SUMMARY OF CHANGES – Consent

NCI Protocol #: 10300
Local Protocol #: 2000028858
Protocol Version Date: 10/23/2024

Protocol Title: BLockade of PD-1 **A**dded to **S**tandard **T**herapy to target **M**easurable **R**esidual **D**isease in **A**cute **M**yeloid **L**eukemia 1 (BLAST MRD AML-1): A Randomized Phase 2 Study of the Anti-PD-1 Antibody Pembrolizumab in Combination with Conventional Intensive Chemotherapy as Frontline Therapy in Patients with Acute Myeloid Leukemia

Informed Consent Version Date: 10/23/2024

I. CTEP Request for Rapid Amendment (RRA) dated 10/9/24

#	Section	Comments
1.	All	Updated Version Date in Header
2.	Title Page	Protocol Version Date and Informed Consent Version Date updated to match protocol version.
3.	Risks	Risk list profile for Pembrolizumab updated to Version 2.8, August 14, 2024

4.	Possible Side Effects of Pembrolizumab	Condensed risk profile has been modified per Version 2.8, August 14, 2024
		• Added New Risk:
		  • Rare and Serious: Inability to digest food which may cause bloating; Swelling of the bowels; Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure
		• Decrease in Risk Attribution:
		  • Changed to Rare and Serious from Occasional: Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
		  • Changed to Also Reported on Pembrolizumab MK-3475 Trials But With Insufficient Evidence for Attribution from Occasional (i.e. Removed from Risk Profile): Cough
		• Provided Further Clarification:

#	Section	Comments
		• Reaction during or following a drug infusion which may cause fever, chills, rash (under Rare) is now reported as Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure (under Occasional)

Research Study Informed Consent Document

Study Title for Participants: Testing the addition of immunotherapy with MK-3475 (pembrolizumab) to the conventional induction chemotherapy for newly diagnosed acute myeloid leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: Protocol 10300, "**BL**ockade of PD-1 **A**dded to **S**tandard **T**herapy to target **M**easurable **R**esidual **D**isease in **A**cute **M**yeloid **L**eukemia 1 (BLAST MRD AML-1): A randomized phase 2 study of the anti-PD-1 antibody pembrolizumab in combination with conventional intensive chemotherapy as frontline therapy in patients with acute myeloid leukemia" (NCT # NCT04214249)

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 myeloid leukemia (AML).

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Will the addition of Pembrolizumab (MK-3475) to conventional intensive chemotherapy increase the rate of deeper/better responses and reduce the chance of the leukemia coming back in patients with newly diagnosed AML?

We want to find out if activating the immune system with Pembrolizumab (MK-3475) to the usual chemotherapy is safe and improves the response rate (elimination of leukemia cells) as compared to what has been reported for usual chemotherapy given in this situation. We are doing this study because we want to find out if this approach is better or worse than the usual approach for your AML. The usual approach is defined as care most people get for newly diagnosed AML.

What is the usual approach to my Acute Myeloid Leukemia (AML)?

The usual approach for patients who are not in a study is treatment with a combination of two chemotherapy drugs cytarabine and daunorubicin or idarubicin (referred to as the "7+3" regimen). The combination of standard dose cytarabine and daunorubicin is Food and Drug Administration (FDA) approved and has been the standard treatment for AML for over 40 years. For patients younger than 60 years who get the usual approach for this cancer, about 60 out of 100 people achieve a complete remission and 35 out of 100 are free of cancer after 5 years. Among older patients and those with adverse genetic risk disease, 35 out of 100 people achieve a complete remission and only 10 out of 100 people are cancer free at 5 years.

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. This type of care only helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. Comfort care does not treat the cancer directly but instead is meant to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

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

If you decide to take part in this study, you will either get cytarabine and either daunorubicin or idarubicin (usual approach arm), or you will get Pembrolizumab (MK-3475), cytarabine, and either daunorubicin or idarubicin (intervention arm).

