell you the results which will be placed in your medical record.
- People with known history of HIV (or AIDS) and hepatitis may be enrolled, if viral loads are undectable by a sensitive testing method called PCR and the absolute lymphocyte count >= 350/ul
- Screening bone marrow biopsy /aspiration is required. A bone marrow aspiration is the removal of small amount of bone marrow fluid through a needle inserted into the bone. A bone marrow biopsy is the removal of small pieces of bone marrow tissue and fluid through a needle inserted into the bone. However, your doctor will let you know if a previous bone marrow biopsy/aspiration, which was used to determine that you are in complete remission may be used, if available.
- Your initial bone marrow biopsy sample at the time of your diagnosis of AML will be obtained for research purpose. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study.
- Approximately 2 teaspoons of blood will be collected for research purposes. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests. They are not part of the usual approach for your type of cancer.

During the study:

Participants in Group 1:

- You will get Nivolumab as a 30 minute infusion every two weeks for 46 dose or until your AML relapses
- Research blood samples will be collected at 2, 3, 6, and 12 months on the study, and when you come off the study due to disease coming back or completion of the study.
- Research bone marrow biopsy /aspiration samples will be obtained at 3 months, 6 months, and 12 months on the study, and anytime your doctor will see any change of your blood to indicate possible disease coming back.

Participants in Group 2:

- You will get no treatment
- Research blood samples will be collected at 2, 3, 6, and 12 months on the study, and when you come off the study due to disease coming back or completion of the study.
- Research bone marrow biopsy /aspiration samples will be obtained at 3 months, 6 months, and 12 months on the study, and anytime your doctor will see any change of your blood to indicate possible disease coming back.]

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 BMS-936558 (nivolumab, MDX-1106) 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 Nivolumab 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 be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

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

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

Drug Risks

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

Side Effect Risks of Nivolumab:

Special precautions Side effects of Nivolumab (BMS-936558) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when BMS-936558 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

BMS-936558 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

BMS-936558 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Visual disturbances which may cause double vision, blurred vision, or loss of vision with a chance of blindness
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Swelling of the brain (meningitis/encephalitis) which may cause: headache, stiff neck, confusion, sleepiness, seizures or injury to the brain which may cause headache, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)

- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut damage), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.

Risks associated with study procedures:

Blood Draws:

- tenderness
- pain
- bleeding
- bruising
- infection at the site of the needle puncture
- Having your blood drawn may also cause you to feel nauseated or lightheaded

Bone marrow biopsy risks:

You may experience

- pain
- bleeding
- swelling
- possible infection
- scarring at the wound site

ECG:

This is a test that measures the electrical activity of your heart. The test is painless but some people's skin reacts to the sticky patches that attach to the chest in order for the test to be done. The irritation usually disappears when the patches are removed.

Risks associated with testing for HIV:

- Loss of confidentiality
- Emotional distress
- Problems with continuing health insurance

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The Nivolumab used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What are my responsibilities in this study?

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

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

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within (23 weeks) after your last dose of study drug.

What are the costs of taking part in this study?

The study drug, Nivolumab will be supplied at no charge while you take part in this study. You or your insurance company may have to pay for the cost of getting Nivolumab ready and giving it to you at our IV therapy. It is possible that nivolumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.
The cost for analyses/processing of the research blood and bone marrow biopsy/aspiration samples will not be billed to you and/or your health plan/insurance company.

You and/or your health plan/insurance company will need to pay for all of the other costs of caring for your cancer while in this study, including the cost of tests, procedures (including, bone marrow biopsy/aspiration), or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors *will not* offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, the National Cancer Institute, and the drug company, Bristol-Meyers Squibb supporting the study

- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

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.

My Signature Agreeing to Take Part in the Main 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 copy of this form. I agree to take part in the main study.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____