NCCN GUIDELINES FOR PATIENTS®

2024

Marginal Zone Lymphomas

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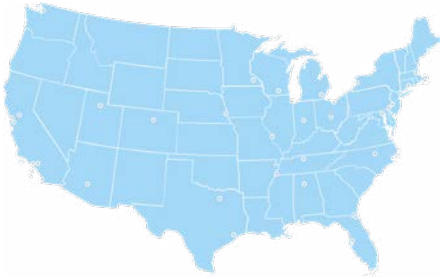

Did you know that top cancer centers across the United States work together to improve cancer care? This alliance of leading cancer centers is called the National Comprehensive Cancer Network® (NCCN®).

Cancer care is always changing. NCCN develops evidence-based cancer care recommendations used by health care providers worldwide. These frequently updated recommendations are the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). The NCCN Guidelines for Patients plainly explain these expert recommendations for people with cancer and caregivers.

These NCCN Guidelines for Patients are based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas Version 1.2024 – January 18, 2024.

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1
Lymphoma basics

Marginal zone lymphoma (MZL) is a slow-growing (indolent) non-Hodgkin lymphoma (NHL). NHLs develop from lymphocytes, a type of white blood cell. In MZL, excess numbers of abnormal B lymphocytes can be found in almost any organ in the body.

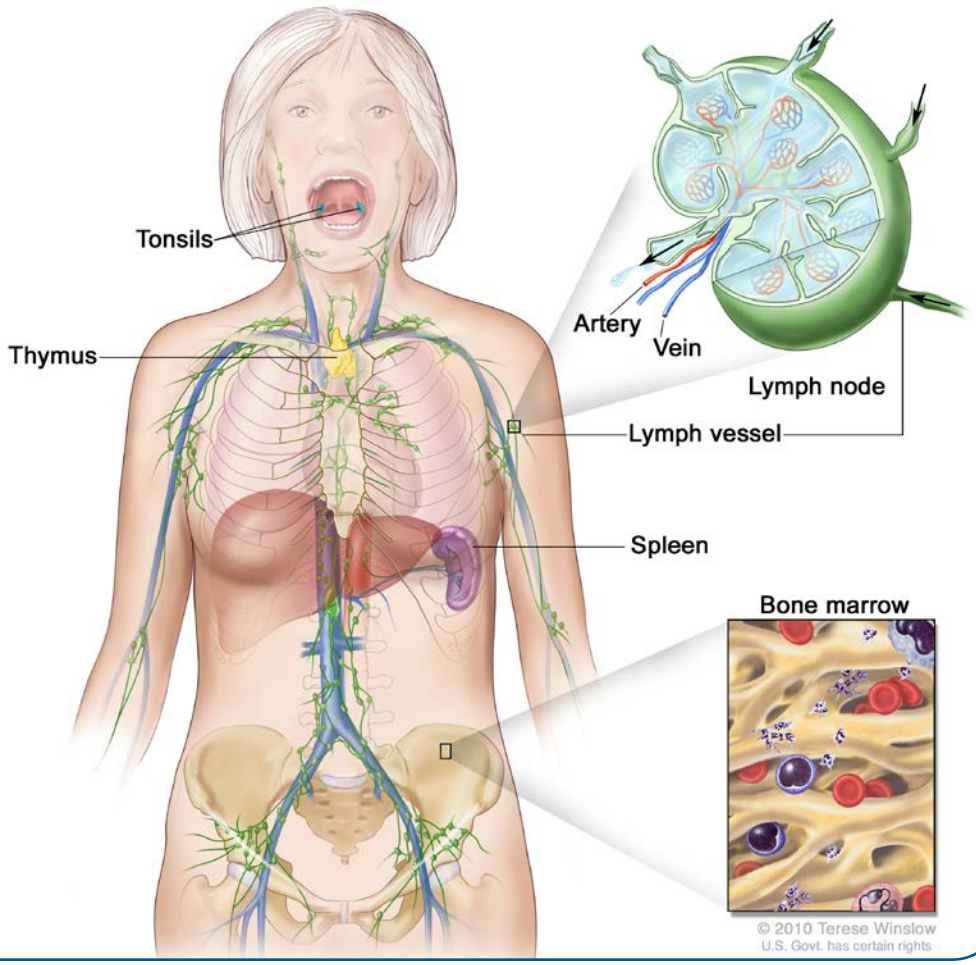
Lymphatic system

Non-Hodgkin lymphoma (NHL) begins in the lymphatic system. The lymphatic or lymph system is a major part of the body's immune system. It is a germ-fighting network of tissues and organs that includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels.

Lymphatic vessels are a network of thin tubes that carry lymphatic fluid (lymph) and white blood cells into all the tissues of the body. Lymph gives cells water and food. White blood cells, such as lymphocytes, help fight infection and disease.

Lymphatic system

The lymphatic or lymph system is part of the immune system. It includes lymph vessels, lymph nodes, tonsils, thymus, spleen, and bone marrow.



As lymph travels throughout your body, it passes through hundreds of small bean-shaped structures called lymph nodes. Lymph nodes make immune cells that help the body fight infection. They also filter the lymph fluid and remove foreign material such as bacteria and cancer cells.

Lymphocytes

Non-Hodgkin lymphoma (NHL) is a cancer of lymphocytes. A lymphocyte is a type of white blood cell that helps fight and prevent infection. Lymphocytes are found in blood and lymph tissue, and every organ in the body. Lymph tissue includes lymph vessels and lymph nodes. Lymphocytes normally grow in response to infection or inflammation. When they grow on their own without proper regulation, they can develop into lymphoma.

There are 3 main types of lymphocytes:

- **B lymphocytes or B cells** make antibodies. An antibody is a protein.
- **T lymphocytes or T cells** help fight infections, kill tumor cells, and control immune responses.
- **Natural killer (NK) cells** can kill tumor cells or virus-infected cells.

Non-Hodgkin lymphoma can develop from B-cell, T-cell, or NK-cell lymphocytes. Marginal zone lymphoma starts in mature B cells. B cells mature into plasma cells, which produce antibodies that are used to attack invading bacteria, viruses, and toxins. The antibody molecules latch onto and destroy invading viruses or bacteria by recruiting other components of the immune system. Cancers of plasma cells are multiple myeloma and not lymphoma.

Marginal zone lymphomas

Marginal zone lymphoma (MZL) is a common type of non-Hodgkin lymphoma (NHL). MZL is considered a slow-growing (indolent) lymphoma. It forms in B-cell lymphocytes that live in the marginal zone part of the spleen, lymph nodes, or lymphoid tissues. Lymphoid or lymph tissues are organized structures that support immune responses. They are where lymphocytes are found. Examples include bone marrow, thymus, and tonsils.

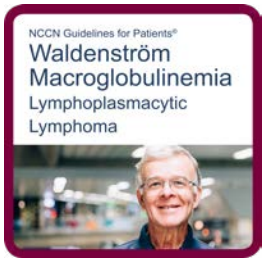
The marginal zone is a very active area that receives large amounts of circulating blood. Here, blood interacts with different types of white blood cells that engulf and digest cancer cells, microbes, cellular debris, and foreign substances. When abnormal marginal zone B cells grow out of control, then marginal zone lymphoma develops. Chronic infection, inflammation, or autoimmune disorders might cause some types of MZL due to the increased activity in the immune system. But, in most cases, the cause of MZL is unknown.

MZL can be divided into 3 distinct subtypes:

- **Extranodal marginal zone lymphoma** (accounts for about 6 out of 10 MZL cases per year)
- **Nodal marginal zone lymphoma** (accounts for about 3 out of 10 MZL cases per year)
- **Splenic marginal zone lymphoma** (accounts for about 1 out of 10 MZL cases per year)

MZL has some features that overlap with another type of lymphoma called Waldenström macroglobulinemia (WM), also known as lymphoplasmacytic lymphoma (LPL). In WM, bone marrow produces too many abnormal white blood cells that crowd out healthy blood cells.

For more information, read *NCCN Guidelines for Patients: Waldenström Macroglobulinemia,* available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Extranodal MZL

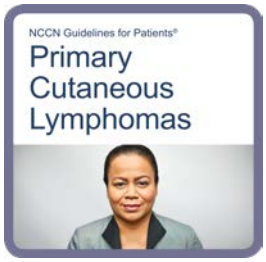
Extranodal marginal zone lymphoma (EMZL) is the most common form of MZL. It is called extranodal because it forms outside the lymph nodes in places such as the stomach (gastric), small intestine, salivary glands, thyroid, eyes, breast, skin (cutaneous), or lungs. Each type is based on location. EMZL found in the skin is called cutaneous MZL.

In the past, the term mucosa-associated lymphoid tissue (MALT) lymphoma was used to describe this type of MZL. Now, EMZL is the preferred term because it more accurately describes all possible EMZL disease sites.

EMZL can be caused by certain types of infection, inflammation, or autoimmune disorders of the affected organ. The most common location for EMZL is the stomach, where it is often caused by the bacteria *Helicobacter pylori (H. pylori)*. *H. pylori* can also cause stomach ulcers.

Mediterranean abdominal lymphoma or immunoproliferative small intestinal disease occurs in young adults in eastern Mediterranean countries. It often forms in the abdomen. Those with this type of EMZL may also be infected with bacteria called *Campylobacter jejuni (C. jejuni)*. Treatment options specific to this type are not covered in this book.

For more information on cutaneous MZL, read the *NCCN Guidelines for Patients: Primary Cutaneous Lymphomas*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Nodal MZL

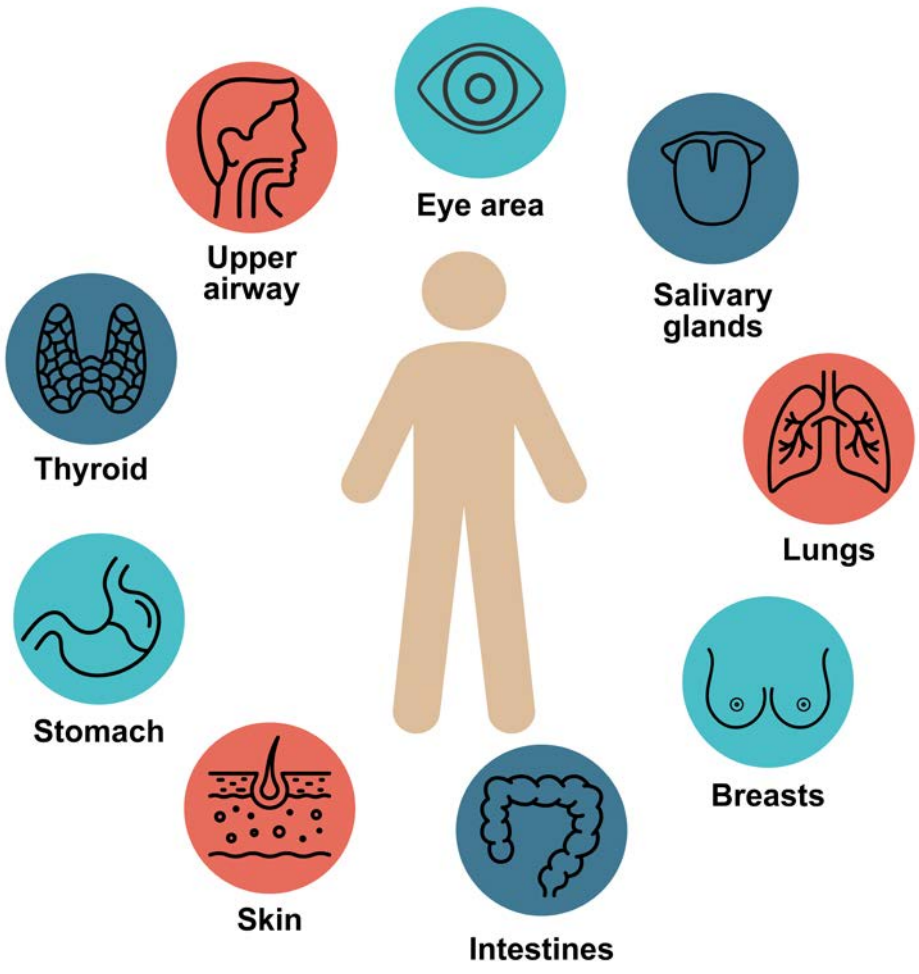
Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. Lymph nodes make immune cells that help the body fight infection. They also filter the lymph fluid and remove foreign material such as bacteria and cancer cells. This type of non-Hodgkin lymphoma (NHL) is also called monocytoid B-cell lymphoma.

