NCI Community Oncology Research Program – Kansas City (NCORP-KC)

Informed Consent

Treatment Study

Study Title for Study Participants: Comparing New Treatment Options to One of the Standard Treatment Options for Older Patients with Newly Diagnosed Acute Myeloid Leukemia

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: S1612, A Randomized Phase II/III Trial of "Novel Therapeutics" versus Azacitidine in Newly Diagnosed Patients with Acute Myeloid Leukemia (AML) or High-Risk Myelodysplastic Syndrome (MDS), Age 60 or Older

What is the usual approach to my leukemia?

You are being asked to take part in this study because you have acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). Also, you and/or your doctor did not think you should get intensive chemotherapy. People who are not in a study are usually treated with single-agent chemotherapy such as azacitidine or decitabine, or with combinations of more intense therapies, that are approved by the FDA. There is not currently an FDA-approved medication for patients that have AML but who cannot tolerate intensive chemotherapy. These patients are usually treated with azacitidine or decitabine, or with palliative medications (medications to help with symptoms but that do not treat cancer). Your doctor should discuss with you what option he or she would recommend if you were not in a clinical trial. For patients who receive the usual approach for this cancer, anywhere from 0 to 10 out of 100 are free of cancer at five years.

What are my other 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.

Why is this study being done?

The purpose of this study is to compare any good and bad effects of using different new treatment options to one of the current standard treatment options given for patients with AML or MDS who cannot tolerate or do not want to get intensive chemotherapy. The investigators will keep testing new treatments to see if they have any different effects on

patients and their cancer when compared to the standard. Each patient will only get one type of treatment on the study. This is described more below. If one of the new treatments seems to help patients more than the current standard, the study will start to use that treatment as the new standard. If any of the treatments is not as helpful for any reason, or the bad effects are too severe, then that treatment will no longer be used in this study. The investigators want to use this study to find better treatment options for AML or MDS patients who do not get intensive chemotherapy.

At any time, the study will have one standard treatment group. The number of experimental treatment groups being tested at any time might be from one to four. The current standard treatment group and the experimental treatment groups that are currently open are discussed below. Some of the drugs used on the study are FDA approved to treat AML and/or MDS, and some are not. This is also discussed below.

There will be between about 500 and 1,556 people taking part in this study.

What are the study groups?

As discussed above, this study will have several treatment groups, but not all of them are going to be open at the same time. You can only take part in one of the currently open groups. The groups that are currently open are outlined below. Your doctor will decide whether you need to be admitted to the hospital for any part or all of your treatment.

- Group A will get the usual drug used for this type of cancer, azacitidine alone. Azacitidine is a drug used for this type of cancer when a person cannot get intensive chemotherapy safely. You will get the drug in cycles that are 28 days long. You will get the drug either as a shot under the skin or by an IV in your vein. You will get drug for 7 out of the first 12 days, and then have a break from the drug for the remainder of the 28-day cycle. Azacitidine has not been approved by the FDA to treat AML or all forms of MDS.

