Consent title: X16034: MLN9708 for the prophylaxis of chronic graft-versus-host disease in patient undergoing allogeneic transplantation

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Medical College of Wisconsin and Froedtert Hospital
CONSENT TO PARTICIPATE IN RESEARCH

Name of Study Subject: _____

X16034: MLN9708 for the prophylaxis of chronic graft-versus-host disease in patient undergoing allogeneic transplantation

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You are invited to take part in this research study. This form tells you why this research study is being done, what will happen in the research study, possible risks and benefits to you, your choices, and other important information. If there is anything that you do not understand, please ask questions. Then you can decide if you want to join this study or not.

A1. INTRODUCTION – WHY ARE WE ASKING YOU ABOUT THIS STUDY?

We invite you to participate in this study because you have had or plan to have an allogeneic (a bone marrow or peripheral blood stem cells from another person—usually a sibling but sometimes from an unrelated donor) transplant and are at risk of suffering a common problem called chronic graft-versus-host disease (cGVHD).

A total of about 58 people are expected to participate in this study at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the study is Mehdi Hamadani, MD in the Department of Medicine. A study team works with Dr. Hamadani. You can ask who these people are.

Millennium Pharmaceuticals, Inc. provides financial support to the Medical College of Wisconsin, including Dr. Hamadani and other key members of his/her study staff, for work on this study as well as others being conducted at the Medical College of Wisconsin. Previously a sub-investigator reviewed safety data for another Millennium study. This sub-investigator received compensation for the work he did reviewing the safety data.

A2. DO I HAVE TO BE IN THIS STUDY?

You can decide whether to take part in this study or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this study, you do not have to stay in it. You may stop at any time.

A research study is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the study procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS RESEARCH STUDY BEING DONE?

MLN9708 (ixazomib) is a new drug which so far has been mostly used in studies for multiple myeloma patients either alone or with other combination of drugs. To date approximately 300 patients have been treated with oral MLN9708 either alone or with other combinations of drugs.

Patients who undergo allogeneic transplants are at risk of suffering a common problem called graft-versus-host disease (GVHD). GVHD is a complication where the donor cells (graft) received during transplant attacks and damages the patient's (transplant recipient) tissues. GVHD can cause skin rash, intestinal problems such as diarrhea, nausea, vomiting and decrease liver function or liver failure, lung damage, dry eyes, dry mouth, tightening of skin, joint problems, increased risk of infections etc. These symptoms can range from mild to severe and may be life threatening and may be fatal in some cases. GVHD disease can occur early (within three months of transplant) or later after an allogeneic transplant). There are no approved therapies for preventing late (also called chronic) GVHD.

The purpose of this study is to learn if prescribing MLN9708 to you starting about two months after transplant will help prevent chronic or late form of GVHD. We also want to see if MLN9708 is safe to use in transplant patients.

MLN9708 is currently not approved by the Food and Drug Administration to treat or prevent GVHD. This means that the use of MLN9708 in this study is considered investigational (or experimental).

B1. WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

The study doctor or a member of the study staff will discuss with you the requirements for being in this study. They will evaluate your ability to be in the study.

Before you begin the study:

You will have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Baseline tests include:

- Medical history and physical examination (includes vital signs, height, weight, and current medications and your current GVHD status)

- Routine blood tests to check your blood counts, organ function and post-transplant status.
- A blood test to check for pregnancy for women of childbearing potential
- Karnofsky Performance Status (KPS) to see how well you perform daily activities
- GVHD Assessments

During the study:

If the exams, tests and procedures show that you can be in the study, and you choose to take part then you will be enrolled in the study.

Treatment: There is no universally accepted standard treatment to prevent GVHD, and different transplant centers in the country use a variety of treatments to prevent this complication. In this study you will be given the standard treatment normally provided at this site to help prevent GVHD. Your study doctor will help you understand the risks involved with these drugs as well.

You will take the usual (or standard) prophylaxis of GVHD until your doctor feels it is safe to quit taking it but in most cases it will be at least until Day 180 post-transplant.

The study consists of a phase I portion and a phase II portion.