In both the usual approach and intervention arms, in the middle of your first cycle (Day 14 to day 21), a bone marrow biopsy, which is taking a sample of the bone marrow, will be performed to assess for any remaining leukemia. If the results of the first cycle are not good enough (*i.e.*, there is evidence of residual leukemia), you will receive another dose of cytarabine and either daunorubicin or idarubicin (referred to as “5+2 regimen”). If you achieve a complete remission at the end of your first part of therapy, the doctor may make a referral to bone marrow

transplantation or continue you on the second part of therapy using high dose cytarabine (HiDAC). For the second part of therapy, you may receive up to 4 cycles of HiDAC alone (usual approach arm) or with Pembrolizumab (MK-3475) (intervention arm). You will be taken off study if you either do not achieve a complete remission at the end of the first part of therapy or if your disease recurs during any of the second part of therapy.

After you finish the second part of therapy, you will either continue to receive only Pembrolizumab (MK-3475) (intervention arm) every 3 weeks as continuation therapy to try to keep the remission or receive no therapy (usual approach arm) for up to 2 years. Your doctor and the study team will check you in the clinic and collect information about your health status and follow-up of any side effects on the study medication (on the intervention arm). You will undergo bone marrow testing every 3 months to assess disease response until your disease gets worse, the side effects become too severe, or you want to stop participating.

After you finish your treatment, your doctor and study team will watch you for side effects. They will check you every 6 months for up to 5 years after you enroll in this study.

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 pembrolizumab (MK-3475) 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 pembrolizumab (MK-3475) 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 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 things to know 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, and some may never go away.

- Some side effects may make it hard for you to have children.
- 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.

The tables below show the most common and the 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."

Benefits

If you agree to take part in this research study, we cannot guarantee that you will receive any additional benefits. We hope that the addition of therapy activating the immune system to chemotherapy will decrease the rate of any cancer cells remaining compared to the current standard of care.

There is evidence that addition of therapy activating the immune system (immunotherapy) to traditional chemotherapy improves outcomes in various cancers. For instance, in lung cancer, immunotherapy has been successfully combined with platinum doublet chemotherapy. Immunotherapy has been combined with chemotherapy (high dose cytarabine followed by MK-3475 [pembrolizumab]) in relapsed and refractory AML. Similarly, other agents in the same class have been previously been tested in combination with chemotherapy as the first type of cancer therapy and found to be feasible and safe. It is not possible to know now if adding the study drug will improve outcomes compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. They will make sure that proper procedures are followed, and a final visit is scheduled to monitor your safety. This will cancel any future research study appointments. If you stop, you can decide if you want to keep letting the study doctor know how you are doing.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study. Women of childbearing potential and sexually active males must use an accepted and effective method of contraception or to abstain from sex from time of registration, while on study treatment, and continue for 120 days after the last dose of study treatment.
- The study is stopped by the Institutional Review Board (IRB), FDA, or study sponsor (NCI). The study sponsor is the organization who oversees the study.

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

What is the purpose of this study?

The purpose of this study is to compare the usual treatment alone to adding immune system activating therapy, Pembrolizumab (MK-3475), to the usual treatment. The addition of Pembrolizumab (MK-3475) to the usual treatment could potentially improve response rates and induce deeper, long-lasting responses to the cancer treatment. But, it could also cause side effects, which are described in the risks section later.

Pembrolizumab (MK-3475), is already approved by the FDA for use in several cancers, including advanced or metastatic small-cell and non-small cell lung cancer, melanoma, head and neck cancer, urothelial cancer, hepatocellular carcinoma, gastric cancer, among others. However, Pembrolizumab (MK-3475) is not approved by the FDA or known to be safe for use in AML either alone or in combination with standard chemotherapy. The drug is given every 3 weeks and is typically used after the standard front-line drugs have stopped working.