Splenic MZL

Splenic marginal zone lymphoma (SMZL) involves the spleen, blood, and bone marrow. The spleen makes immune cells, filters the blood, stores blood cells, and removes old blood cells. The most common sign of SMZL is an enlarged spleen. This type of MZL is sometimes associated with hepatitis C infection.

Extranodal MZL

The diagram shows the most common sites for extranodal MZL. Extranodal MZL accounts for about 6 out of every 10 cases of MZL per year.



Key points

- The lymphatic or lymph system is a network of tissues and organs that helps your body fight infections and disease. It is part of the immune system.
- Non-Hodgkin lymphoma (NHL) is a cancer that develops from lymphocytes, a type of white blood cell.
- Lymphocytes normally grow in response to infection or inflammation. When they grow on their own without proper regulation, they can develop into lymphoma.
- Marginal zone lymphoma (MZL) starts in B cells that normally live in the marginal zone part of the spleen, lymph nodes, or lymphoid tissues.
- Chronic infection, inflammation, or autoimmune disorders may cause some types of MZL due to the increased activity in the immune system. But, the cause of MZL is unknown in many cases.
- Extranodal marginal zone lymphoma (EMZL) occurs outside the lymph nodes in places such as the stomach, small intestine, salivary gland, thyroid, eyes, breast, skin, and lungs.
- Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes.
- Splenic marginal zone lymphoma (SMZL) involves the spleen, blood, and bone marrow.

Those with marginal zone lymphoma should be treated at centers experienced in their type of cancer.

2
Testing for MZL

Accurate testing is essential to diagnose and treat marginal zone lymphoma (MZL). This chapter presents an overview of possible tests you might receive and what to expect.

Test results

Results from biopsy and imaging studies will be used to determine your treatment plan. Treatment will be based on these findings. It is important you understand what these tests mean. Ask questions and keep copies of your test results. Online patient portals are a great way to access your test results. Please discuss your results with your doctor or health care team.

Keep these things in mind:

- Choose a friend, family member, or peer who can drive you to appointments, provide meals, or offer emotional support during diagnosis and treatment.
- Bring someone with you to doctor visits, if possible.
- Write down questions and take notes during appointments. Don't be afraid to ask your care team questions. Get to know your care team and help them get to know you.
- Get copies of blood tests, imaging results, and reports about the specific type of cancer you have.
- Organize your papers. Create files for insurance forms, medical records, and test results. You can do the same on your computer.
- Keep a list of contact information for everyone on your care team. Add it to your phone. Hang the list on your refrigerator or keep it in a place where someone can access it in an emergency. Keep your primary care physician (PCP) informed of changes to this list. You are encouraged to keep your PCP in the loop. They are great partners in your care. In your contact list, include information on the exact type of cancer you have, as well as any treatments you've received and the date each treatment started.
- Set up a MyChart or health record account if it's available, which will help you track your appointments and communicate with your care team.

General health tests

Some general health tests are described next.

Medical history

A medical history is a record of all health issues and treatments you have had in your life. Be prepared to list any illness or injury and when it happened. Bring a list of old and new medicines and any over-the-counter (OTC) medicines, herbals, or supplements you take. Some supplements interact with and affect medicines that your care team may prescribe. Tell your care team about any symptoms you have. A medical history, sometimes called

a health history, will help determine which treatment is best for you.

Family history

Marginal zone lymphoma is not inherited from your biological parents. However, some cancers and other diseases can run in families. Your care team will ask about the health history of family members who are blood relatives. This information is called a family history. Ask family members on both sides of your family about their health issues like heart disease, cancer, and diabetes, and at what age they were diagnosed. It's important to know the specific type of cancer or where the cancer started, if it is in multiple locations, and if they had genetic testing.

Physical exam

During a physical exam, your doctor may:

- Check your temperature, blood pressure, pulse, and breathing rate
- Check your height and weight
- Listen to your lungs and heart
- Look in your eyes, ears, nose, and throat
- Feel and apply pressure to parts of your body to see if organs are of normal size, are soft or hard, or cause pain when touched
- Feel for enlarged lymph nodes in your neck, underarm, and groin

Fertility (all genders)

Treatment such as chemotherapy can affect your fertility, the ability to have children. If you think you want children in the future, ask your care team how cancer and cancer treatment might change your fertility. To preserve your fertility, you may need to take action before starting cancer treatment. Those who want to have children in the future should be referred to a fertility specialist to discuss the options before starting treatment.

Fertility preservation is all about keeping your options open, whether you know you want to have children later in life or aren't sure at the moment. Fertility and reproductive specialists can help you sort through what may be best for your situation.

More information on fertility preservation in adolescents and young adults is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Changes in fertility

Treatment might cause your fertility to be temporarily or permanently impaired or interrupted. This loss of fertility is related to your age at time of diagnosis, treatment type(s), treatment dose, and treatment length. Talk to your care team about your concerns and if you are planning a pregnancy.

Preventing pregnancy during treatment

Cancer and cancer treatment can affect the ovaries and damage sperm. If you become pregnant during chemotherapy, radiation therapy, or other types of systemic therapy, serious birth defects can occur. Speak with your care team about preventing pregnancy while being treated for cancer. Hormonal birth control may or may not be recommended, so ask your doctor about options such as intrauterine devices (IUDs) and barrier methods. Types of barrier methods include condoms, diaphragms, cervical caps, and the contraceptive sponge.

Those with ovaries

Those who can become pregnant will have a pregnancy test before starting treatment. Cancer treatment can hurt the developing baby if you are or become pregnant during treatment. Therefore, birth control to prevent pregnancy during and after treatment is recommended. If you are pregnant or breastfeeding at the time of your cancer diagnosis, certain treatments will need to be avoided.

Menstruation, menses, menstrual flow, or your period may stop during treatment, but often returns within 2 years after treatment in those 35 years of age and under. It is still possible to become pregnant even though you might not have a period. Therefore, birth control is recommended during and after treatment. Consult your doctor for the best time to plan a pregnancy.

Those with testicles

Cancer and cancer treatment can damage sperm. Therefore, use contraception (birth control) such as condoms to prevent pregnancy during and immediately after cancer treatment.

Performance status

Performance status (PS) is a person's general level of fitness and ability to perform daily tasks. Your state of general health will be rated using a PS scale called ECOG (Eastern Cooperative Oncology Group). PS is one factor taken into consideration when choosing a treatment plan. Your preferences about treatment are always important.

The ECOG PS scores range from 0 to 5.

- **PS 0** means the person is fully active.
- **PS 1** means the person is still able to perform light to moderate activity, but with some limitations.
- **PS 2** means the person is limited to the chair or bed less than half of the day and still able to care for self.
- **PS 3** means the person is limited to the chair or bed more than half of the day.
- **PS 4** means the person is totally confined to the bed or chair and completely disabled.
- **PS 5** means the person is not alive.

Good PS is usually PS 0 or PS 1.

Blood tests

Blood tests check for signs of disease and how well organs are working. They require a sample of your blood, which is removed through a needle placed into your vein. Be prepared to have many blood tests during MZL treatment and recovery to check treatment results, blood counts, and the health of organs like your liver and kidneys.

Complete blood count and differential

A complete blood count (CBC) measures the levels of red blood cells (RBCs), white blood cells (WBCs), and platelets (PLTs) in your blood. A CBC is a key test that gives a picture of your overall health. A differential counts the number of each type of WBC (neutrophils, lymphocytes, monocytes, eosinophils, and basophils). It also checks if the counts are in balance with each other.

Comprehensive metabolic panel

A comprehensive metabolic panel (CMP) measures 14 different substances in your blood. It is usually done on the plasma part of your blood. A CMP provides important information about how well your kidneys and liver are working, among other things.

Creatinine

Creatinine is a waste produced in the muscles. Every person generates a fixed amount of creatinine every day based on how much muscle they have. It is filtered out of the blood by the kidneys. The level of creatinine in the blood tells how well the kidneys are working. Higher levels of creatinine mean the kidneys aren't working as well as they were when someone had lower levels of creatinine.

Electrolytes

Electrolytes help move nutrients into cells and help move waste out of cells. Electrolytes are ions or particles with electrical charges that help the nerves, muscles, heart, and brain work as they should. Your body needs electrolytes to function properly.

Helicobacter pylori

Helicobacter pylori or *H. pylori* is a type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with *H. pylori* infections may be more likely to develop cancer in the stomach, including extranodal marginal zone lymphoma (EMZL).

Hepatitis B and hepatitis C

Hepatitis B (HBV) and hepatitis C (HCV) are types of liver disease caused by a virus. A hepatitis blood test will show if you had hepatitis in the past or if you have it today. Some cancer treatments can wake up (or reactivate) the virus. If this happens, it can cause harm to the liver. People with HCV may be more likely to develop splenic marginal zone lymphoma (SMZL).

HIV

Human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS). An HIV antibody test checks for HIV antibodies in a sample of blood, urine, or saliva. It's important to let your doctor know if you have ever been infected with HIV.

HLA typing

Human leukocyte antigen (HLA) is a protein found on the surface of most cells. It plays an important role in your body's immune response. HLAs are unique to each person. They mark your body's cells. Your body detects these markers to tell which cells are yours. In other words, all your cells have the same set of HLAs. Each person's set of HLAs is called the HLA type or tissue type.

HLA typing is a blood test that detects a person's HLA type. This test is done before a donor (allogeneic) hematopoietic cell transplant. To find a donor match, your proteins will be compared to the donor's proteins to see how many proteins are the same. A very good match is needed for a transplant to be a treatment option. Otherwise, your body will reject the donor cells or the donor cells will react against your body. Blood or tissue samples from you and your blood relatives will be tested first.

Immunoglobulins

The quantitative immunoglobulin blood test measures abnormal levels of immunoglobulins, also known as antibodies, in your blood. Antibodies are proteins made by the immune system. An immunoglobulin (Ig) test usually measures 3 specific types (classes) of immunoglobulins called IgG, IgM, and IgA. These immunoglobulins may be abnormally high due to your lymphoma or abnormally low due to prior and current lymphoma treatment.

Infections related to MZL

Certain infections can cause ongoing (chronic) inflammation and increased activity of the immune system. Infections such as Helicobacter pylori (*H. pylori*), *Chlamydia psittaci (C. psittaci),* Campylobacter jejuni (C. jejuni), Borrelia burgdorferi (B. burgdorferi), and hepatitis C virus (HCV) have been found in those with MZL. These infections are different from infections that can be a result of treatment.

Lactate dehydrogenase

Lactate dehydrogenase (LDH) or lactic acid dehydrogenase is a protein found in most cells. Dying cells release LDH into the blood. Fast-growing cells also release LDH and cause levels of this protein to be elevated in the blood.

Pregnancy test

If planned treatment might affect pregnancy, then those who can become pregnant will be given a pregnancy test before treatment begins.

SPEP

Serum protein electrophoresis (SPEP) examines specific proteins in the blood called globulins, which may be increased in certain conditions.

Biopsy

A biopsy is the removal of a sample of tissue or fluid for testing. It is an important part of an accurate diagnosis of lymphoma. Your sample should be reviewed by a pathologist who is an expert in the diagnosis of lymphoma. The pathologist will note the overall appearance and the size, shape, and type of your cells. This review is often referred to as histology, histopathology, or hematopathology review. Tests will be done on the biopsied cells. Ask questions about your biopsy results and what they mean for your treatment.

Types of possible biopsies include the following:

- **Lymph node biopsy** removes tissue from a lymph node.
- **Endoscopic biopsy** uses a thin, tube-shaped tool guided through the mouth to take a sample of the stomach and intestines.