Phase I
The purpose of the phase I portion of the study is to find out the maximum dose of study drug (i.e. MLN9708), which is safe for administration in post allogeneic transplant patients The first few patients enrolled will participate in the phase I part of the study. In phase I, the dose of the study drug is gradually and carefully increased in successive groups of 6-9 patients. Starting on day +60 to +74 after your allogeneic transplant, you will take MLN9708 by mouth on days 1,8,15 and 22. It was determined that the maximum tolerated dose is 4mg. Phase I is closed.

Phase II
The maximum safe dose was determined to be 4mg. All remaining patients will receive MLN9708 (ixazomib) 4mg in the phase II portion of the study.

You will start taking the MLN9708 study medication weekly for four weeks, approximately two to three months after your donor allogeneic transplant

You will need to keep taking MLN9708 (the study drug) until one of the following happens:

- You finish four weekly oral doses
- You develop a moderate grade of acute GVHD, which normally occurs within the first 100 days of the transplant

- You develop severe chronic GVHD
- You have a serious side effect or reaction to the study drug (MLN9708)

On Study Tests:

Post-transplant visits follow routine care practice at our center. The following routine clinical tests, procedures, and assessments may be done:

- Physical examinations (includes vital signs, height, weight)
- Routine blood tests to check your blood counts, organ function and post-transplant status.
- Karnofsky Performance Status (KPS) to see how well you perform daily activities
- Research blood samples
- GVHD assessments

We will talk to you about any side effects you may have experienced during this study at your normal clinic visits of hospital stays.

Follow-up:

During the follow up period we will follow you for disease status and GVHD status.

Samples for Optional Research

Throughout the study we would like to draw some of your blood and store it to do research related to this study. This will be stored in a laboratory at the Medical College of Wisconsin. We will keep these samples for as long as we need to complete the research. We will do tests to look at parts of your blood that might help us learn more about this study. The lab testing of your samples could involve both genetic and non-genetic tests. The genetic tests do not involve research about diseases being passed on in families.

Approximately 6 tablespoons will be collected at each visit during the two years you are in the study for the optional research samples.

You do not have to agree to store your blood for research to be in the main part of this study.

Please indicate next to one of the statements below whether or not you agree to allow storages of your samples for research related to this study.

Yes_____ No _____ I agree to allow blood samples to be stored for research.

B2. HOW LONG WILL I BE IN THE STUDY?

You will be in this research study for about 5 years.

B3. CAN I STOP BEING IN THE STUDY?

You are free to withdraw from the study at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the study doctor.

⇒ The doctor can tell you about the effects of stopping, and you and the doctor can talk about what follow-up care would help you the most.
⇒ You might be asked to come back for one more visit to check your health.

The study doctor may take you out of this study at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the study rules.
- The whole study is stopped.

If this happens, the study doctor will tell you.

B4. ARE THERE ANY SPECIAL INSTRUCTIONS WHILE I AM IN THE STUDY?

Patients should be instructed to swallow MLN9708 capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

MLN9708 should not be taken if you have ever had an allergic reaction to boron or boron containing products.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE STUDY?

There are risks to taking part in any research study. There is a risk that you may get a drug, drug combination or dose of a drug that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from drug itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the study for problems (side effects). **You need to tell the study doctor or a member of the study team immediately if you experience any problems, side effects, or changes in your health.** If you have problems, call Dr. Hamadani immediately at 414-805-6800. In an emergency, call 911.

C2. RISKS OF TREATMENT

The research drug itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away. Many go away soon after you stop taking the drug. Drugs can affect individuals in different ways.

Complications of some of the side effects below may lead to life-threatening events such and possibly death.

Side Effects of Study Drugs and Treatments

All drugs can have side effects, including the standard therapy for GVHD (steroids). Your doctor will watch you carefully and will change your treatment if side effects develop.

Infections

Because chronic GVHD is caused by an immune attack on your tissues from the transplanted donor cells, all treatments for chronic GVHD include drugs to control (suppress) that immune attack. There is a higher risk of infection in patients with chronic GVHD and in people who take steroids like prednisone or methylprednisolone, the standard therapy for chronic GVHD.

You will need to take several antibiotics to prevent infection. You will also be watched carefully for any infections while you are being treated for chronic GVHD. Tell your doctors promptly if you get a fever, chills, cough or any other symptoms that might be a sign of an infection.

