PRINCIPAL INVESTIGATOR: Clare Sun, M.D.

STUDY TITLE: Natural History Study of Monoclonal B Cell Lymphocytosis (MBL), Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), Lymphoplasmacytic Lymphoma (LPL)/Waldenström Macroglobulinemia (WM), and Splenic Marginal Zone Lymphoma (SMZL)

STUDY SITE: The National Institutes of Health (NIH), Clinical (CC)

Cohort: Standard

Consent Version: 08/02/2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Clare Sun, MD, tel: 301-402-2399, email: clare.sun@nih.gov

Study Coordinator: Susan Soto, RN, M.S.N., tel: 301-402-0797, email: sotos@nhlbi.nih.gov

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

We are conducting a variety of laboratory research experiments that require blood, bone marrow, tissue samples and/or imaging studies from patients diagnosed with monoclonal B cell lymphocytosis (MBL), chronic lymphocytic leukemia (CLL), Small Lymphocytic Lymphoma (SLL), lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM), or splenic marginal zone lymphoma (SMZL)

Why are you being invited to participate?

You have been diagnosed with MBL/CLL/SLL/LPL/WM/SMZL, If you choose to participate, you will undergo tests and procedures designed to evaluate the status of your disease. You will also have the opportunity to donate samples which will be sent to investigators at National Heart Lung and Blood Institute, National Institutes of Health to be used strictly in laboratory research experiments. The laboratory experiments performed on your samples will help us better understand MBL/CLL/SLL/LPL/WM/SMZL, and know more about how cancer cells survive and grow and how your immune system is affected.

How many people will take part in this research study?

1000 patients with MBL/CLL/SLL/LPL/WM/SMZL will take part in this research study.

How long will you take part in this research study?

Your participation on this protocol will continue until you withdraw from the study or the study is closed, at which time your participation will end. We may also withdraw you from the study if it is determined to be in your best interest.

What do we do to decide if you are eligible for this research study?

The results of the assessments (history, physical examination, and laboratory testing) completed on the screening protocol indicate that you meet the criteria for participation on this study.

What procedures are involved in this research study?

The following assessments are routinely performed in patients with MBL/CLL/SLL/LPL/WM/SMZL and will typically be done every 6 to 12 months during the first 2 years and every 12 to 24 months thereafter as part of your participation on this study

History and Physical Examination: A physician or nurse practitioner at the NIH will review your medical history with you, and you will have a physical examination every 6 to 24 months.

Blood Tests: About 4-20 tablespoons of blood will be drawn every 6 to 24 months to monitor your disease and for laboratory research purposes. Blood samples will be used to evaluate blood counts, liver and kidney function, presence of infectious diseases, and presence of specific abnormalities in a variety of genes.

In certain instances (e.g., public health crisis), we may conduct assessments via an NIH approved telehealth platform.

The following assessments are not routinely performed in patients with MBL/CLL/SLL/LPL/WM/SMZL but may be requested:

Lymphapheresis*:* The procedure for obtaining blood cells through leukapheresis is a very common procedure that is done routinely here in the Clinical Center with very few risks. White blood cells (lymphocytes) are removed from you using a serum cell separator machine. This requires putting a needle into your arm to obtain blood to go into the machine. The machine divides whole blood into red cells, plasma (the liquid part) and lymphocytes (white cells). The lymphocytes will be taken out,

and the plasma and red cells returned to you through a second needle in your other arm. The procedure takes between 4-6 hours to complete.

Imaging studies that provide detailed pictures of the inside of your body, are routinely performed for monitoring of CLL/SLL/LPL/WM/SMZL. We plan to perform a CT scan within the first 2 years on study and if you have large lymph nodes we may also recommend doing a PET scan. If you likely have MBL, a CT scan will be done to rule out that there are enlarged lymph nodes. In MBL we do not do PET scans. Scans may be repeated if medically necessary.

Computerized tomography (CT) scan of the neck, chest, abdomen and/or pelvis provides detailed pictures of the inside of the body and uses radiation, similar to an X-ray. CT scans may be done with or without an oral or intravenous contrast agent. The scan may take between 30-90 minutes to complete depending on the areas of the body being scanned and the type of scanner.

Positron emission tomography (PET) scan is another way to monitor disease activity. Rapidly growing tissue, such as cancer, takes up and uses more sugar than normal tissue. To detect areas of rapidly growing tissue, we will inject a radioactive sugar into the body through a vein. Then we will use a special scanner that senses the uptake of the radioactive sugar to produce images identifying areas of rapidly growing tissue in the body.