This study will help the study doctors find out if this different approach is better than the usual approach. To decide if it is better, the study doctors will be looking to see if the addition of pembrolizumab results in fewer detectable leukemia using new methods. Minimal residual disease or MRD is the name given to small numbers of leukemic cells (cancer cells from the bone marrow) that remain following the achievement of "complete" remission but are below the limits of detection using conventional morphologic assessment. MRD is thought to be responsible for most of the relapses after initial disease response and is currently the most powerful prognostic indicator in AML. It must be noted the MRD status will not decide whether you should be taken off study. MRD analysis will be performed on bone marrow aspirate specimens using a highly sensitive method called the multicolor flow cytometry (MFC) assay. In general terms, flow cytometry refers to an automated procedure in which a suspension of cells

flows past a detector. The principle behind this assay is that leukemia cells display certain proteins which normal cells do not. MFC can identify MRD based on the expression of antigens.

What are the study groups?

This study has 2 study groups. We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose, and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2

- **Group 1**

  If you are in this group, you will get the usual study drugs, cytarabine at 100 mg/m^2/day continuous infusion on Days 1-7 and either daunorubicin at 60 mg/m^2/day or idarubicin at 12 mg/m^2/day intravenously (IV) on Days 1-3. If you have evidence of residual leukemia in the bone marrow at Day 14, you will receive a second round of the first part of therapy (5+2 chemotherapy), which means cytarabine at 100 mg/m^2/day continuous infusion on Days 1-5 and either daunorubicin at 60 mg/m^2/day or idarubicin at 12 mg/m^2/day IV on Days 1-2. If you have a complete remission after the first part of therapy, you will continue with the second part of therapy that consists of up to four cycles of high dose cytarabine. If you remain in complete remission after second part of therapy, you will be monitored without further therapy for up to 3 years. If you proceed with a transplant, you will forgo any remaining protocol-defined therapy.

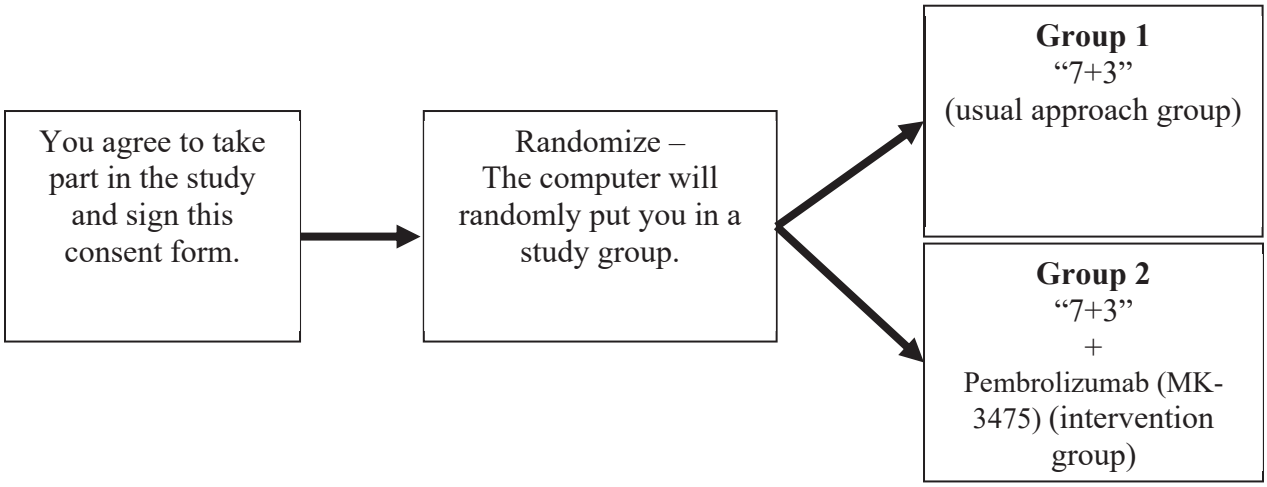
  There will be about 25 people in this group.

