ID: UMCC 2012.025

NCT01750567

A Pilot Study of Metformin Therapy in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL) and Untreated CLL

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:

A Phase II Pilot Study of Metformin Therapy in Patients with Relapsed Chronic Lymphocytic Leukemia and untreated CLL patients with genomic deletion 11q

1.2 Company or agency sponsoring the study:

There is no company or agency sponsoring this study.

1.3 Names, degrees, and affiliations of the researchers conducting the study:

Study Team:

Sami Malek, MD Department of Internal Medicine, Division of

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Metformin is an anti-diabetic drug which has shown to decrease levels of circulating insulin, as well as to reduce cancer cell growth. It is a generally well tolerated drug in both diabetics and non-diabetics. This research study is being done to learn what the effects of treatment with Metformin on chronic lymphocytic leukemia are and to learn whether this medication delays progression of the disease.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your medical treatment does not depend on your participation in this study.

3.1 Who can take part in this study?

You are being asked to participate in this study because you have chronic lymphocytic leukemia and do not currently have symptoms from this disease.

3.2 How many people (subjects) are expected to take part in this study?

Approximately 40 subjects are expected to participate, all within the University of Michigan Comprehensive Cancer Center.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

You will take Metformin by mouth every day and the dose will be increased to twice a day as tolerated. You will have your blood drawn for various tests, including tests to determine how you handle the drug's effect on blood sugar and to uncover what determines your possible response. The total blood volume will be approximately 10-15 cc or 2 to 3 teaspoons per visit.

We will draw blood samples for laboratory tests prior to starting Metformin and at 3 months, and 6 months while on Metformin, and every 3 months thereafter if therapy is continued. You will be followed up with outpatient clinic visits every 3 months while on Metformin. Each clinic visit is expected to last about 30-60 minutes.

Prior to therapy, at 3 months and at 6 months, we will also draw fasting blood samples in the morning (after an overnight fast of at least 10 hours) and draw blood samples 1 hour and 2 hours after giving you a sugar drink. This particular study will only occur 3 times during the study. Each of these visits is expected to last at least 2 hours. The total blood volume will be approximately 20 cc or 4 teaspoons per visit.

The purpose of some of these blood tests is to see if variations in your genes can help us determine your disease susceptibility and for measuring how well this drug therapy helps your CLL.

You will also fill out a simple medication diary form at home to keep track of how many Metformin pills you are taking. You will bring this form and your Metformin pill bottles to your clinic visits.

4.2 How much of my time will be needed to take part in this study?

Each subject will take Metformin for at least 6 months and have at least 3 clinic follow up visits (prior to starting, at 3 months, and at 6 months).

These visits are expected to take 30-60 minutes.

Blood draws to measure blood sugar levels (after fasting and taking a sugar drink) will take approximately 2 hours total (only during the 3 times we perform a fasting study in the first 6 months of the study).

4.3 When will my participation in the study be over?

The study will continue for at least 6 months (or less if you do not respond, have any severe adverse events, or decide to discontinue the study).

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks of Metformin are:

Most common side effects (occurring in more than 10% of patients):

- gastrointestinal upset (diarrhea, nausea, vomiting)
- flatulence

All doses of Metformin should be taken with meals to reduce this risk.

Less common side effects (1-10% of patients):

- chest discomfort
- flushing
- palpitation
- headache
- chills
- dizziness
- lightheadedness
- rash
- indigestion
- abdominal discomfort
- abdominal distention
- abnormal stools
- constipation
- heartburn
- taste disorder
- muscle pain
- shortness of breath
- upper respiratory tract infection
- excessive sweating
- flu-like syndrome
- nail disorders
- low glucose levels (very rare if you are eating meals on a regular basis)
- weakness

There is also a risk of vitamin B12 deficiency, which is mild and causes low blood counts; however, this can be treated if diagnosed.

Rare side effects (less than 0.01%) include:

- leukocytoclastic vasculitis (inflammation of the small blood vessels in the body)
- megaloblastic anemia (a blood disorder in which there is anemia with larger-than-normal red blood cells)
- pneumonitis (inflammation of lung tissue)
- lactic acidosis, which is a very rare but serious metabolic disorder. For this reason, we do not give this drug to patients with renal failure. The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as:
    - Feeling tired (malaise)
    - Muscle pain (myalgia)

- Breathing problems (respiratory distress)
- Feeling frequently sleepy (increasing somnolence)
- Stomach ache (nonspecific abdominal distress)
- Feeling cold (associated hypothermia)
- Low blood pressure (hypotension)
- Slow heart rates (resistant bradyarrhythmias)

If you experience any of these symptoms, notify your physician immediately.