Tissue collection: While your donation of cellular products is essential to the purpose of this study, you may refuse these tests and still be eligible to participate in the study.

Saliva (preferred) and/or buccal swab: We may scrape the inside of your cheek with a soft cotton swab to obtain cells. If we do not use a cotton swab to collect cheek cells, we may ask you to spit into a cup to collect saliva.

Bone marrow aspiration and biopsy: A bone marrow biopsy and aspiration may be required for the diagnosis of CLL/SLL/LPL/WM/SMZL and can provide important additional information. We will ask you to undergo such a biopsy within the first year in this protocol. Whenever we ask you for such a biopsy we will be clear whether it is necessary for a medical purpose or whether it is proposed for research.

To collect bone marrow, an area of the hip bone on the backside is injected and numbed with xylocaine, a local anesthetic. There may be some temporary stinging and burning. When the area is numb, a thin hollow needle is passed through the skin and into the bone. Then, a sample of the bone marrow is removed through the needle. The amount of marrow taken is very small (about ½ to 1 teaspoon) and will not change your body's ability to form blood cells. Between two and four such aspirates may be obtained for each bone marrow procedure. The bone marrow biopsy removes a small piece of bone with marrow inside. This piece has about the thickness of a lead inside a pencil and may be up to one inch long. A second piece may be requested for research. The amount of bone removed does not affect bone stability or bone marrow function.

The bone marrow procedure may be done using local anesthesia at the bedside or if necessary using conscious sedation in the day hospital, operating room, or intensive care unit. You would receive two drugs that sedate, relax, and prevent any memory of the procedure, but they do not completely put you to sleep. Sedation is performed in the intensive care unit to allow close monitoring of breathing. The drugs wear off in a few hours, allowing return to the regular hematology unit or home if you have an escort with you. You will be asked to sign a separate consent form for the bone

marrow aspiration and biopsy and for the conscious sedation if used.

Lymph node biopsy: A lymph node biopsy is usually not required for diagnosis, but can provide important additional information. We may ask you to undergo such a biopsy on this protocol. Whenever we ask you for such a biopsy, we will be clear whether it is clinically indicated or for research. The lymph node biopsy allows us to compare cancer cells to those obtained from blood or bone marrow. We have found that cancer cells receive signals from the lymph node that let them survive and grow. We therefore think that lymph node samples are important to study. Lymph node biopsy for research will only be performed in patients who have lymph nodes that can be sampled by an outpatient interventional radiology or surgical procedure. We will perform a maximum of two lymph node biopsies during your participation in this study and will ask for your permission each time. Because the lymph node biopsy is a surgical procedure, a separate consent (obtained by the physicians performing the procedure) would be obtained prior to the procedure. A lymph node biopsy may become necessary for medical reasons, for example to rule out an infection, and such a biopsy would be recommended to you as clinically indicated.

In a **core needle biopsy,** a thin needle is inserted through the skin to remove cells.

In an **open biopsy,** tissue is removed through a cut in the skin. This can be done under local anesthesia. While somewhat more cumbersome, the value of this biopsy for diagnostic evaluation and for research is greater.

Genomic Testing

Tumor and blood samples collected for research purposes on this study may be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. While normal tissue contains the DNA (instructions) that you were born with, DNA in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow. RNA (also called ribonucleic acid) carries the instructions from the DNA to the parts of your cells that make proteins.

To look at your DNA and RNA, we may use do what is called "DNA or RNA sequencing." This is where we will do special tests in the lab to look at the sequence, or order, of how your DNA or RNA are put together. This is what makes you unique.

To determine which parts of the DNA or RNA have mutated, we will compare the DNA or RNA in your tumor cells to DNA or RNA from normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA or RNA that are common to a particular type of tumor.

However, you should know that the analyses that we perform in our laboratory are for research purposes only; they may not be as accurate as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you, and this is described later in this consent form in the section called "Will the results of the laboratory research studies be shared with you?".

WHAT ARE THE RISKS AND DISCOMFORTS OF THIS RESEARCH STUDY?

Related to blood sampling

Side effects of blood sampling include pain and bruising in the area where the blood was drawn, lightheadedness, or rarely fainting due to transient lowering of blood pressure. If you feel dizzy, you should lie down for a few minutes to avoid hurting yourself if you fall. Infection at the blood-drawing site could also occur.