Possible Discomforts and Risks of MLN9708 (Study drug)

There are risks to taking part in any research study. During the study, you may have problems or discomforts and risks from MLN9708, MLN9708 and other drug combinations, and/or study procedures. The more commonly occurring discomforts and risks are listed below, as are the rare but serious discomforts and risks. You should discuss these with your study doctor. There is always the possibility that unknown risks may occur, however your doctor will watch closely for problems or discomforts and risks.

If any discomforts and risks occur, you must tell your study doctor or study staff, even if you do not think they are related to the study drug.

Based on studies of MLN9708, it is possible to predict some of the discomforts and risks. However, it is possible that MLN9708 may cause risks that have not yet been observed in patients. The following risks might be seen:

- Low platelet count which may increase the chance of bleeding;
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
- Feeling tired or weak
- Nausea

- Vomiting
- Diarrhea
- Numbness or tingling or pain feelings in hands and feet
- Constipation
- Lowered red cells or anemia which may make you feel tired
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever

- Other discomforts and risks reported in studies with MLN9708, which may have been due to the patient's disease, MLN9708, other medications, or some combination of these include:

  - Not feeling like eating
  - Electrolyte imbalance (blood chemical imbalance)
  - Loss of water from the body (dehydration) because of vomiting and/or loose stools
  - High blood creatinine and renal failure which creatinine means your kidneys are having trouble working well; Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
  - Flu-like symptoms and other upper respiratory tract infections
  - Lung infections including pneumonia or pneumonitis
  - Chills
  - Pain in the abdomen or back
  - Swelling or fluid buildup in the arms or legs
  - Lowered blood pressure that can commonly cause you to feel light headed, faint or pass out when you stand up
  - Lowered white blood cells called lymphopenia
  - Pain (muscular) in extremities

The following discomforts and risks that occur with lesser frequency (<1%) than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience, we do not know if MLN9708 causes such diseases. Stevens Johnson's Syndrome, a severe, life-threatening or deadly condition that may involve rash, skin peeling and mouth sores has been reported in ongoing MLN9708 studies. Stevens Johnson Syndrome is a disorder of the immune system, which differs from a regular skin rash.

Toxic epidermal necrolysis (TEN) and DRESS syndrome have also been reported in MLN9708 studies. TEN is a disease that causes the top layer of skin to detach from the lower layers of the skin leaving the body susceptible to severe infection.

DRESS syndrome may cause rash, fever, inflammation of internal organs, enlarged lymph nodes and abnormalities In the blood.

In addition posterior reversible encephalopathy syndrome has also been reported with MLN9708 with lesser frequency (<1%). This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible.

Transverse myelitis, also a rare condition, is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving MLN9708. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether MLN9708 causes transverse myelitis, however, as it happened to a patient receiving MLN9708, we are not able to exclude the possibility that MLN9708 may have contributed to transverse myelitis.

PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1%) in patients taking MLN9708. It is not known whether MLN9708 may contribute to the development PML.

Other drugs and supplements may affect the way MLN9708 works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

C3. OTHER RISKS OF THIS RESEARCH STUDY

Other procedures that are part of the study also involve some risks:

Venipuncture: Although you may require a central venous catheter to donate cells, there may be an occasional need to have an intravenous catheter placed in your arm(s) or you may need to have blood withdrawn from the veins of your arm(s). Drawing blood from the arm may be associated with bleeding into the skin and may very rarely result in an infection.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant

The drugs in this study might affect a baby, before or after the baby is born. We do not know if the drugs causes harm to a baby, so we do not want anyone who might be pregnant to enter the study. You should not become pregnant or nurse a baby while in this study.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. You must tell the study doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the study.

You must have a negative pregnancy test prior to enrolling in the study.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see examples below).

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex or non-latex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

Risks of fathering a child
You should not father a baby while taking part in this study because it is unknown if the drugs in this study could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non-latex condom with a spermicidal agent) during the entire study drug treatment period, and for 90 days after completing study drug treatment. You must tell the study doctor right away if you think your partner is pregnant.