- **Group 2**

  If you are in this group, you will get the usual study drugs, cytarabine at 100 mg/m^2/day continuous infusion on Days 1-7 and either daunorubicin at 60 mg/m^2/day or idarubicin at 12 mg/m^2/day IV on Days 1-3. If you have evidence of residual leukemia in the bone marrow at Day 14, you will receive second dose of the first part of therapy (5+2 chemotherapy), which means cytarabine at 100 mg/m^2/day continuous infusion on Days 1-5 and either daunorubicin at 60 mg/m^2/day or idarubicin 12 mg/m^2/day IV on Days 1-2. Regardless of your bone marrow findings on Day 14, you will receive Pembrolizumab (MK-3475) IV on Day 8. This drug is not approved by the FDA for treatment of your disease. If you have a complete remission after the first part of therapy, you will continue with the second part of therapy that consists of up to four cycles of high dose cytarabine with Pembrolizumab (MK-3475). If you remain in complete remission after the second part of therapy, you will be monitored without Pembrolizumab (MK-3475) therapy on Day 1 of each 21-day cycle for up to 2 years. If you proceed with a transplant, you will forgo any remaining protocol-defined therapy.

  There will be about 25 people in this group.

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 begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health include:

- Blood tests at every clinic visit for 1 year (if applicable, drawn when routine blood samples are taken).
- In the intervention arm, thyroid testing (with thyroid stimulating hormone or TSH) will be performed at baseline and <3days prior to first dose of Pembrolizumab (MK-3475) only. Additional thyroid tests (T3 and T4) will be performed as clinically indicated, if TSH is abnormal, or if symptoms are suggestion of thyroid dysfunction.
- Bone marrow aspirations before you begin treatment, on Day 14 and at the end of the first part of therapy, and the last cycle of the 2nd part of therapy and collection of one bone marrow biopsy before you begin the treatment.

- An exam to look at your heart called an echocardiogram (ECHO) before you begin the first part of therapy and on Day 9 before you begin the second round of the first part of therapy (5+2 chemotherapy).
- Blood tests every 3 weeks during the third part of therapy.
- An ECG at pre-study and any time your doctor indicates it is necessary
- An optional chest CT scan before you begin treatment.

If you agree, collection of left-over samples from your bone marrow samples will be discussed in the section on optional studies. The increased volume collections will have no patient impact.

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

A skin punch biopsy before you begin treatment.

You will need to have two additional bone marrow aspirations, after the first cycle of the second part of therapy and at the end of the third part of therapy. You will also need to have two additional bone marrow biopsies at the end of the second part of therapy and at the end of the third part of the therapy. These samples are a required part of the study. The study takes small bone marrow from your body. This is like the bone marrow aspiration and biopsy you had that helped diagnose your cancer. If bone marrow cannot be obtained, your study doctor will let you know if you are still able to participate in the study.

Blood samples will also be taken for the study. The blood samples will be collected on the same days as the bone marrow aspirations. Additional blood samples will be take 6 months after starting treatment, 1 year after starting treatment, and every 3 months during the 3rd part of therapy.

Apart from testing the aspirate for MRD using flow cytometry, the bone marrow aspirate and blood samples will be additionally submitted for MRD evaluation using another method called duplex sequencing. This is to find out how the duplex sequencing method of MRD evaluation compares to the standard flow cytometry MRD assay and if it is a better method of MRD evaluation. Additional optional studies include assessment of impact of therapy on anti-leukemia immune responses at the molecular level and their correlation with clinical outcomes used to see if new methods for detecting left over leukemia cells can predict your response to therapy. You and your study doctor will not get the results of this testing.

Researchers will obtain genetic material (DNA and RNA) from your tumor tissue and blood samples. Your DNA and RNA will be sequenced to evaluate changes in your DNA and RNA that may occur during treatment. You and your study doctor will not get any results of this testing. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

Stool samples will be collected for research purposes. A stool sample will be collected before you start treatment and again at the end of the first cycle of part two of the study (consolidation treatment).

A patient study calendar is attached at the end of this document. It shows how often these tests and procedures will be done.