A lymph node biopsy can done in the following ways:

- **Fine-needle aspiration (FNA)** and **core biopsy (CB)** use needles of different sizes to remove a sample of tissue or fluid.
- **Incisional biopsy** removes a small amount of tissue through a cut in the skin or body.
- **Excisional biopsy** removes the entire tumor through a cut in the skin or body.

A biopsy is usually done with other lab methods to accurately diagnose the type of MZL. Core or excisional biopsies are often preferred for diagnosing MZL.

These other lab methods include:

- Immunohistochemistry (IHC)
- Flow cytometry (FCM)
- Biomarker testing to detect gene rearrangements and karyotype or fluorescence in situ hybridization (FISH) for major translocations

In a gene rearrangement, there is either loss or gain of chromosomal material. A translocation refers to the transfer of genetic material from one chromosome to another.

Lymph node biopsy

A lymph node biopsy is recommended to diagnose MZL. Lymph nodes are usually too small to be seen or felt. Sometimes, lymph nodes can feel swollen, enlarged, hard to the touch, or don't move when pushed (fixed or immobile). A lymph node biopsy can be done using a needle biopsy procedure or as a small surgery to remove (excise) a lymph node.

Bone marrow tests

Bone marrow tests might be done in certain cases.

There are 2 types of bone marrow tests that are often done at the same time:

- Bone marrow aspirate
- Bone marrow biopsy

Your bone marrow is like a sponge holding liquid and cells. An aspirate takes some of the liquid and cells out of the sponge, and a biopsy takes a piece of the sponge.

For many, this is an uncomfortable procedure. Your care team will try to make you as comfortable as possible. The samples are usually taken from the back of the hip bone (pelvis). You will likely lie on your belly or side. For an aspirate, a hollow needle will be pushed through your skin and into the bone. Liquid bone marrow will then be drawn into a syringe. For the biopsy, a wider needle will be used to remove a small piece of the bone. You may feel bone pain at your hip for a few days. Your skin may bruise.

Testing takes time. It might take days or weeks for all test results to come in.

"Don't let yourself stop doing the things you enjoy doing. Whatever your hobbies are, whatever things you like to do, keep doing them. It'll help you feel more like yourself and stay positive during what is an extremely exhausting, mentally straining time."

Immunophenotyping

Immunophenotyping is a process that uses antibodies to detect the presence or absence of certain antigens. Antigens are proteins or markers that can be found on the surface of or inside all cells, including white blood cells. Specific groupings of antigens are normal. However, some specific patterns of antigens called the immunophenotype are found on abnormal cells including non-Hodgkin lymphoma (NHL) and MZL.

Immunophenotyping can be done using specialized techniques called flow cytometry or immunohistochemistry (IHC). These techniques are used to distinguish MZL from other types of lymphoma. Immunophenotype can change as cancer progresses.

MZL immunophenotype is usually negative for the proteins CD10, CD5, cyclin D1, and BCL2, while positive for CD20. Immunophenotyping is used to help support a diagnosis. However, an accurate diagnosis of MZL requires a trained pathologist to review the tissue for abnormal cells seen under a microscope. More testing may be needed to establish an MZL subtype.

Flow cytometry

Flow cytometry (FCM) is a laboratory method used to detect, identify, and count specific cells. Flow cytometry involves adding a light-sensitive dye to cells. The dyed cells are passed through a beam of light in a machine. The machine measures the number of cells, things like the size and shape of the cells, and other unique features of cells. Flow cytometry may be used on cells from circulating (peripheral) blood, bone marrow, or a biopsy. The most common use of flow cytometry is in the identification of markers on cells, particularly in the immune system (called immunophenotyping).

Immunohistochemistry

Immunohistochemistry (IHC) is a special staining process that involves adding a chemical marker to immune cells. The cells are then studied using a microscope. IHC looks for the immunophenotype of cells from a biopsy or tissue sample.

Biomarker and genetic tests

Biomarker and genetic tests are used to learn more about your type of MZL, to guide treatment, and to determine the likely path your cancer will take (prognosis). This genetic testing is different from family history genetic testing or genetic cancer risk testing. This testing looks for changes only in the MZL cells that have developed over time, and not changes in the rest of your body's cells. Biomarker testing includes tests of genes or their products (proteins) and identifies the presence or absence of mutations and certain proteins that might suggest the lymphoma subtype. It is sometimes called molecular testing, tumor profiling, gene expression profiling, or genomic testing.

Inside our cells are deoxyribonucleic acid (DNA) molecules. These molecules are tightly packaged into what is called a chromosome. Chromosomes contain most of the genetic information in a cell. Normal human cells contain 23 pairs of chromosomes for a total of 46 chromosomes. Each chromosome contains thousands of genes. Genes are coded instructions that determine what proteins

are made in your cells. A mutation is when something goes wrong in the genetic code. This causes a change in your DNA. Proteins are written like this: BCL6. Genes are written with italics like this: *BCL6*. When a gene or protein is found (expressed), it is shown with a plus sign (+) like this: CD10+. When a gene or protein has not been found, it is written with a negative sign (-) like this CD10-.

MZL cells sometimes have changes in genes and chromosomes that can be seen under a microscope or found with other tests. These DNA changes may affect your MZL diagnosis, treatment options, and prognosis.

MZL mutation testing

A sample of your blood or bone marrow will be used to see if the MZL cancer cells have any specific mutations. Some mutations can be targeted with specific therapies. This is separate from the genetic testing for mutations that you may have inherited from your biological parents.

Mutation testing includes tests of genes or their products (proteins). Subtle new drug-resistant mutations may occur over time. Mutations can also happen during treatment. Mutation testing is used to look for these new mutations. Some mutations lead to resistance to certain targeted therapies. There are many possible mutations.

Mutations

MZL cells can have changes in genes and chromosomes. Mutation testing looks for these changes or abnormalities that are unique to MZL cells. Examples of such changes are called deletion, insertion, amplification, translocation (rearrangement), and point mutation.

- ✓ **Amplification** – When part or whole a chromosome or gene is increased (for example, duplicated)
- ✓ **Deletion** – When part of a chromosome or gene is missing
- ✓ **Insertion** – When a new part of a chromosome or gene is included
- ✓ **Inversion** – Switching of parts within one chromosome
- ✓ **Point mutation** – When part of a gene is changed
- ✓ **Chromosome translocation and gene rearrangement** – Switching of parts between 2 chromosomes. When described at the chromosome level, it is called a translocation. When described at the gene level, it is called rearrangement.

Deletions

When part of a chromosome is missing, it is called a deletion. For example, in del(7q) the q part of chromosome 7 is missing (deleted). Specific chromosomal deletions can be found in some types of marginal zone lymphomas but can also be found in other types of blood cancers and disorders.

FISH

Fluorescence in situ hybridization (FISH) is a method that involves special dyes called probes that attach to pieces of DNA. Since this test doesn't need growing cells, it can be performed on bone marrow, lymph nodes, or a blood sample.

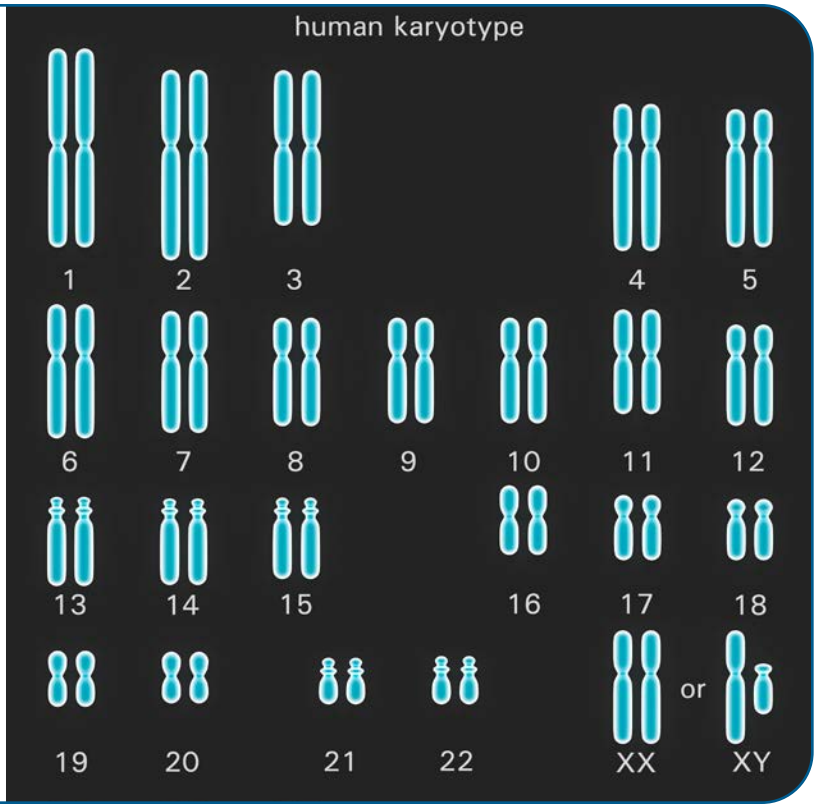
FISH can find translocations that are too small to be seen with other methods. A translocation occurs when parts of two chromosomes switch with one another. However, FISH can only be used for known changes. It cannot detect all the possible changes found within the chromosomes and genes.

Karyotype

A karyotype is a picture of chromosomes. Normal human cells contain 23 pairs of chromosomes for a total of 46 chromosomes. A karyotype will show extra, missing (deletion), rearranged, or abnormal pieces of chromosomes. Since a karyotype requires growing cells, a sample of bone marrow or blood must be used.

Karyotype

A karyotype is a picture of your chromosomes.



Translocations

Translocation is a switching of parts between two chromosomes. A translocation between chromosomes 11 and 18 is written as t(11;18). Specific translocations can help distinguish between types of blood cancers and disorders.

Gene rearrangements

In gene rearrangements, part of a gene has broken off and attached to another gene, creating a new gene. When one cell divides many times, the entire group of cells is called clonal or clonality. In clonal rearrangements, the same gene rearrangements are found in a group of cancer cells.

PCR

A polymerase chain reaction (PCR) is a lab process that can make millions or billions of copies of your DNA or RNA (genetic information). PCR is very sensitive. It can find 1 abnormal cell among more than 100,000 normal cells. These copies, called PCR product, might be used for high-throughput sequencing (HTS) or next-generation sequencing (NGS). This is important when testing for treatment response or remission.

Comparative genomic hybridization

Comparative genomic hybridization (CGH) is a technique that compares DNA samples from normal tissue and tumor tissue. It is used to detect abnormal chromosomes.

High-throughput sequencing

High-throughput sequencing (HTS) is capable of sequencing hundreds of millions of DNA molecules at a time.

Next-generation sequencing

Next-generation sequencing (NGS) is a method used to determine a portion of a person's DNA sequence. It shows if a gene has any mutations that might affect how the gene works. NGS looks at the gene in a more detailed way than other methods and can find mutations that other methods might miss.

Genetic cancer risk testing

Genetic cancer risk testing is done using blood or saliva (spitting into a cup). The goal is to look for gene mutations inherited from your biological parents called germline mutations. Some mutations can put you at risk for more than one type of cancer. You can pass these genes on to your children. Also, family members might carry these mutations. Tell your care team if there is a family history of cancer.

Imaging tests

Imaging tests take pictures of the inside of your body to look for cancer deposits. A radiologist, an expert in interpreting imaging tests, will write a report and send this report to your doctor. While these reports might be available to you through your patient portal or patient access system, please wait to discuss these results with your care team.

Contrast material

Contrast material is used to improve the pictures of the inside of the body. Contrast materials are not dyes, but substances that help enhance and improve the images of several organs and structures in the body. It is used to make the pictures clearer. The contrast is not permanent and will leave your body in your urine immediately after the test. The types of contrast vary and are different for CT and MRI.

Tell your care team if you have had allergic reactions to contrast in the past. This is important. You might be given medicines to avoid the effects of those allergies. Contrast might not be used if you have a serious allergy or if your kidneys aren't working well.