Related to imaging studies:

CT scan: You will receive oral and intravenous contrast agents to enhance the pictures taken during the scan. Oral and intravenous contrast agents are usually well tolerated. However, some patients will experience allergic reactions to intravenous contrasts. To lower the risk of allergic reactions, the NIH Clinical Center uses contrast agents that are not likely to cause a reaction. Approximately 2% to 7% of patients who receive contrast agents will experience a temporary reduction in kidney function lasting up to 2 weeks following infusion. In rare instances, permanent renal damage can result from the use of the IV contrasting agent; therefore, if you have impaired kidney function, we may not use intravenous contrast. Total radiation dose from CT is 1.3 rem.

PET imaging: You may develop swelling or pain at the injection site. The radiation dose from this procedure is 1.32 rem.

Total radiation from imaging studies.

During your participation in this research study, you may be exposed to radiation from CT scan and Pet scan each year. The amount of radiation exposure from these procedures is equal to approximately 2.62 rem. A rem is a unit of absorbed radiation.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT and PET scan that you get in this study will expose you to roughly the same amount of radiation as 9 years of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

Related to tissue procurement procedures

Bone marrow aspiration and biopsy. You may feel a pulling sensation and brief discomfort as the marrow is withdrawn and a pressure sensation when the needle is being inserted. The amount of marrow taken is very small and will not change your body's ability to form blood cells. Potential complications of this procedure are local bleeding and infection. Both of these are very rare. Bleeding can be stopped by applying local pressure and an infection can be treated with antibiotics. If the aspiration is done from the breast bone, an additional potential

very rare complication of this procedure is nicking a large blood vessel near the breast bone which may lead to bleeding into the chest. If this happens, it could lead to the placement of a tube into your chest until the injury heals.

Lymphapheresis

The risks of leukapheresis include pain, bruising, lightheadedness or dizziness, nausea, vomiting and chills. Bruising may last up to 72 hours.

Tingling around the mouth, fingers, or toes and mild muscle cramps may develop from slight lowering of the blood calcium by the blood thinner used during the procedure. These symptoms can be treated by either temporarily stopping the procedure or by giving a calcium pill. Leukapheresis uses a completely closed sterile system. The risk of infection is minimized by cleaning the skin before the needle stick. No infections from leukapheresis have been noted in thousands of such procedures performed over the last 10 years at the NIH.

Rarely, there can be a malfunction of the apheresis machinery that might prevent the return of your blood being processed in the machine. The amount of blood lost would be very small and not harmful. It is also rare for people to faint, have seizures, or have air trapped in the bloodstream.

Temporary or permanent nerve damage may occur at the needle placement sites. This is very rare. At the NIH, to this point, there have been no cases of permanent nerve damage with leukapheresis.

During the leukapheresis procedure, your platelet count may decrease because platelets are collected with the white blood cells. Platelets are cells that help your blood to clot. Taking aspirin in combination with a lowered platelet count may increase your chance of developing bleeding. Therefore, you should not take aspirin or aspirin-containing drugs for 2 weeks after the procedure without physician approval.

Saliva (preferred) and/or buccal swab

There are no known risks to buccal swab and providing a sample of saliva. We may perform DNA sequencing to evaluate lymphoma and leukemia-associated genetic mutations. The samples you donate are used for research and not as part of clinical testing. Therefore, we do not intend to report genetic mutations identified from these studies to you.

Lymph node biopsy

There are several ways to do a biopsy.

During a **core needle biopsy,** a thin needle is used to remove cells. Patients will feel only a quick sting from the local anesthesia used to numb the skin and may feel some pressure from the biopsy needle. After a core needle biopsy, the site may be tender for 2 to 3 days.

During an **open biopsy,** tissue is removed through a cut in the skin. This can be done under local anesthesia. After the open biopsy, the biopsy site may feel tender, firm, swollen, and/or bruised. Subjects may be advised to not do any heavy lifting or other activities that stretch or pull the muscles around the area. As patients are at risk of infection at the biopsy site, we will show you how to care for the site and ask you to report any swelling, redness, or discharge to the research team so that appropriate antibiotics can be started if necessary

Related to genetic testing

Privacy risks associated with genetic testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives.

Are there any benefits to you if you take part in this research study?

This is a natural history study and there is no direct benefit to you from participation on this study. You will receive evaluation and monitoring of your MBL/CLL/SLL/LPL/WM/SMZL by medical experts. The use of your specimens for research purposes will not benefit you. However, your participation in this protocol may contribute to advances in the understanding and development of treatments for MBL/CLL/SLL/LPL/WM/SMZL.