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 a drug that activates the immune system to the conventional standard dose cytarabine and daunorubicin may not be better than the usual "7+3" approach for your cancer at improving the response rates.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- May not be able to take part in future studies

The study drugs used in this study may have adverse effects on a fetus in utero. Furthermore, it is not known if Pembrolizumab (MK-3475) has transient adverse effects on sperm. 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 120 days after you have completed the study. If you inadvertently become pregnant while on treatment with Pembrolizumab (MK-3475) or within 120 days of the last dose of study treatment, you need to call the study doctor immediately. Do not breast-feed while you take this drug or for 120 days after your last dose.

Potential risks associated with combining Pembrolizumab (MK-3475) to AML therapy:

While combinations of immune activating agents with chemotherapies or targeted agents had benefits in clinical trials and have been approved in some solid cancers, clinical trials to date have not demonstrated a benefit of combining immune activating therapy with standard leukemia treatment. Combining a drug that activates the immune system with the conventional standard dose of cytarabine and daunorubicin called "7+3" may be associated with an increased risk of side effects than the usual "7+3" approach for your cancer. In a trial of older patients with AML who were considered not able to tolerate intensive therapy such as the "7+3" that you will be getting, and instead received a less intensive standard treatment combined with a different immune activating agent, there was additional toxicity (side effects) that created concern that the treatment decreased survival. For this reason, we will be monitoring your toxicity very carefully. If you experience any concerning symptoms such as cough, shortness of breath, diarrhea, abdominal pain, or any other new or severe symptoms, you should contact your physician immediately.

Genetic Testing Risks

The genetic test used in this study will test your tumor for genetic alterations in frequently mutated genes in AML. Rarely, these genetic changes also may be present 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.

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 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.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. The biopsy needle will go through the skin into the bone and may produce a brief, sharp pain. Since the inside of the bone cannot be numbed, this procedure may cause some discomfort, however not all patients experience discomfort. The possible side effects associated with a bone marrow biopsy include pain, bleeding, bruising, and infection, as well as a reaction to the numbing agent. Pain can be treated with regular pain medications.

Common risks of a skin punch biopsy are a small amount of bleeding at the time of the procedure, bruising, pain, the possibility of an adverse reaction consisting of local swelling, bleeding, infection, and scar formation at the biopsy site. There also could be a small risk of infection. The pain associated with injection of a local anesthetic is mild and transitory. Allergic reactions to lidocaine, a local anesthetic cream, are extremely rare (less than 1 in 10,000). Occasionally, patients may get swelling at the injection site. Significant bleeding from the biopsy site(s) is rare and infrequent. A small scar will result at the biopsy site.

Blood Draw Risks

You may feel discomfort during some of the tests or procedures during this study or may experience some inconveniences. Some of the risks from drawing blood from your arm may include pain, bruising, lightheadedness, and rarely, infection. 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.

Transplant-Associated Risks

Stem cell transplant poses numerous risks. Some people experience minimal problems with a transplant, while others can have serious complications that require treatment or hospitalization. Sometimes, complications are life-threatening. Your particular risks depend on many factors, including the disease or condition that caused you to need a transplant, the type of transplant, and your age and overall health. Possible complications include graft-versus-host disease (GVHD; a disease caused when cells from a donated stem cell graft attack the normal tissue of the transplant patient), graft failure, organ damage, infections, infertility, cataracts, new cancers, death. There could be a concern that receiving Pembrolizumab (MK-3475) before transplant could increase risk of occurrence or severity of GVHD. However, in other early studies using other immune activating drugs in patients with AML who subsequently underwent stem cell transplant, it did not appear that there were significantly increased risks or severity of GVHD. Nonetheless, this remains a theoretical risk and the study and patients will be monitored closely for this issue.

Side Effect Risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

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

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

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

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

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Allergy Risk

All drugs have a potential risk of allergic reaction. Allergic reactions may range from mild (rash, hives) to severe (difficulties to breath, blood pressure collapse). A severe allergic reaction needs immediate attention and could results in permanent disability or death.