CT scan

A computed tomography (CT or CAT) scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make one detailed picture. A CT scan of your head, neck, chest, abdomen, and pelvis may be one of the tests to look for cancer. In most cases, contrast will be used.

MRI scan

A magnetic resonance imaging (MRI) scan uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use x-rays. Because of the very strong magnets used in the MRI machine, tell the technologist if you have any metal in your body. During the test, you will likely be asked to hold your breath for 10 to 20 seconds as the technician collects the images. Contrast is often used.

A closed MRI has a capsule-like design where the magnet surrounds you. An open MRI has a magnetic top and bottom, which allows for an opening on each end. Closed MRIs are more common than open MRIs, so if you have claustrophobia (a dread or fear of enclosed spaces), be sure to talk to your care team about it.

PET scan

A positron emission tomography (PET) scan uses a radioactive drug called a tracer. A tracer is a substance injected into a vein to see where cancer cells are in the body and if they are using sugar produced by your body to grow. Cancer cells show up as bright spots on PET scans. However, not all tumors will appear on a PET scan. Also, not all bright spots are cancer. It is normal for the brain, heart, kidneys, and bladder to be bright on PET. Inflammation or infection can also show up as a bright spot. When a PET scan is combined with CT, it is called a PET/CT scan.

Heart tests

Certain treatments can affect heart (cardiac) function. Heart tests might be used to see how well your heart works. These tests might be used as a baseline and before giving chemotherapy. You might be referred to a heart specialist called a cardiologist.

Electrocardiogram

An electrocardiogram (ECG or EKG) shows electrical changes in your heart. It reveals information about your heart rate and rhythm. Prolonged corrected QT interval (or QTc) occurs when your heart muscle takes longer than normal to recharge between beats. Often, this electrical disturbance can be seen on an ECG. Certain treatments for MZL can cause prolonged QTc. If the QTc becomes too prolonged, it can cause dangerous heart rhythms.

Echocardiogram

An echocardiogram (or echo) uses sound waves to make pictures. For this test, small patches will be placed on your chest to track your heartbeat. Next, a wand with gel on its tip will be slid across part of your bare chest. A picture of your beating heart will be seen on a screen. The pictures will be recorded for future viewing.

An echocardiogram is one way of measuring ejection fraction, which is the amount of blood pumped out of the left side of your heart every time it beats. In low ejection fraction, the amount of blood pumping from the left side of the heart is lower than normal.

MUGA

A multigated acquisition (MUGA) scan is used to evaluate the pumping function of your heart. During the test, a small amount of radiotracer is injected into a vein. A special camera, called a gamma camera, will create computer-generated movie images of your beating heart.

MUGA scan might show low ejection fraction. This is when the amount of blood pumping from the left side of the heart is lower than normal.

Key points

- Blood and imaging tests check for signs of disease, how well organs are working, and treatment results.
- A biopsy is the removal of tissue or fluid for testing. It is an important part of an accurate MZL diagnosis.
- Immunophenotyping is used to distinguish MZL from other types of lymphoma.
- A sample from your biopsy may undergo lab tests to learn more about your subtype of MZL and choose the best treatment for you.
- Biomarker testing includes tests of genes or their products (proteins). It identifies the presence or absence of mutations and certain proteins that might suggest treatment.
- Imaging tests are used to look for areas of lymphoma involvement and are part of your staging workup.
- Certain treatments can affect heart function. Heart tests might be used to see how well your heart works.
- Online patient portals are a great way to access your test results. Be sure to discuss these results with your care team before drawing any conclusions about what the results might mean.

Create a medical binder

A medical binder or notebook is a great way to organize all of your records in one place.

- ✓ Make copies of blood tests, imaging results, and reports about your specific type of cancer. It will be helpful when getting a second opinion.
- ✓ Choose a binder that meets your needs. Consider a zipper pocket to include a pen, small calendar, and insurance cards.
- ✓ Create folders for insurance forms, test types (ie, blood, imaging, pathology, radiology, genetics), treatments, and procedures. Organize items in the folder by date.
- ✓ Use online patient portals to view your test results and other records. Download or print the records to add to your binder.
- ✓ Add a section for questions and to take notes.

Bring your medical binder to appointments. You never know when you might need it!

3
Treating MZL

There is more than one treatment for marginal zone lymphomas. This chapter presents an overview of the possible types of treatment and what to expect. Not everyone will receive the same treatment. Treatment options are based on many factors. Together, you and your care team will choose a treatment plan that is best for you.

Marginal zone lymphoma (MZL) is highly treatable and may be curable in certain circumstances. Treatment for MZL usually consists of radiation therapy, chemotherapy, immunotherapy, targeted therapy, antibiotic therapy, or combinations of these treatments (often called chemoimmunotherapy). Surgery may be an option in very select cases of localized marginal zone lymphoma. Localized means confined to an area.

It is important to have regular talks with your care team about your goals for treatment and your treatment plan.

Care team

Those with MZL should seek treatment at experienced cancer centers.

Treating cancer takes a team approach. Treatment decisions should involve a multidisciplinary team (MDT). An MDT is a team of health care and psychosocial care professionals from different professional backgrounds who have knowledge (expertise) and experience in your type of cancer. This team is united in the planning and implementing of your treatment. Ask who will coordinate your care.

Some members of your care team will be with you throughout cancer treatment, while others will only be there for parts of it. Get to know your care team and help them get to know you.

Depending on your diagnosis, your team might include the following specialists:

- **A hematologist or hematologic oncologist** is a medical expert in blood diseases and blood cancers. Other types of oncologists include medical, radiation, and surgical oncologists.
- **A medical oncologist** treats cancer using systemic (drug) therapy.
- **A pathologist or hematopathologist** analyzes the cells and tissues removed during a biopsy and provides cancer diagnosis, staging, and information about biomarker testing.
- **A gastroenterologist** is an expert in diseases of the digestive tract.
- **An advanced practice nurse (APN) or a physician assistant (PA)** help

provide an extra layer of support with your cancer-related symptoms.

- **Oncology nurses** provide your hands-on care, like giving systemic therapy, managing your care, answering questions, and helping you cope with side effects.
- **Oncology pharmacists** are experts in knowing how to use medicines to treat cancer and to manage symptoms and side effects.
- **Palliative care specialists** concentrate on preventing and alleviating suffering and improving quality of life.
- **Nutritionists and dietitians** can provide guidance on what foods are most suitable for your condition.
- **An occupational therapist** helps people with the tasks of daily living.
- **A physical therapist** helps people move with greater comfort and ease.
- **Psychologists and psychiatrists** are mental health experts who can help manage issues such as depression, anxiety, or other mental health conditions that can affect how you think and feel.
- **Social workers** help people solve and cope with problems in their everyday lives. Clinical social workers also diagnose and treat mental, behavioral, and emotional issues. The anxiety a person feels when diagnosed with cancer might be managed by a social worker in some cancer centers. They, or other designated professionals, can help navigate the complexities of financial and insurance stresses.

You know your body better than anyone

Help your care team understand:

- ✓ How you feel
- ✓ What you need
- ✓ What is working and what is not

Keep a list of names and contact information for each member of your team. This will make it easier for you and anyone involved in your care to know whom to contact with questions or concerns.

Get to know your care team and help them get to know you.

- **Spiritual care specialists** identify and support those with spiritual distress or unmet spiritual needs.
- **A research team** helps to collect research data and coordinate care if you are in a clinical trial. Clinical trials help bring new therapies to patients and advance the treatment for everyone. Consider asking your care team about access to clinical trials.

Treatment phases

The goal of treatment is remission. MZL might relapse more than once. Here are some terms you might hear used by your care team. Not all phases are used in the treatment of MZL.

Induction

Induction or first-line therapy is the first phase of treatment. The goal of induction is complete response (CR) or complete remission. After induction, you will have tests to look for a response (remission).

Maintenance

Maintenance is treatment to prevent cancer from returning. It may be given for a long time and occur over years. Not everyone will receive maintenance therapy. Maintenance may be recommended depending on your type of disease, treatments received in the past for your lymphoma, and risk of relapse.

Remission

There are different types of treatment response. When there are no signs of cancer, it is called a complete response (CR) or complete remission. Remission can be short-term (temporary) or long-lasting (permanent). In partial response (PR), cancer is still present, but it has reduced in size.

Relapse

When MZL returns after a period of remission, it is called a relapse. The goal of treatment is to achieve remission again. A relapse can be serious. It is important to ask about your prognosis.

Refractory

When MZL remains and does not respond to treatment, it is called refractory or resistant cancer. This cancer may be resistant at the start of treatment or it may become resistant during treatment. Refractory disease is very serious. It is important to ask about your prognosis.

Surveillance and monitoring

You will be monitored throughout treatment. Surveillance watches for any changes in your condition after remission or a hematopoietic cell transplant (HCT). You will have tests during surveillance to check for relapse.

Observation without treatment

Some slow-growing (indolent) lymphomas do not require immediate treatment, including MZL. Observation is sometimes called active surveillance or watch and wait. During observation, your care team will monitor for symptoms to appear. Once specific signs or symptoms appear, you will start treatment. Ask your care team what specific signs or symptoms they will be looking for.

A sign can be seen by someone else like your doctor or nurse. A symptom is something only you can feel.

Systemic therapy

Systemic therapy works throughout the body. Types include chemotherapy, chemoimmunotherapy, immunotherapy, and targeted therapy. Systemic therapy might be used alone or with other therapies. Goals of systemic therapy may be curative or palliative and should be discussed before starting treatment.

The choice of therapy takes into consideration many factors, including age, other serious health issues, and future treatment possibilities like a hematopoietic cell transplant (HCT). Your preferences about treatment are important. If you have any religious or personal beliefs about certain kinds of treatment, now would be the time to share them with your care team.

For systemic therapy examples, **see Guide 1.**

Guide 1
Systemic therapy examples

Chemotherapy examples	• Bendamustine (Treanda, Bendeka) • Chlorambucil (Leukeran) • Cyclophosphamide (Cytoxan, Neosar) • Doxorubicin (Adriamycin, Rubex) • Vincristine (Oncovin, Vincasar PFS) • Cyclophosphamide, vincristine, and prednisone (CVP)
Chemoimmunotherapy example	• Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP)
Immunotherapy examples	• Rituximab (Rituxan) • Obinutuzumab (Gazyva)
Immune modulator	• Lenalidomide (Revlimid)
Targeted therapy (BTKi) examples	• Acalabrutinib (Calquence) • Ibrutinib (Imbruvica) • Zanubrutinib (Brukinsa)

Chemotherapy

Chemotherapy kills fast-dividing cells throughout the body, including cancer cells and some normal cells. More than one chemotherapy may be used to treat MZL. When only one drug is used, it's called a single agent. A combination or multi-agent regimen is the use of two or more chemotherapy drugs. An example of a chemotherapy drug combination (regimen) is cyclophosphamide, vincristine, and prednisone (CVP).

Some chemotherapy drugs are liquids that are infused into a vein or injected under the skin with a needle. Other chemotherapy drugs may be given as a pill that is swallowed. The final dose differs between people because it is based on body weight and height. Intrathecal chemotherapy is injected into spinal or brain fluid.

In most cases, chemotherapy is given in cycles of treatment days followed by days of rest. This allows the body to recover before the next cycle. Cycles vary in length depending on which chemotherapy is used. You will have tests to see how the cancer is responding to treatment. You might spend time in the hospital during treatment.

Chemoimmunotherapy

Chemoimmunotherapy, also called immunochemotherapy, includes chemotherapy and immunotherapy drugs (agents) to treat cancer. One example is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP).

Immunotherapy

Immunotherapy is drug therapy that increases the activity of your immune system. By doing so, it improves your body's ability to find and destroy cancer cells. Immunotherapy can be given alone or with other types of treatment. Lenalidomide (Revlimid) is an example of an immune modulator.

Monoclonal antibody therapy

Antibody therapy uses special proteins normally produced by white blood cells and infection-fighting cells to help the body fight cancer, infection, or other diseases. Monoclonal antibodies (mAbs) used in cancer treatment may kill cancer cells directly or help the immune system recognize and then kill the cancer cells. As with other treatments, there is the potential for complications.