Are there reasons that your research participation may end early?

Participation in this investigational treatment protocol is voluntary; you may discontinue your participation in the protocol at any time. There are no penalties imposed for withdrawing from the protocol. You may refuse any of the research procedures (biopsy, apheresis, etc.) and still remain a part of this study.

What will happen when the research study is over?

When the protocol is closed, data and sample analysis will continue for some time. Your samples will be kept until they are no longer of scientific value, at which time they will be destroyed.

Will your clinical and test results be shared with you?

Your clinical information, such as how quickly your disease progresses, will be correlated with findings in the laboratory. Any significant new findings that relate to your disease will also be discussed with you. The results of all clinical testing will be shared with you, and you may request a copy of all clinical findings through the NIH Medical Records Department, Release of Information Office 301-496-3331.

Will the results of the laboratory research studies be shared with you?

Results of some tests we do for research will be discussed with you whenever possible. For many other laboratory research studies it is very unlikely that what we learn will be directly applicable to you or of direct benefit to you; therefore, the results of these tests will not be reported to you. However, the information learned from these studies may benefit other patients in the future. The results from studies may be published, but you will not be identified in the publications. By agreeing to participate in this study, you do not waive any rights that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Sun.

We do not plan to give you any individual or summary results from genetic sequencing. This is because it will probably take a long time for this project to produce health-related information that we will know how to interpret accurately.

Will any of your blood, tissue or other samples be stored and used for research in the future?

Research samples are stored in our laboratory, under the care and supervision of the investigators on this protocol for use in future research. Some of the samples are assigned a unique code known only to the investigator, which will serve as a link to you. Other samples have no code and no way of linking your name to the sample. Some of your sample may be provided to other investigators, without any personal identifying information, meaning these samples could never be traced back to you. If the investigator is from outside the NHLBI, before your sample is sent, the outside investigator will be required to sign an agreement detailing the tests he or she will be allowed to conduct on your sample and the Institutional Review Board (IRB) will be notified. It is also possible that the stored specimens may never be used.

Genomic Data Sharing

As part of this study, we will put your genomic data in a large database which will be freely available to the public. These databases are commonly called data repositories. These data are intended for other researchers to use and learn from but anyone can gain access to them, including law enforcement. The information in this database will include but is not limited to genetic information, race, ethnicity and sex. If your individual data are placed in one of these repositories, they will be labeled with a code and not with your name or other information that could be used to easily identify you. This information when combined with information from other public sources could be used to identify you, though we believe it is unlikely that this will happen.

Summary information about all of the participants included in this study (including you*)* is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

What other choices do you have?

As this is not a treatment protocol, your alternative is to choose not to participate. MBL is thought to be a precursor state to CLL/SLL, for which there is no standard treatment at this time. However, if your CLL/SLL/LPL/WM/SMZL progresses and requires treatment, the following treatment approaches include:

- Cytotoxic chemotherapy
- Monoclonal antibody therapy

- Small molecule inhibitors
- Radiation (X-ray) treatments
- Bone marrow transplantation
- Experimental therapy
- No therapy

Making your decision

If you have any questions, please talk to your doctor or nurse. No matter what you decide to do, it will not affect your care. You will be given a copy of the consent for your records.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

The reimbursement will be consistent with NHLBI Travel and Lodging Compensation of Clinical Research Subjects policy.

Participants will be reimbursed for hotel and travel. Receipts must be provided for all expenses.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

Your medical care and the costs of the laboratory and radiographic studies done at the Clinical Center, NIH will be at no expense to you. The NIH cannot, however, reimburse you for the costs of other types of medical care delivered outside the NIH, even if you are seeking medical attention as a result of side effects from a procedure done here, unless permission is granted in advance by the principal investigator of this study. Similarly, we do not ordinarily reimburse the costs of diagnostic radiology tests (such as CT scans, MRI, or chest X-rays) done outside the NIH, even if they are done for the purposes of this study (for example MRI).

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. 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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical records we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your medical record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

POLICY REGARDING RESEARCH-RELATED INJURIES

The NIH Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Clare Sun, MD, Bldg. 10, CRC 3-5140, 301-402-1806. Other researchers you may call are: Susan Soto, RN, M.S.N., at 301-402-0797. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness to the oral short-form consent process only:

Signature of Witness*	Print Name of Witness	Date

***NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:**

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.