Highly effective methods	**Other effective methods (barrier methods)**
Vasectomy	Latex or non-latex condom with or without a spermicidal agent
	Diaphragm with spermicide; Cervical cap with spermicide; Sponge with spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

If you think that you have fathered a baby while you are taking this experimental drug or within 90 days after you have stopped taking it, we ask that you inform the study doctor immediately. At that time the study doctor will ask permission of your partner for the use and disclosure of her health information regarding the pregnancy. She will be asked to sign a separate consent form. She can choose to do this or not. She will be asked to sign this form to allow your study doctor to contact her obstetrician to collect information on the progress of the pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring.

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE STUDY?

We don't know if this study will help you. Your condition may get better but it could stay the same or even get worse. We hope the information from this study will help us prevent late GVHD. Information obtained from this study may benefit other patients in the future.

D1. ARE THERE ANY COSTS TO BEING IN THE STUDY?

Most of the medical care that you will receive in this study is considered routine care for your condition and would be recommended whether you join the study or not. Costs for routine care will be billed to you or your insurance carrier.

Activities / costs that are part of the study will not be billed to you or your insurance company. These are the study drug MLN9708,and the processing and storage of research samples.

Some insurers will not pay for drugs, tests or hospitalization that are part of research studies, so check with your insurer before you join this study. If you have questions regarding study costs, please contact Dr. Hamadani.

If you participate in this research study, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance

D2. WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

There is no payment for being in this study

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this study. You are free to say yes or no. If you do not join this study, your doctor can discuss other healthcare choices with you.
Your other choices may include:

- Routine care for this condition or symptoms
- Joining a different research study

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE STUDY?

If we learn any important new information about the drug that might change your mind about being in the study, we will tell you about it right away. You can then decide if you want to stay in the study.

D5. WHAT HAPPENS IF I AM HARMED BECAUSE I TOOK PART IN THE STUDY?

Emergency medical treatment for injuries directly related to your participation in this research study will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this study, contact the study doctors right away. Contact information: Dr. Hamadani at 414-805-6700.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

- If you have more questions about this study at any time, you can call Dr. Hamadani at 414-805-6700.
- If you have questions about your rights as a study participant, want to report any problems or complaints, obtain information about the study, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this study?

To do this research study, we need your permission to collect and use some of your health information, or you cannot be in the study. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the study.

The health information to be collected and used for this study is:
All or portions of your medical chart:

- ⇨ Hospital/Medical Records
- ⇨ Physician/Clinical Records
- ⇨ Lab and/or Pathology Reports
- ⇨ Radiology Reports
- ⇨ Biological Samples

E2. Who will see the health information collected for this study?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the study team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The study team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this study. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this study, we plan to share information with those doctors, researchers or government representatives working with us on this study at the institutions or companies listed here:

- U.S. Food and Drug Administration, Rockville, MD
- Millennium and its collaborators or designees
- Representatives of Central Laboratories
- Any Independent ethics committee, which approved this study
- Other Regulatory Agencies and/or Their Designated Representatives
- Those required by law

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different study without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed, the information might be used or released for other purposes without asking you. Results of the study may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?
One risk of taking part in a research study is that more people will handle your personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the study doctor about whether this could apply to you.

E4. How long will you keep the health information for this study?
If you sign this form, we plan to keep your information without any end-date in case we need to check it again for this study.

E5. Can I cancel my permission to share this health information?
If you change your mind later and do not want us to collect or share your health information, you need to send a letter to:

Mehdi Hamadani, MD
Froedtert & Medical College of Wisconsin
Division of Hematology and Oncology
9200 W. Wisconsin Avenue
Milwaukee, WI 53226

The letter must say that you have changed your mind and do not want the researcher to collect and share your health information. At that time, we may decide that you cannot continue to be part of the study. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE STUDY

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 look up this study by referring to the ClinicalTrials.gov number (NCT02250300) or by asking the study team for a printed copy.

CONSENT TO PARTICIPATE IN THE STUDY

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The study's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the study team use and share the health information and other information gathered for this study.
- I voluntarily agree to participate in this research study. I agree to follow the study procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**
Name of Legally Authorized Representative (if applicable) *please print*	**Signature of Legally Authorized Representative**	**Date**
Name of Witness (if applicable**)** *please print* (for short form consent process, or consent of blind or illiterate subject)	**Signature of Witness**	**Date**
*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the study team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. In all research study protocols the Principal Investigator is responsible and accountable for the study.*