There is a very low risk of reducing your blood glucose (sugar) levels while on this medication if you are consistently eating a regular diet. You should notify us if you are losing your appetite or decreasing your food intake. If you are feeling lightheaded or dizzy, or feel like you are going to pass out, you should check your blood glucose with a glucometer at home, and drink fruit juice immediately. Glucometers will be provided in the clinic when you start the medication.
You should be immediately evaluated in the emergency room if you have a hypoglycemic episode and symptoms. You should notify your doctor if you are having recurrent episodes while participating in this study.

You should not drink alcohol to excess while taking Metformin and the tablets should not be crushed or chewed.

If you undergo a contrast study (CT, angiography, etc.) or elective surgery, Metformin should be held prior to this procedure and for at least 48 hours, and may resume if there is no concern of kidney failure.

You should also notify us if you have a new diagnosis of diabetes during the course of your therapy, as other diabetic medications can lower your glucose levels.

Reproductive Risks
Based on FDA (Food and Drug Administration) criteria, Metformin is generally considered safe during pregnancy. However, there could be unforeseen risks to a fetus in this study. If you are taking part in sexual activity that could result in pregnancy, you and/or your partner are advised to use at least one acceptable method of birth control (i.e. condom, IUD, pill, vasectomy) while taking part in this study.

Nursing Mothers
Because the potential for hypoglycemia in nursing infants may exist, Metformin should be used with caution by nursing mothers.

Genetic Analysis
A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.
Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

As with any research study, there may be additional risks that are unknown or unexpected.

You should notify your primary doctor that you will be taking Metformin.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. If we find that Metformin therapy significantly delays progression of CLL, this would be a potential benefit of the research for you and other CLL patients.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Ask the researchers or your doctors about other options you may have.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If

you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information” (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

There should not be any harm to you. However, we would like to draw blood for tests 4 weeks after you stop Metformin.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers’ number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan’s medical reviewer.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Malek immediately, at 734-763-2194. The doctor will either treat you or send you to another doctor for treatment.

You will get free medical care at the UMHS for any hospitalization directly caused by the study drug, device, or procedure. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study.

The UMHS will pay for your treatment only if it has been caused by the study drug, device or procedure. This means that you or your health plan must pay for any treatment that is part of your usual medical care or that is related to a medical condition you had before participating in the study

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

No. You will not be paid for taking part in this study.

8.3 Who could profit or financially benefit from the study results?

No person or organization has a financial interest in the outcome of this study.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the researchers to link the information to you. However, if the researcher orders any tests, the order and results may become part of your regular medical record.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- Your AIDS/HIV status
- All records relating to your chronic lymphocytic leukemia, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may

no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

In case you decide to cancel your participation in the study, we will stop treating you with Metformin and will not draw additional blood samples. If we have already obtained research results, then these will be kept and used to preserve the scientific value and integrity of this study. Unused samples will be destroyed.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator:	Sami Malek, MD
Mailing Address:	Cancer Center Floor B1 Reception B 1500 E Medical Center Dr SPC 5911 Ann Arbor, MI 48109
Telephone:	734-763-2194

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth RoadBuilding 520, Room 3214
Ann Arbor , MI 48109-2800

Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Medication Diary

12. SIGNATURES

Research Subject:
I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with Dr. Malek or his designee. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Name (print legal name): _____

Signature of Subject: _____

Date of signature: _____

Patient ID: _____ *Date of Birth (mm/dd/yyyy):* _____

Principal Investigator (or Designee):
I have given this research subject (or his/her legally authorized representative, if applicable) information about this study that I believe is accurate and complete. The subject has indicated that he or she understands the nature of the study and the risks and benefits of participating.

Name: _____

Title: _____

Signature: _____

Date of Signature: _____

Witness (optional):
I observed the above subject (or his/her legally authorized representative, if applicable) sign this consent document.

Name: _____

Title: _____

Signature: _____

Date of Signature: _____

PERSONAL CENSUS FORM

Study #UMCC: 2012.025

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]
2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as "Haitian" or "Negro" are sometimes used in addition to "Black" or "African American.")

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" is sometimes used in addition to "Hispanic" or "Latino."