CD20-targeting monoclonal antibody therapy

CD20-targeting mAbs (also called anti-CD20 mAbs) such as rituximab (Rituxan) and obinutuzumab (Gazyva) work against the protein CD20 found on the surface of B cells and MZL. The drug attaches to the CD20 protein causing direct cell death. It also alerts the immune system to the cancer. This triggers normal immune cells to kill the cancer cells.

Bispecific monoclonal antibody therapy

Bispecific antibodies (BsABs) bind to 2 different proteins (CD20 and CD3 antigen) at the same time. It treats cancer by engaging T cells. Bispecifics such as epcoritamab-bysp (Epkinly) and glofitamab-gxbm (Columvi) might be an option after an HCT or CAR T-cell therapy for those with MZL that has transformed into diffuse large B-cell lymphoma

(DLBCL). Bispecifics can cause a side effect called cytokine release syndrome.

CD19-targeting CAR T-cell therapy

CAR T-cell therapy is made by removing T cells from your body and then training your own immune cells to fight the lymphoma for you by adding a CAR (chimeric antigen receptor) to the T cells. This programs the T cells to find cancer cells. The programmed T cells will be infused back into your body to find and kill cancer cells. This treatment is not for everyone. There can be severe and sometimes life-threatening reactions to this treatment.

CAR T-cell therapy is one way to target the CD19 protein found on almost all B-cell lymphomas, including MZL. There are currently 4 kinds of CD19-directed CAR T-cell therapies FDA-approved in different subtypes of lymphoma. While none is specifically FDA-approved for marginal zone lymphomas, axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), and lisocabtagene maraleucel (Breyanzi) have been studied in this disease and may be an option in third-line or later treatment.

More information on CAR T-cell therapy can be found at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Warnings about supplements and drug interactions

You might be asked to stop taking or avoid certain herbal supplements when on a systemic therapy. Some supplements can affect the ability of a drug to do its job. This is called a drug interaction.

It is critical to speak with your care team about any supplements you may be taking. Some examples include:

- Turmeric
- Ginkgo biloba
- Green tea extract
- St. John's Wort
- Antioxidants

Certain medicines can also affect the ability of a drug to do its job. Antacids, heart or blood pressure medicine, and antidepressants are just some of the medicines that might interact with a systemic therapy or supportive care medicines given during systemic therapy. Therefore, it is very important to tell your care team about any medicines, vitamins, over-the-counter (OTC) drugs, herbals, or supplements you are taking.

Bring a list with you to every visit.

Targeted therapy

Targeted therapy is drug therapy that focuses on specific or unique features of cancer cells. Targeted therapies seek out how cancer cells grow, divide, and move in the body. These drugs stop or inhibit the action of proteins within the cancer cells that help cancer cells grow and/or survive.

- **Bruton tyrosine kinase inhibitors (BTKi)** such as acalabrutinib (Calquence), ibrutinib (Imbruvica), and zanubrutinib (Brukinsa) block the BTK protein, which the lymphoma cancer relies on for survival. Since the main signal for MZL growth is blocked, the lymphoma cells eventually die off.

A biosimilar or substitute might be used in place of rituximab. A biosimilar is an almost identical version of a drug made by another company. It is used in the exact same way and at the same dose as rituximab. Biosimilars for rituximab include: Riabni, Hycela, Ruxience, and Truxima.

Immune modulator

An immunomodulator changes your immune system so it can work more effectively. Lenalidomide (Revlimid) is an example of an immune modulator.

Your preferences about treatment are always important. If you have any religious or personal beliefs about certain kinds of treatment, share them with your care team and make your wishes known. A karyotype is a picture of your chromosomes.

Radiation therapy

Radiation therapy (RT) uses high-energy radiation from photons, electrons, or protons, and other sources to kill cancer cells and shrink tumors. RT may be used as the main treatment to cure cancer (curative treatment), or as supportive care or palliative care to help ease pain or discomfort caused by cancer.

Radiation is typically delivered from outside the body by a computerized device, which can shape the treatment to closely fit the location and size of the tumor. Treatment is given in small daily doses, on workdays, with weekends off. RT treatments for those with MZL can be as short as 2 days (otherwise known as 4 Grays), or as much as 15-20 days (or 30-40 Grays).

You will see your radiation oncologist at least weekly to review your progress and to help with side effects, such as sunburn-like rash. Ask your care team which radiation option(s) are best for your situation, if RT will be combined with chemotherapy, and what side effects to expect. RT puts you at a small risk of developing another cancer in the future.

A four-dimensional (4D) CT scan might be used to plan RT. A 4D-CT records multiple images over time. It allows playback of the scan as a video, so that internal movement can be tracked and observed.

External beam radiation

External beam radiation therapy (EBRT) uses a machine outside of the body to aim radiation at the tumor(s) or areas of the body.

Common types of EBRT that may be used to treat your cancer include the following:

- **Three-dimensional conformal radiation therapy (3D-CRT)** uses computer software and CT images to aim beams that match the shape of the tumor.
- **Intensity-modulated radiation therapy (IMRT)** uses small beams of different strengths to match the shape of the tumor.
- **Involved-site radiation therapy (ISRT)** treats the cancer site or cancer found in or near lymph nodes (nodal disease).

Total body irradiation

Total body irradiation (TBI) is radiation of the whole body given before bone marrow transplant.

Hematopoietic cell transplant

A hematopoietic stem cell is an immature cell that can develop into any type of blood cell. A hematopoietic cell transplant (HCT) replaces hematopoietic stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy as part of the transplant process. You might hear it called a stem cell transplant (SCT) or a bone marrow transplant (BMT). This book will refer to it as HCT. HCTs are performed in specialized centers.

There are 2 types of HCTs:

- **Autologous** – stem cells come from you. An autologous HCT (autotransplant) is generally not used as a treatment in MZL.
- **Allogeneic** – stem cells come from a donor who may or may not be related to you.

Allogeneic transplant

An allogeneic hematopoietic cell transplant (allogeneic HCT) uses healthy stem cells from a donor. The donor may or may not be related to you. Before an HCT, treatment is needed to destroy bone marrow cells. This is called conditioning, and it creates room for the healthy donor stem cells. It also weakens the immune system so your body won't kill the transplanted cells. Chemotherapy is used for conditioning. Radiation therapy may also be given as part of conditioning treatment.

After conditioning, you will receive a transfusion of the healthy stem cells from a donor matched to you. A transfusion is a slow injection of blood products into a vein. This can take several hours. The transplanted stem cells will travel to your bone marrow and grow. New, healthy blood cells will form. This is called engraftment. It usually takes about 2 to 4 weeks. Until then, you will have little or no immune defense. You may need to stay in a very clean room at the hospital or be given antibiotics to prevent or treat infection. Transfusions are also possible. A red blood cell transfusion is used to prevent bleeding and to treat anemia (below normal red blood cell count). A platelet transfusion is used to treat a low platelet count or bleeding. While waiting for the cells to engraft, you will likely feel tired and weak.

The goal of the transplant is for the new immune system to recognize the lymphoma as foreign and destroy it.

Possible side effects

Every treatment has side effects. You will be monitored for infections, decreases in your blood counts that require blood transfusions, disease relapse, and graft-versus-host disease (GVHD). In GVHD, the donor cells attack your normal, healthy tissue. There are treatments for GVHD. Ask your care team about the possible side effects or complications of HCT and how this might affect your quality of life.

More information on GVHD can be found NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Surgery

Typically, surgery is not used to treat MZL. Surgery is an operation or procedure to remove cancer from the body. Surgery might include the removal of the spleen called a splenectomy. If surgery is needed, seek the opinion of an experienced surgeon. The surgeon should be an expert in performing your type of surgery in those with MZL. Hospitals that perform many surgeries often have better results. You can ask for a referral to a hospital or cancer center that has experience in treating your type of cancer.

Clinical trials

A clinical trial is a type of medical research study. After being developed and tested in a laboratory, potential new ways of treating cancer need to be studied in people. If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. Food and Drug Administration (FDA).

Everyone with cancer should carefully consider all of the treatment options available for their cancer type, including standard treatments and clinical trials. Talk to your doctor about whether a clinical trial may make sense for you.

Phases

Most cancer clinical trials focus on treatment. Treatment trials are done in phases.

- **Phase I trials** study the dose, safety, and side effects of an investigational drug or treatment approach. They also look for early signs that the drug or approach is helpful.
- **Phase II trials** study how well the drug or approach works against a specific type of cancer.
- **Phase III trials** test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase IV trials** study the long-term safety and benefit of an FDA-approved treatment.

Who can enroll?

Every clinical trial has rules for joining, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, lab tests, or general health. These requirements ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Informed consent

Clinical trials are managed by a group of experts called a research team. The research team will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss with family,

friends, or others whom you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Start the conversation

Don't wait for your doctor to bring up clinical trials. Start the conversation and learn about all of your treatment options. If you find a study that you may be eligible for, ask your treatment team if you meet the requirements. If you have already started standard treatment you may not be eligible for certain clinical trials. Try not to be discouraged if you cannot join. New clinical trials are always becoming available.

Frequently asked questions

There are many myths and misconceptions surrounding clinical trials. The possible benefits and risks are not well understood by many with cancer.

Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in cancer clinical trials. It is common to receive either a placebo with a standard treatment, or a new drug with a standard treatment. You will be informed, verbally and in writing, if a placebo is part of a clinical trial before you enroll.

Do I have to pay to be in a clinical trial?

It depends on the study, your health insurance, and the state in which you live. In general, procedures, drugs, or tests that are considered standard of care will be billed to you or your insurance, whereas those considered research are covered by the trial sponsor. Your treatment team and the research team can help determine if you are responsible for any costs.

Finding a clinical trial

In the United States

NCCN Cancer Centers
NCCN.org/cancercenters

The National Cancer Institute (NCI)
cancer.gov/about-cancer/treatment/clinical-trials/search

Worldwide

The U.S. National Library of Medicine (NLM)
clinicaltrials.gov

Need help finding a clinical trial?

NCI's Cancer Information Service (CIS)
1.800.4.CANCER (1.800.422.6237)
cancer.gov/contact

Supportive care

Supportive care will be specific to your needs. Supportive care is health care given to prevent, reduce, and relieve suffering, and to improve quality of life. Supportive care might include pain relief, palliative care, emotional or spiritual support, financial aid, or family counseling. Tell your care team how you are feeling and about any side effects so they can be managed. Supportive care, best supportive care, and palliative care often mean the same thing.

It is very important to take care of yourself by eating well, drinking plenty of fluids, exercising, and doing things that make you feel energized. Strength is needed to sustain you during treatment.

Side effects

All cancer treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person. Some side effects may be harmful to your health. Others may just be unpleasant. Treatment can cause several side effects. Some are very serious.

Ask for a complete list of side effects of your treatments. Also, tell your treatment team about any new or worsening symptoms. There may be ways to help you feel better. There are also ways to prevent some side effects. You will be monitored closely for side effects.

Late effects

Late effects are side effects that occur months or years after a disease is diagnosed or after treatment has ended. Late effects may be caused by cancer or cancer treatment. They may include physical, mental, and social problems, and second cancers. The sooner late effects are treated the better. Ask your care team about what late effects could occur. This will help you know what to look for.

Survivorship

A person is a cancer survivor from the time of diagnosis until the end of life. After treatment, your health will be monitored for side effects of treatment and the return of cancer. This is part of your survivorship care plan. It is important to keep any follow-up doctor visits and imaging test appointments. Seek good routine medical care, including regular doctor visits for preventive care and cancer screening.

A personalized survivorship care plan will contain a summary of possible long-term effects of treatment called late effects and list follow-up tests. Find out how your primary care provider will coordinate with specialists for your follow-up care.

Side effects

Some potential side effects are described next. They are not listed in order of importance. Some side effects are very rare.

Blood clots

Cancer can cause blood clots to form. This can block blood flow and oxygen in the body. Blood clots can break loose and travel to other parts of the body causing stroke or other problems.