Drug Risks

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

Study Group 1 and Group 2 – Possible side effects of cytarabine and either daunorubicin or idarubicin are listed in the tables below. These drugs are part of the usual approach for treating this type of cancer:

Possible Side Effects of Cytarabine (Table Version Date: July 27, 2015)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, more than 20 and up to 100 may have:
• Blood clot • Rash • Swelling in the rectum which may cause rectal pain • Diarrhea, loss of appetite, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Anemia which may cause tiredness, or may require blood transfusions • Fever

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Cytarabine, from 4 to 20 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Numbness and tingling of the arms and legs • Severe blood infection • Kidney damage which may cause swelling, may require dialysis • Headache • Dizziness • Chest pain • Hair loss • Liver damage which may cause yellowing of skin or eyes • Swelling and redness of the eye

RARE, AND SERIOUS In 100 people receiving Cytarabine, 3 or fewer may have:
• Coma

Possible Side Effects of Daunorubicin (Table Version Date: October 10, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, more than 20 and up to 100 may have:
• Pink or red colored urine, sweat, or saliva • Nausea, vomiting • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Daunorubicin, from 4 to 20 may have:
• Damage to the heart which may cause shortness of breath, tiredness • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may require transfusion • Pain and sores in mouth and throat • Diarrhea • Redness and pain at the site of previous radiation • Swelling and redness at the site of injection • Loss of nails • Dark discoloration of the nail, skin

RARE, AND SERIOUS In 100 people receiving Daunorubicin, 3 or fewer may have:
• Cancer of the bone marrow (leukemia) caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Possible Side Effects of Idarubicin (Table Version Date: October 10, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Idarubicin, more than 20 and up to 100 may have:
• Pain • Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may cause tiredness, or may require transfusion • Headache • Diarrhea, nausea, vomiting • Hives • Redness, pain or peeling of palms and soles

COMMON, SOME MAY BE SERIOUS In 100 people receiving Idarubicin, more than 20 and up to 100 may have:
• Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Idarubicin, from 4 to 20 may have:
• Heart failure or attack which may cause shortness of breath, swelling of ankles, and tiredness • Abnormal heartbeat • Liver damage which may cause yellowing of eyes and skin • Sores in mouth which may cause difficulty swallowing • Reddish discoloration of the urine, sweat and saliva • Swelling and redness at the site of injection • Swelling and redness at the site of previous radiation • Loss of nails • Darkening of the skin and nails

RARE, AND SERIOUS In 100 people receiving Idarubicin, 3 or fewer may have:
• Cancer of the bone marrow (leukemia) caused by chemotherapy • Kidney damage which may require dialysis

Study Group 2 - In addition to side effects listed above, people who are in Group 2 may also have some side effects from Pembrolizumab (MK-3475). These side effects are listed below. Also, you may potentially require steroids if you develop immune related side effects related to Pembrolizumab (MK-3475).

``Possible Side Effects of Pembrolizumab (MK-3475) (CAEPR Version 2.9, August 14, 2024)

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab (MK-3475), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab (MK-3475), from 4 to 20 may have:

- Nausea
- Loss of appetite
- Pain in back
- Joint stiffness
- Swelling and redness of the skin

Pembrolizumab (MK-3475) 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:

- Anemia which may require blood transfusion
- Pain in lymph nodes
- Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness
- 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
- 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
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Pain in belly
- Sores in the bowels
- Chills, fever
- Reaction during or following a drug infusion which may cause fever, chills, rash, low blood pressure
- 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
- Pain or swelling of the joints
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving pembrolizumab (MK-3475), 3 or fewer may have:

- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss
- Inability to digest food which may cause bloating
- Swelling of the gall bladder
- Swelling of the spinal cord
- Feeling of "pins and needles" in arms and legs
- Redness, pain or peeling of palms and soles

Pembrolizumab (MK-3475) 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:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.
- Swelling and redness of the eye which may cause blurred vision with a chance of blindness
- Swelling of the bowels
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin
- Damage to organs in the body when the body produces too many white cells
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures and stiff neck
- 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.
- Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin rash developing 1-8 weeks after a drug is given which may be accompanied by fever, lymph node swelling and organ failure
- Swelling or tenderness of blood vessels

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Additional Drug Risks

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

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

- Keep your study appointments.
- Tell your doctor about:
    1. all medications and supplements you are taking
    2. any side effects
    3. any doctors' visits or hospital stays outside of this study
    4. 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 120 days after your last dose of study drug.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.
- the costs of getting the cytarabine and either daunorubicin or idarubicin ready and giving it to you.
- your insurance co-pays and deductibles.