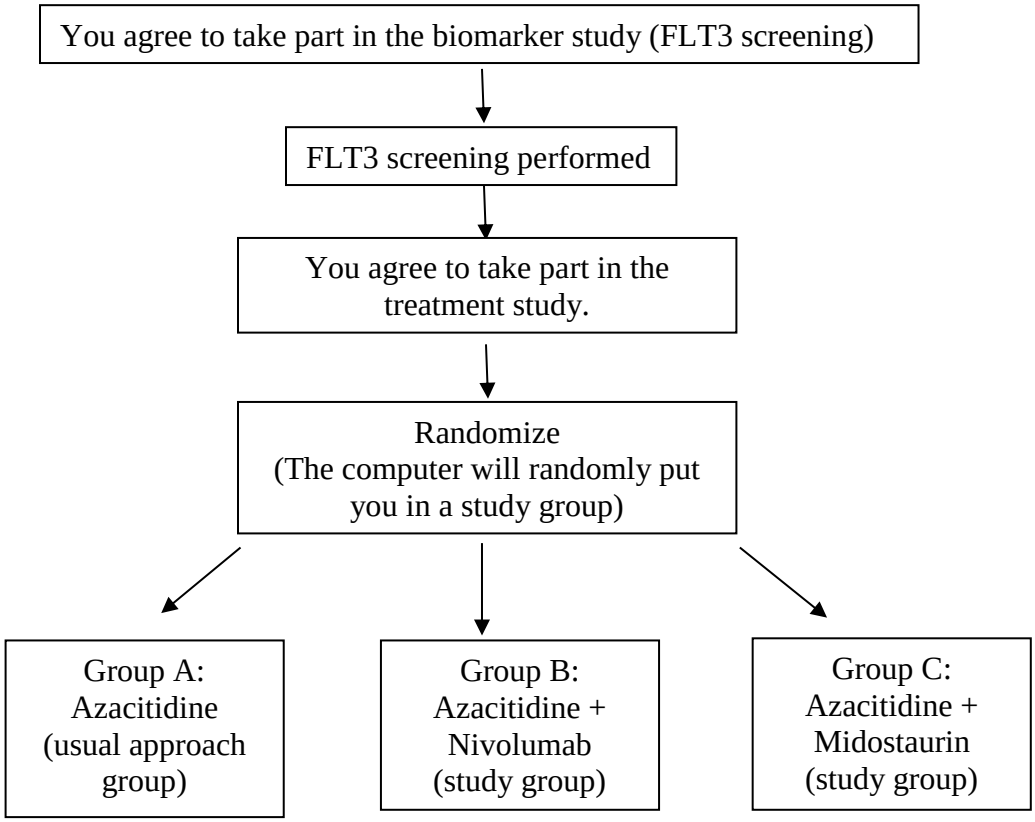
- Group B will get the usual drug used for this type of cancer, azacitidine just like Group A. Group B will also get a study drug called nivolumab. Nivolumab will be given by an IV into your vein on Days 1 and 15 of each 28-day cycle. Nivolumab is approved by the FDA to treat some types of cancers, but not AML or MDS.

- Group C will get the usual drug used for this type of cancer, azacitidine, just like Group A. Group C will also get a study drug called midostaurin. Midostaurin will be taken by mouth as capsules twice a day on Days 8-21 of each 28-day cycle. Midostaurin has been approved for use by the FDA for patients with FLT3 + AML (AML with a specific mutation in a gene called FLT3) when used in combination with the drugs cytarabine and daunonibicin, but not in combination with azacitidine.

The cycles for all study groups will repeat until your disease gets worse or your or your doctor decide that you should stop.

A computer will by chance assign you to one of these 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 others. Some study groups do not allow patients with certain physical conditions to participate. If you have one of the conditions, you can still be in the study, but the computer will not assign you to a study group that does not allow that condition.

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



How long will I be in this study?

You will receive the study treatment for as long as you and your doctor think the treatment is helping you. After you stop taking study treatment, your doctor will continue to watch you for side effects and follow your condition for up to 5 years after you are registered to the study. At minimum, you will have clinic visits every 3 months for the first year, every 6 months for the second and third years, and then annually until 5 years after you are randomized to study treatment .

What extra tests and procedures will I have if I take part in this study?

All of the exams, tests, and procedures you will have are part of the usual approach for your cancer.

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

If you choose to take part in this study, there is a risk that:

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**
- **The study drugs may not be better, and could possibly be worse, than the usual approach for your cancer.**
- **There is a risk someone could get access to the personal information in your medical records or other information researchers have kept about you. Someone might be able to trace this information back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with 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.** *[For non-U.S. participants, please verify the existence of such laws before including the following sentence.]* **There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.**
- **There can also be a risk in finding out new genetic information about you. New health information about inherited traits that might affect you or your blood relatives could be found during a study.**

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 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.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The 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 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.