Cytokine release syndrome

Cytokine release syndrome (CRS) is a condition that may occur after treatment with some types of immunotherapy, such as monoclonal antibodies and CAR T cells. It is caused by a large, rapid release of cytokines from immune cells affected by the immunotherapy. Signs and symptoms of CRS include fever, muscle aches, nausea, headache, rash, fast heartbeat, low blood pressure, and trouble breathing.

Diarrhea

Diarrhea is frequent and watery bowel movements. Your care team will tell you how to manage diarrhea. It is important to drink lots of fluids.

Distress

Depression, anxiety, and sleeping issues are common and are a normal part of cancer diagnosis. Talk to your care team and with those whom you feel most comfortable about how you are feeling. There are services, people, and medicines that can help you. Support and counseling services are available.

Fatigue

Fatigue is extreme tiredness and inability to function due to lack of energy. Fatigue may be caused by cancer or it may be a side effect of treatment. Let your care team know how you are feeling and if fatigue is getting in the way of doing the things you enjoy. Eating a balanced diet, exercise, yoga, acupuncture, and massage therapy can help. You might be referred to a nutritionist or dietitian to help with fatigue.

Hair loss

Chemotherapy may cause hair loss (alopecia) all over your body—not just on your scalp. Some chemotherapy drugs are more likely than others to cause hair loss. Dosage might also affect the amount of hair loss. Most of the time, hair loss from chemotherapy is temporary. Hair often regrows 3 to 6 months after treatment ends. Your hair may be a different shade or texture.

Hand-foot syndrome

Hand-foot syndrome is a common side effect of chemotherapy. Small amounts of chemotherapy leak out of very small blood vessels called capillaries in the palms of the hands and soles of the feet. It causes redness, swelling, and pain. Sometimes blisters appear. You will want to protect your hands and feet by applying moisturizer or lotion.

Hypersensitivity, allergy, and anaphylaxis

Certain treatments can cause an unwanted reaction. Hypersensitivity is an exaggerated response by the immune system to a drug or other substance. This can include hives, skin welts, and trouble breathing. An allergy is an

immune reaction to a substance that normally is harmless or would not cause an immune response in most people. An allergic response may cause harmful symptoms such as itching or inflammation (swelling). Anaphylaxis or anaphylactic shock is a severe and possible life-threatening allergic reaction.

Infections

Infections occur more frequently and are more severe in those with a weakened immune system. Drug treatment for MZL can weaken the body's natural defense against infections. If not treated early, infections can be fatal.

Neutropenia, a low number of white blood cells, can lead to frequent or severe infections. When someone with neutropenia also develops a fever, it is called febrile neutropenia (FN). With FN, your risk of infection may be higher than normal. This is because a low number of white blood cells leads to a reduced ability to fight infections. FN is a side effect of some types of systemic therapy.

Loss of appetite

Sometimes side effects from cancer or its treatment, and the stress of having cancer might cause you to feel not hungry or sick to your stomach (nauseated). You might have a sore mouth or difficulty swallowing. Healthy eating is important during treatment. It includes eating a balanced diet, eating the right amount of food, and drinking enough fluids. A registered dietitian who is an expert in nutrition and food can help. Speak to your care team if you have trouble eating or maintaining weight.

Supportive care resources

More information on supportive care is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Low blood cell counts

Some cancer treatments can cause low blood cell counts.

- **Anemia** is a condition where your body does not have enough healthy blood cells, resulting in less oxygen being carried to your cells. You might tire easily if you are anemic.
- **Neutropenia** is a decrease in neutrophils, a type of white blood cell. This puts you at risk for infection.
- **Thrombocytopenia** is a condition where there are not enough platelets found in the blood. This puts you at risk for bleeding.

Lymphedema

Lymphedema is a condition in which lymph fluid builds up in tissues and causes swelling. It may be caused when part of the lymph system is damaged or blocked, such as during surgery to remove lymph nodes, or by radiation therapy. Cancers that block lymph vessels can also cause lymphedema. Swelling usually develops slowly over time. It may develop during treatment, or it may start years after treatment. If you have lymphedema, you may be referred to an expert in lymphedema management. The swelling may be reduced by exercise, massage, compression devices, and other means.

Nausea and vomiting

Nausea and vomiting are common side effects of treatment. You will be given medicine to prevent nausea and vomiting.

Seek out support groups at your local hospital, through social media, or from those listed in the back of this book. Look to friends, relatives, neighbors, and coworkers for social support.

Neurocognitive or neuropsychological effects

Some treatments can damage the nervous system (neurotoxicity) causing problems with concentration and memory. Survivors are at risk for neurotoxicity and might be recommended for neuropsychological testing. Neuropsychology looks at how the health of your brain affects your thinking and behavior. Neuropsychological testing can identify your limits and doctors can create a plan to help with these limits.

Neuropathy

Neuropathy is a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse over time. Neuropathy may be caused by cancer or cancer treatment such as chemotherapy. Most of the time, neuropathy goes away after treatment.

Neurotoxicity

Some treatments can damage the nervous system (neurotoxicity) causing problems with concentration and memory. Seizures and confusion can occur.

Organ issues

Treatment might cause your kidneys, liver, and heart to not work as well as they should.

Keep a pain diary

A pain diary is a written record that helps you keep track of when you have pain, how bad it is, what causes it, and what makes it better or worse. Use a pain diary to discuss your pain with your care team. You might be referred to a specialist for pain management.

Include in your pain diary:

- ✓ The time and dose of all medicines
- ✓ When pain starts and ends or lessens
- ✓ Where you feel pain
- ✓ A description of your pain. Is it throbbing, sharp, tingling, shooting, or burning? Is it constant, or does it come and go?
- ✓ Does the pain change at different times of day? When?
- ✓ Does the pain get worse before or after meals? Does certain food or drink make it better?
- ✓ Does the pain get better or worse with activity? What kind of activity?
- ✓ Does the pain keep you from falling asleep at night? Does pain wake you up in the night?
- ✓ A rating of your pain from 0 (no pain) to 10 (worst pain you have ever felt)
- ✓ Does pain get in the way of you doing the things you enjoy?

Pain

Tell your care team about any pain or discomfort. You might meet with a palliative care specialist or with a pain specialist to manage pain.

Quality of life

Cancer and its treatment can affect your overall well-being or quality of life (QOL). For more information on quality of life, see *NCCN Guidelines for Patients: Palliative Care* at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Therapy-related toxicity

Many of the drug therapies used to treat marginal zone lymphomas can be harmful to the body. You will be closely monitored for therapy-related toxicity.

All cancer treatments can cause unwanted health issues called side effects. It is important to tell your care team about all of your side effects so they can be managed.

Tumor lysis syndrome

Cancer treatment causes cell death. In tumor lysis syndrome (TLS), waste released by dead cells builds up in the body causing kidney damage and severe blood electrolyte disturbances. Changes in creatinine, lactic acid, uric acid, phosphorus (Phos), potassium (K), and calcium (Ca) levels can be a sign of TLS. TLS is rare.

Weight gain

Weight gain is one side effect of high-dose steroids. This can be uncomfortable and cause distress. It is important to maintain muscle mass. Find a physical activity you enjoy. Ask your care team what can be done to help manage weight gain.

Key points

- Marginal zone lymphoma (MZL) is highly treatable and curable in certain circumstances. The goal of treatment is to achieve a complete response (CR) or complete remission.
- Treatment can affect fertility in all sexes. Those who want to have children in the future should be referred to a fertility specialist before starting chemotherapy and/or radiation therapy to discuss the options.
- Systemic (drug) therapy works throughout the body. It includes chemotherapy, targeted therapy, and immunotherapy.
- Radiation therapy (RT) uses high-energy radiation from photons, protons, electrons, and other sources to kill cancer cells and shrink tumors.
- A hematopoietic cell transplant (HCT) replaces damaged stem cells with healthy stem cells.
- A clinical trial is a type of research that studies a treatment to see how safe it is and how well it works.
- Supportive care is health care that relieves symptoms caused by cancer or its treatment and improves quality of life. Supportive care is always given.
- Eating a balanced diet, drinking enough fluids, exercise, and doing the things you enjoy can help manage side effects.
- Some side effects, called late effects, may take years to appear. Risk for late effects will depend on the type(s) of cancer treatment you had, and the dose and the length of time you were treated. It is important to keep follow-up appointments.

4

Extranodal MZL (stomach only)

Extranodal marginal zone lymphoma (EMZL) can be found in almost any part of the body with the stomach being the most common site. This chapter is for EMZL of the stomach. Together, you and your care team will choose a treatment plan that is best for you.

Overview

The stomach is part of the digestive or gastrointestinal (GI) tract. The GI tract also includes the esophagus, small intestine, colon, and rectum. The innermost layer of the GI tract is called the mucosa. Extranodal marginal zone lymphoma (EMZL) of the stomach forms in cells in the mucosa that help make antibodies. Antibodies are proteins that protect you when an unwanted substance or infection enters your body. Those with EMZL of the stomach may also have infection in the stomach caused by *Helicobacter pylori* (*H. pylori*) or an autoimmune disease, such as Hashimoto thyroiditis or Sjögren syndrome. EMZL of the stomach is also called gastric EMZL. Most EMZLs grow slowly and tend not to spread to other places in the body.

EMZL cancer stages

Cancer staging is used to reflect prognosis and help guide treatment decisions. The American Joint Committee on Cancer (AJCC) created a staging system to determine how much cancer is in your body, where it is located, and what subtype you have. Other common staging systems used for EMZL include the Lugano Staging System for Gastrointestinal Lymphomas and Lugano Modification of Ann Arbor Staging System.

Staging is based on a combination of information to reach a final numbered stage. Often, not all information is available at the initial evaluation. More information can be gathered as treatment begins. Your care team may explain your cancer stage in different ways than described next.

- **Early-stage or stage 1 disease** – Cancer is found only in the stomach.
- **Stage 2 disease** – Cancer is also found in the lymph nodes near the stomach.
- **Stage 2E disease** – Cancer has grown though the layers of the stomach wall (serosa) and into nearby organs and tissues.
- **Stage 4 disease** – Cancer has spread from the stomach and is found on both sides of the diaphragm or in distant sites such as bone marrow or distant lymph nodes.

In EMZL of the stomach, staging is based on a biopsy taken during an endoscopy and testing for *H. pylori.* In an endoscopy, a device is guided down the throat into the stomach. You will likely have more than one endoscopy and biopsy through the course of diagnosis, treatment, and follow-up for your EMZL.