There will be no charge to you or your insurance provider for the Pembrolizumab (MK-3475). There will be no charge to you or your insurance provider for tests or procedures noted with an asterisk (in the study calendar) as these are performed for study purposes only. All other tests and procedures will be charged to you or your insurance provider in the usual way as these are standard of care. This may include other tests and procedures not listed in this consent if your doctor feels it is necessary for your care, such as additional laboratory tests for monitoring your safety.

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 which are not standard of care. These include:

- The bone marrow biopsies after the last cycle of the second part of therapy (that is during your consolidation treatment) and at the end of the third part of the therapy.
- The bone marrow aspirations after the first cycle of the second part of therapy (that is during your consolidation treatment) and at the end of the third part of therapy.
- Blood sample collections as a part of research studies
- The optional CT scan of your chest
- The skin punch biopsy to before you begin study treatment

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.

*** You will be responsible for paying for the procedure if any or all the standard of care bone marrow samples are not reimbursed by your insurance company.

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

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case.

However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at or receive copies of some of the information in your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company supporting the study now or in the future. This would include any organization helping the company with the study.
- The NCI Central IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The U.S. Department of Health and Human Services (DHHS) agencies
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of 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 AML 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 and 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 collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Unknown future studies

If you choose to take part in this optional study, blood and bone marrow will be collected and stored. Storing samples for future studies is called "biobanking." The biobank is being run by 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. This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

Right now, we don't know what research may be done in the future using your blood and bone marrow samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your samples.

Unknown future research studies may include sequencing of all or part of your DNA. This is called genomic sequencing. Sequencing allows researchers to identify your genetic code. Changes in your genetic code may just be in your tumor tissue. These are called somatic changes. Changes may also be in your normal tissue and passed down through your family. For example, these genetic changes may be passed down to your children in the same way that eye and hair color are passed down. These are called germline changes.

If only tumor tissue is sequenced, we will not know if a genetic change in your tumor is also in your normal tissue. This is why sometimes both normal tissue and tumor tissue are sequenced.

This helps researchers understand if a genetic change happened only in your cancer tissue, or in your normal tissue as well.

What is involved in this optional sample collection?

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

1. About 2 additional teaspoons of bone marrow will be collected from your bones and will be sent to the biobank.
2. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to a bone marrow aspirate is a small amount of bleeding at the time of the procedure, bruising, and pain at the procedure site. Pain can be treated with regular pain medications. Rarely, an infection, significant bleeding, or collapsing of the lung can occur.
- 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.

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information. Only your study doctor and a few study researchers will have access to the master list linking the code numbers to names. The biobank and the genomic sequencing laboratory will receive your samples with the following information only: your sample code number; your age, race/ethnicity, and gender; your type of cancer; any previous treatments you received for your cancer; and the treatment you will receive for this current study.

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. The researchers must be trained in the handling of private information. Any researcher who wants to study your stored samples and genetic information must apply and be approved to do so.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance for exams, tests, and procedures done for research purposes only; these include the biopsy, blood draw, immune cell analysis, and biobanking of your specimen(s). You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, (*insert name of study doctor for main trial*), at (*insert telephone number of study doctor for main trial*), who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I need my tissue or blood samples to be returned?

Tumor tissue or blood samples that remain in the biobank can be returned if needed for medically necessary events or procedures to assure appropriate medical care, such as for DNA or RNA analysis. Specimens may also be returned if tissue is needed to determine eligibility for enrollment in a research protocol or clinical trial. Every effort will be made to facilitate medically necessary events or procedures to assure appropriate medical care for a patient with a serious or life-threatening illness.