STUDY GROUPS A, B, and C:

Possible side effects of azacitidine, the usual approach for this type of cancer:

Possible Side Effects of Azacitidine

COMMON, SOME MAY BE SERIOUS In 100 people receiving azacitidine, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, nausea, vomiting • Tiredness, fever • Swelling and redness at the site of the medication injection • Infection, especially when white blood cell count is low • Bruising, bleeding • Loss of appetite • Shortness of breath • Rash

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving azacitidine, from 4 to 20 may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Fluid around heart • Abnormal heartbeat • Swelling and redness of the eye • Pain • Heartburn, hemorrhoids • Difficulty swallowing or sleeping • Bleeding from multiple sites including the nose • Internal bleeding which may cause black tarry stool, blood in vomit, or coughing up blood • Sores in mouth • Chills • Swelling of the arms, legs • Weight loss • Muscle weakness • Dizziness, headache • Worry, confusion, depression • Cough, postnasal drip • Hair loss, itching • Increased sweating • Sores on the skin • Low blood pressure which may cause feeling faint • Pale skin

RARE, AND SERIOUS In 100 people receiving azacitidine, 3 or fewer may have:
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Kidney damage which may cause swelling, may require dialysis**

Reproductive risks: Men: You should not father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of pregnancy prevention to use while in this study.

STUDY GROUP B: -

In addition to side effects outlined above for azacitidine, people who are in Group B may also experience the possible side effects of nivolumab listed below. Some side effects of either drug might also be more frequent because of the drug combination.

Possible Side Effects of BMS-936558 (Nivolumab)

Special Precautions Side effects of BMS-936558 (nivolumab) may happen any time 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 BMS-936558 (nivolumab), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving BMS-936558 (nivolumab), from 4 to 20 may have:

- **Anemia which may require blood transfusion**
- **Swelling and redness of the eye**
- **Pain in belly**
- **Diarrhea, nausea, loss of appetite**
- **Dry mouth**
- **Fever**
- **Swelling and redness at the site of the medication injection**
- **Bruising, bleeding**
- **Pain or swelling of the joints**
- **Reaction during or following 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 urine; dizziness or fainting.**

RARE, AND SERIOUS **In 100 people receiving BMS-936558 (nivolumab), 3 or fewer may have:**
• **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** **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 inflammation 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 inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine** • **Inflammation of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck** • **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.** • **Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received BMS-936558 therapy, since the risk and severity of transplant-associated complications may be increased.**

<u>Additional Reproductive Risks for Group B</u>: Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 31 weeks after the last dose of nivolumab.

STUDY GROUP C: -

In addition to side effects outlined above for azacitidine, people who are in Group C may also experience the possible side effects of midostaurin listed below. Some side effects of either drug might also be more frequent because of the drug combination.

Possible Side Effects of Midostaurin

COMMON, SOME MAY BE SERIOUS In 100 people receiving midostaurin, more than 20 and up to 100 may have:
• **Diarrhea, nausea, vomiting**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving midostaurin, from 4 to 20 may have:
• **Anemia, which may require blood transfusion** • **Tiredness** • **Bruising, bleeding** • **Headache**

Additional Reproductive Risks for Group C: Sexually-active men must use a condom while receiving midostaurin and for five (5) months after the last dose. Vasectomized men must also use a condom to avoid delivering drug in the seminal fluid.

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.

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study drugs are 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.

Can I stop taking part in this study?

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.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the Central Institutional Review Board at 888-657-3711.

What are the costs of taking part in this study?

Nivolumab and midostaurin will be supplied at no charge while you take part in the study. The costs of getting nivolumab and midostaurin ready and giving them to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the drugs may not continue to be supplied while you are on the study. Although this is not likely, if it occurs, your study doctor will talk to you about your options.

Azacitidine is commercially available and will not be supplied. You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, 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 or hurt 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, SWOG, and any drug company 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.

Who can answer my questions about this study?

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).*

Release

By signing this form you authorize NCORP-KC to access and obtain information that is required for the study. this may include your medical records, labs, radiologic films and reports and pathology specimens. This authorization to disclose your medical records shall not expire, even upon death, unless specifically revoked in writing by you.

You will get a copy of this form. If you want more information about this study, ask your study doctor.

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 _____

Participant's signature_____

Date of signature_____

Person obtaining consent_____

Signature of person obtaining consent_____

Date of signature_____