H. pylori

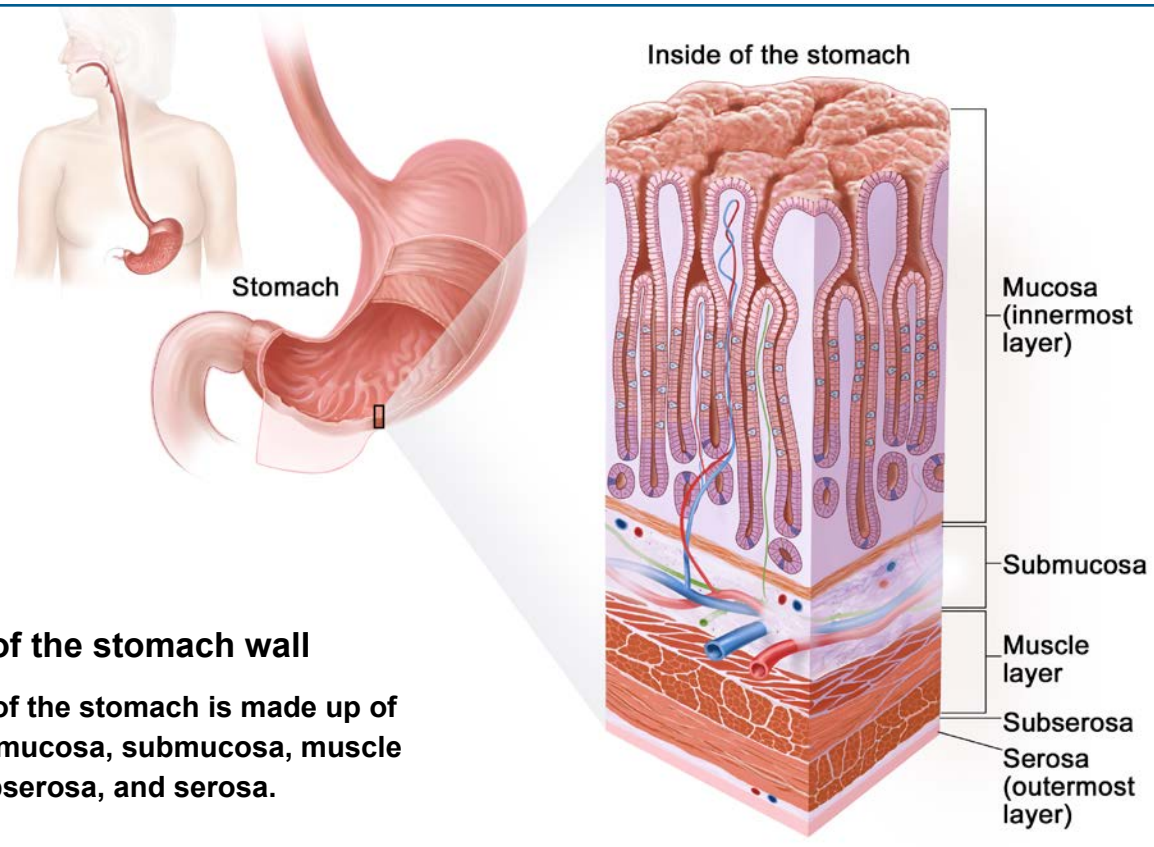
Helicobacter pylori or *H. pylori* is a type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with *H. pylori* infections may be more likely to develop cancer in the stomach, including EMZL of the stomach. You will be tested for *H. pylori* before starting treatment.

Lymph nodes

EMZL of the stomach can sometimes spread to nearby lymph nodes. There are hundreds of lymph nodes throughout your body. They work as filters to help fight infection and remove harmful things from your body. Regional lymph nodes are found near the stomach.

Lymph drains from the stomach wall into lymphatic vessels in the mucosa and submucosa. From here it drains into lymph nodes outside the stomach. There are several groups of regional lymph nodes that drain the wall of the stomach. They include pyloric (pylorus area of stomach), perigastric, pericardiac at the esophagogastric junction, and lymph nodes near organs and arteries such as the pancreas, spleen (splenic), and liver (hepatic).

The largest group of stomach lymph nodes are the perigastric lymph nodes found along the lesser and greater curves of the stomach and in the omenta. The omentum is a fold of the thin tissue that lines the abdomen (peritoneum)



Layers of the stomach wall

The wall of the stomach is made up of 5 layers: mucosa, submucosa, muscle layer, subserosa, and serosa.

that surrounds the stomach and other organs in the abdomen.

Testing

To diagnose extranodal MZL of the stomach, a biopsy sample will be taken during an endoscopy. In an endoscopy, a device is guided down the throat into the stomach. The sample will be tested to confirm you have EMZL of the stomach, to learn more about the cancer, and to plan treatment. EMZL of the stomach immunophenotype is usually CD10-, CD5-, CD20+, cyclin D1-, and BCL2-. This means that the abnormal B cells express CD20, but not CD10, CD5, cyclin D1, or BCL2.

A translocation is a switching of parts between two chromosomes. A translocation between chromosome 11 and 18 is written as t(11;18). t(11;18) occurs specifically in some cases of EMZL of the stomach and is the most frequent genetic abnormality found in this tumor. If this translocation is found, the tumor tends not to respond to antibiotic treatment in gastric EMZL cancers caused by *H. pylori* infection. Therefore, radiation therapy and/or rituximab will usually be given with antibiotics.

Tests used to diagnose EMZL of the stomach are found in **Guide 2.**

Guide 2
Tests to diagnose EMZL of the stomach

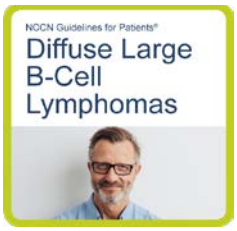
Needed	• Endoscopic biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/ lambda, CD21 or CD23, cyclin D1, and BLC6 with or without cell surface marker analysis by flow cytometry: kappa/ lambda, CD19, CD20, CD5, CD23, and CD10 • If positive for *H. pylori*, then PCR or FISH for t(11;18)
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements and *MYD88* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL) • Karyotype or FISH: t(1;14); t(3;14); t(11;14) • FISH or PCR: t(14;18)

Treatment

Tests used to plan treatment are found in **Guide 3.**

Any area of diffuse large B-cell lymphoma (DLBCL) should be treated as DLBCL.

For more information, read the *NCCN Guidelines for Patients: Diffuse Large B-Cell Lymphomas,* available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Guide 3
Tests to plan treatment: EMZL of the stomach

Endoscopic biopsy and hematopathology review
Immunophenotyping with immunohistochemistry (IHC) and flow cytometry (FCM)
Physical exam with performance status (PS)
Complete blood count (CBC) with differential, lactate dehydrogenase (LDH), comprehensive metabolic panel (CMP), and hepatitis B, hepatitis C, and *H. pylori* testing
CT with contrast of chest, abdomen, and pelvis (C/A/P) or PET/CT scan
Pregnancy test if chemotherapy or radiation therapy will be used
Possible: • Bone marrow biopsy with or without aspirate • Echocardiogram or multigated acquisition (MUGA) scan • Endoscopy with ultrasound (if available) with multiple biopsies of sites • Discussion of fertility preservation • Serum protein electrophoresis (SPEP) blood test

Stage 1

Stage 1 cancer is confined to the stomach. Since EMZL of the stomach is often the result of an infection with *H. pylori,* the initial treatment is antibiotic therapy, usually combined with proton pump inhibitors (PPIs). PPIs reduce the production of stomach acid to help prevent or heal ulcers. Many of these lymphomas go away following antibiotic and PPI treatment, although this may take several months. Additional treatment might include radiation therapy or rituximab. Involved-site radiation therapy (ISRT) treats the cancer site or cancer found in or near lymph nodes (nodal disease).

After treatment with antibiotics only

After about 6 months of completing treatment, the lymphoma will be restaged with an endoscopic biopsy to see if *H. pylori* or lymphoma remain and to rule out diffuse large B-cell lymphoma (DLBCL).

Treatment options after antibiotics:

- If *H. pylori* remains, then you will be given another round of antibiotics.
- If lymphoma remains and you have symptoms, then you might be given ISRT.
- If both remain and disease is stable, then you will likely be given another round of antibiotics.
- If both remain and disease is progressing or you have symptoms, then you will likely be given antibiotics with ISRT.

After treatment with ISRT or rituximab

After about 6 months of completing treatment, the lymphoma will be restaged with an endoscopic biopsy to see if *H. pylori* or lymphoma remain and to rule out diffuse large B-cell lymphoma (DLBCL).

Treatment options after ISRT or rituximab:

- If *H. pylori* remains, then you might be given another round of antibiotics.
- If lymphoma remains, then you will be given first-line systemic therapy. First-line therapy is the first set of drug treatment given. **See Guide 4.**
- If both lymphoma and *H. pylori* remain, then you will be given first-line systemic therapy. **See Guide 4.**
- If there is no sign of *H. pylori* or lymphoma, then you will have regular follow-up appointments every 3 to 6 months for 5 years and then every year as needed.

Stages 2, 2E, and 4

Stage 2 disease is found in lymph nodes near the stomach. Stage 2E disease has extended outside the stomach into the surrounding organs or tissues. Disease that has grown outside the stomach, has spread to distant areas of the body (stage 4), or is causing symptoms might be referred to as distant nodal or advanced stage.

Treatment will likely start when you have any the following:

- Symptoms
- Gastrointestinal (GI) bleeding
- Threatened end-organ function (refers to damage occurring in major organs fed by the circulatory system such as the heart, kidneys, brain, and eyes)
- Significant bulky disease
- Steady or rapid progression

Treatment includes first-line systemic therapy or ISRT. A clinical trial is always an option even in those without signs or symptoms.

First-line therapy

First-line systemic therapy is the first set of drug treatment given. For a list of first-line therapy options, **see Guide 4.**

Guide 4
First-line therapy options: EMZL

Preferred options	• Bendamustine with rituximab • Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab
Other recommended	• Lenalidomide with rituximab • Rituximab
	For those who are older or unwell: • Chlorambucil with or without rituximab • Cyclophosphamide with or without rituximab

*An FDA-approved biosimilar might be used in place of rituximab.

Second- and next-line therapy

Second-line therapy is the next set of drug treatment given if the cancer does not respond to the current treatment or relapses (comes back) during or after systemic therapy. After 2 or more lines of systemic therapy, CAR T-cell therapy (axicabtagene ciloleucel) might be given. **See Guide 5.**

Recurrence

If lymphoma returns after treatment (called recurrence or relapse) or does not respond to current treatment (refractory), then treatment options include antibiotics, radiation therapy, second-line systemic therapy, and/or a clinical trial. Second-line therapy is the next treatment given if cancer progresses during or after systemic therapy. Sometimes, a hematopoietic cell transplant (HCT) is an option. After 2 or more lines of systemic therapy, CAR T-cell therapy (axicabtagene ciloleucel) might be given.

Second-line and next-line therapy options can be found in **Guide 5.**

Guide 5
Second-line and next-line therapy options: EMZL

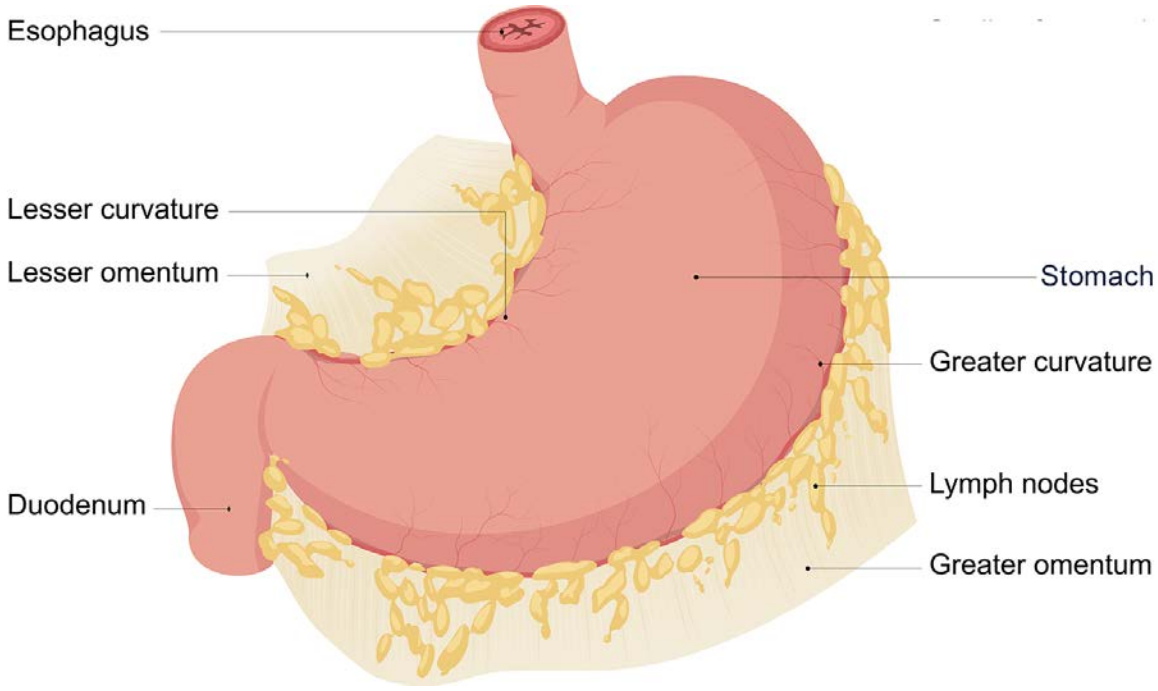
Preferred options	• Bendamustine with obinutuzumab or rituximab (not recommended if you had bendamustine before) • Acalabrutinib or zanubrutinib • Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab • Lenalidomide with rituximab
Other recommended	• Ibrutinib • Lenalidomide with obinutuzumab • Rituximab
	For those who are older or unwell: • Chlorambucil with or without rituximab • Cyclophosphamide with or without rituximab • Ibrutinib

*An FDA-approved biosimilar might be used in place of rituximab.