Tumor tissue or blood samples and genetic material (DNA and RNA) that is no longer in the biobank or that has already been given to or used by researchers cannot be returned. No samples will be returned for matters related to patients needing or wanting genetic testing to determine medically important risks.

What if I have questions about this optional sample collection?

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

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

Samples for known future studies:

I agree that my samples and related health information may be used for the laboratory studies above.

YES NO

Samples for unknown future studies:

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

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Participant's signature

Date of signature

Signature of person(s) conducting the informed consent discussion

Date of signature

Attachment A: Study Calendar

	Before the Study	During the Study																			After the Study	
	Pre-Study	First Part of Therapy											Second Part of Therapy								Third Part of Therapy	After 6 months of treatment	After 1 year of treatment	End of Study	Post-Treatment Follow-Up
													Cycle 1				Cycles 2, 3, 4								
		D1	D2	D3	D4	D5	D6	D7	D8	D9	D14	D28	D1	D3	D5	D28	D1	D3	D5	D28					
Cytarabine		Continuous Infusion									X[a]		X	X	X		X	X	X						
Daunorubicin or Idarubicin		X	X	X							X[a]														
Pembrolizumab (MK-3475)* Only if you are randomized to Group 2									X----------Every 3 weeks----------X												X[l]				
Pre-study procedures including informed consent, demographics, eligibility, height, weight, and medical history	X																								
Concurrent meds		X----------X																							
Survival Status																									X
Mandatory Stool Collection[j]	X															X									
ECG (at pre-study and any time your doctor indicates it is necessary)	X																								
Vital signs and physical exam	X	X									X	X[c]				X				X	X			X	X
General well-being assessment	X											X[c]				X				X	X			X	
Side effects evaluation			X----------X																						

	Before the Study	During the Study																				After the Study	
	Pre-Study	First Part of Therapy											Second Part of Therapy								Third Part of Therapy	After 6 months of treatment	After 1 year of treatment	End of Study	Post-Treatment Follow-Up
													Cycle 1				Cycles 2, 3, 4								
		D1	D2	D3	D4	D5	D6	D7	D8	D9	D14	D28	D1	D3	D5	D28	D1	D3	D5	D28					
Blood draws for complete blood count and general health status	X	X	X	X	X	X	X	X	X[i]	X[i]	X	X[c]	X			X	X			X	X			X	X
Blood or urine collection for pregnancy test	X																								
Urine tests	X	X									X	X[c]				X				X	X				X
Thyroid tests[k]	X								X			X									X				
Mandatory skin punch biopsy	X																								
Mandatory bone marrow and blood draws for health and research purposes	X[g]										X[b]	X[c]								X[d,g]					
Mandatory bone marrow and blood draws for research purposes only*																X					X[e]	X[f,g]	X[f,g]	X[g]	
Optional bone marrow draws every 3 months, only when it is collected for health status																					X				
An exam to look at your heart (ECHO) or MUGA	X									X[h]															
An optional CT scan of your chest	X																								

a Only if you still have leukemia cells present.

b To be collected between Day 14 and Day 21.

c To be collected between Day 28 and Day 42.

d To be collected after last cycle of Second Part of Therapy only.

e Blood draws only.

f Only blood draws are mandatory. Bone marrow aspirate and biopsies are optional.

g Collection of both bone marrow biopsies and bone marrow aspirate.

h Repeat ECHO prior to starting the second round of the first part of therapy (5+2 chemotherapy).

i Only if you are randomized to Group 2.

j Stool specimen sample collected "before treatment/Pre-study" and again at the time of bone marrow collection after the completion of the first cycle of the second part of therapy (+/- 3 days).

k. For patients in Group 2, thyroid testing will be performed within 3 days of each pembrolizumab administration.

l. Day 1 of each 21-day cycle for up to 2 years.

* An asterisk indicates that there will be no charge to you or your insurance provider for that test or procedure.