Key points

- The stomach is the most common site for extranodal marginal zone lymphoma (EMZL).
- EMZL of the stomach forms in cells in the innermost layer of the digestive tract called the mucosa.
- EMZL of the stomach can be the result of an infection with *H. pylori.*
- If EMZL of the stomach tests positive for *H. pylori,* then the initial treatment is antibiotic therapy.
- If EMZL of the stomach tests negative for *H. pylori,* the preferred treatment is involved-site radiation therapy (ISRT).
- For disease that has grown outside the stomach, has spread to distant areas of the body, or is causing symptoms, treatment might include systemic therapy.

EMZL of the stomach can sometimes spread to nearby lymph nodes and other tissues and organs outside of the stomach.



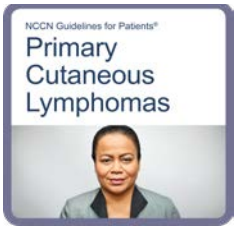
5
Extranodal MZL (other sites)

Extranodal marginal zone lymphoma (EMZL) can develop in almost any part of the body. This chapter is for EMZL not found in the stomach (non-gastric). Together, you and your care team will choose a treatment plan that is best for you.

Overview

Extranodal marginal zone lymphoma (EMZL) can be found in almost any part of the body. Each type is based on location. Typical sites include the following: bowel (small and large), breast, head and neck, lung, around the eye (ocular adnexa), ovary, parotid, prostate, and salivary gland. EMZL may return many years after treatment.

EMZL of the skin (cutaneous) is not covered in this chapter. For primary cutaneous marginal zone lymphoma (PCMZL), read the *NCCN Guidelines for Patients: Primary Cutaneous Lymphomas* available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Standard of care is the best-known way to treat a particular disease based on past clinical trials. There may be more than one treatment regimen that is considered standard of care. Ask your care team what treatment options are available and if a clinical trial might be right for you.

Testing

To diagnose EMZL, a biopsy sample will be taken and tested. EMZL immunophenotype is usually CD10-, CD5-, CD20+, CD23-/+, CD43-/+, cyclin D1-, and BCL2-. This means that the abnormal B cells express CD20, but not CD10, CD5, cyclin D1, or BCL2. CD23 or CD43 may be present.

Translocation is a switching of parts between two chromosomes. A translocation between chromosome 11 and 18 is written as t(11;18). t(11;18) occurs specifically in EMZL and is the most frequent genetic abnormality found in this tumor.

Tests used to diagnose EMZL of non-stomach sites can be found in **Guide 6.**

What's the difference between a sign and symptom?

A sign can be seen by someone else like a doctor or nurse. A symptom is something only you can feel.

Guide 6
Tests to diagnose EMZL not found in the stomach

Needed	• Biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/ lambda, CD21 or CD23, and cyclin D1 with or without cell surface marker analysis by flow cytometry: kappa/ lambda, CD19, CD20, CD5, CD23, and CD10
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements and *MYD88* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL), PCR for t(11;18) • Karyotype or FISH: t(11;18); t(1;14); t(3;14) • FISH or PCR: t(14;18)

Treatment

EMZL can appear in a variety of areas throughout the body. Therefore, treatment is based on the exact location and extent of spread. In cases where primary site is thought to be in the head, neck, or lungs, an upper GI endoscopy should be considered. In an upper gastrointestinal (GI) endoscopy or esophagogastroduodenoscopy (EGD), a device is guided down the throat into the esophagus, stomach, and beginning parts of the small intestine (duodenum). An EGD is used to inspect the lining of these organs and to look for any signs of cancer or other abnormalities such as enlarged blood vessels or ulcers. An EGD can also be referred to as a duodenoscopy.

Tests used to plan treatment are found in **Guide 7.**

Guide 7
Tests to plan treatment: EMZL not found in the stomach

Biopsy and hematopathology review
Immunophenotyping with immunohistochemistry (IHC) and flow cytometry
Physical exam with performance status (PS)
Complete blood count (CBC) with differential, lactate dehydrogenase (LDH), comprehensive metabolic panel (CMP), and hepatitis B and hepatitis C testing
PET/CT scan or CT with contrast of chest, abdomen, and pelvis (C/A/P)
Pregnancy test if chemotherapy or radiation therapy will be used
Possible: • Echocardiogram or multigated acquisition (MUGA) scan • Bone marrow biopsy with or without aspirate • Endoscopy with multiple biopsies of sites • MRI with contrast for neurologic evaluation • MRI of head/neck, skull, and eyes • Neck CT scan with contrast • Evaluation for autoimmune disease • Serum protein electrophoresis (SPEP) blood test • Discussion of fertility preservation

Stage 1 and 2 (limited)

The preferred treatment for disease that is limited to the organ is involved-site radiation therapy (ISRT). In some cases, surgery might be an option for sites such as the skin, lung, breast (lumpectomy), thyroid, colon, and small bowel. ISRT might follow surgery. In some cases, rituximab or observation may also be options.

Stage 4 (advanced)

Advanced disease has spread to distant sites. Observation is an option in some cases. For advanced disease treatment options, see *Stages 3 and 4 (advanced)* in *Chapter 6: Nodal MZL.*

Follow-up care

After treatment, you will be monitored for signs or symptoms that cancer has returned. During this time, you will have a physical exam with lab tests every 3 to 6 months for 5 years and then every year afterward. Imaging tests such as CT and PET/CT scans may be offered during this surveillance period depending on if you have new or worsening symptoms.

Recurrence

Local

A local recurrence is the return of cancer near the same place as before. You might receive involved-site radiation therapy (ISRT) if you did not have it before. For other treatment options, see *Stages 3 and 4 (advanced)* in *Chapter 6: Nodal MZL.*

Systemic

In systemic recurrence, cancer is found in the blood, bone marrow, or in multiple different areas.

Treatment will likely start when you have any of the following:

- Symptoms
- Gastrointestinal (GI) bleeding
- Threatened end-organ function (refers to damage occurring in major organs fed by the circulatory system such as the heart, kidneys, brain, and eyes)
- Significant bulky disease
- Steady or rapid progression

If you did not have systemic therapy before, then you will be treated with first-line therapy. **See Guide 4**.

If you were previously treated with rituximab, then you will be treated with second-line therapy. **See Guide 5.**

Key points

- Extranodal marginal zone lymphoma (EMZL) may be found in almost any part of the body.
- Typical non-gastric sites include the following: bowel (small and large), breast, head and neck, lung, around the eye (ocular adnexa), ovary, parotid, prostate, and salivary gland.
- Treatment is based on the exact location and extent of spread.
- Treatment options may include a combination of surgery, radiation therapy, and chemoimmunotherapy depending on the location of the cancer and if it is early or advanced disease. Observation and clinical trials may also be considered.
- Your preferences about treatment are always important. Make your wishes known.

Take our survey,
and help make the
NCCN Guidelines for Patients
better for everyone!

NCCN.org/patients/comments

6
Nodal MZL

Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. However, NMZL can be found outside of the lymph nodes in the bone marrow or blood. Together, you and your care team will choose a treatment plan that is best for you.

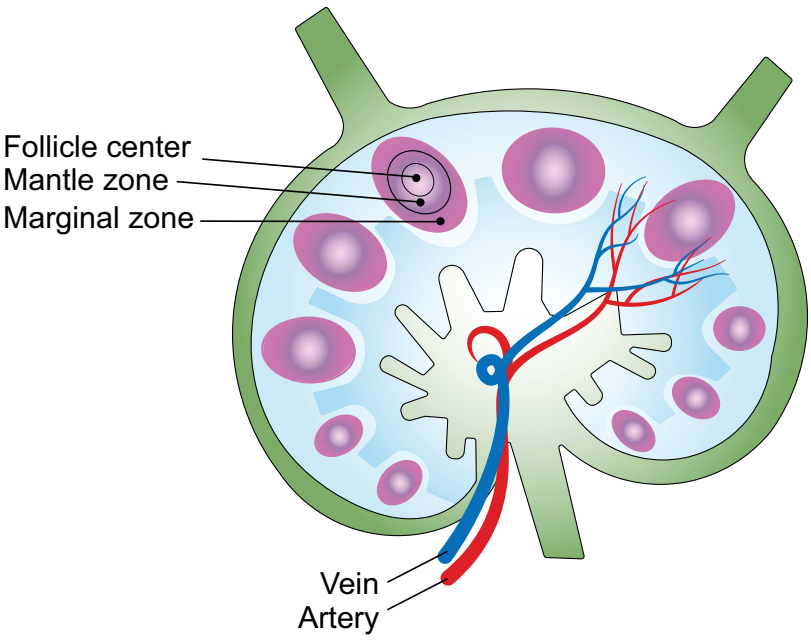
Overview

Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. However, NMZL can be found outside of the lymph nodes in the bone marrow or blood. Lymph nodes make immune cells that help the body fight infection. They also filter the lymph fluid and remove foreign material such as bacteria and cancer cells.

Most people with NMZL are diagnosed with advanced-stage disease (stage 3 or 4). This is cancer found in lymph nodes on both sides of the diaphragm, spleen, or any other organs besides the lymph nodes. At diagnosis, almost everyone with NMZL has lymph nodes that are abnormal in size or consistency. This is called lymphadenopathy and many do not have symptoms (asymptomatic).

The lymph node

Nodal marginal zone lymphoma (NMZL) is found in the marginal zone area of the lymph node.

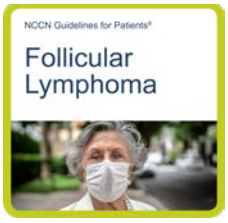


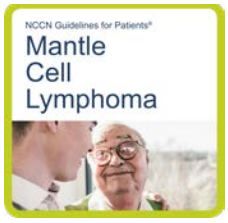
Testing

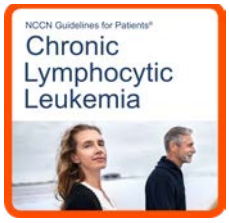
Testing is used to distinguish NMZL from nodal follicular lymphoma (FL), mantle cell lymphoma (MCL), lymphoplasmacytic lymphoma (LPL), and chronic lymphocytic leukemia (CLL), all of which are more common. NMZL immunophenotype is usually CD10-, CD5-, CD20+, CD23-/+, CD43-/+, and cyclin D1-, and BCL2-.

More information on FL, MCL, and CLL is available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Tests used to diagnose NMZL are found in **Guide 8.**







Guide 8
Tests to diagnose NMZL

Needed	• Biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/ lambda, CD21 or CD23, and cyclin D1 with or without cell surface marker analysis by flow cytometry: kappa/ lambda, CD19, CD20, CD5, CD23, and CD10
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements and *MYD88* and *CXCR4* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL), PCR for t(11;18) • Karyotype or FISH: t(11;18); t(1;14); del(13q), del(7q) • FISH or PCR: t(14;18)

Treatment

Since nodal MZL is most often a slow-growing (indolent) disease, your care team might wait until symptoms appear before starting treatment. This is called active surveillance, observation, or watch and wait. During active surveillance, your care team will monitor for symptoms to appear. Once specific signs or symptoms appear, you will start treatment. Treatment options include radiation therapy, chemotherapy, immunotherapy, or a clinical trial. Involved-site radiation therapy (ISRT) treats cancer located in a small region or one area of your body.

Tests used to plan treatment are found in **Guide 9.**

Guide 9 **Tests to plan treatment: NMZL**
Biopsy and hematopathology review
Immunophenotyping with immunohistochemistry (IHC) and flow cytometry (FCM)
Physical exam with performance status (PS)
Complete blood count (CBC) with differential, lactate dehydrogenase (LDH), comprehensive metabolic panel (CMP), and hepatitis B and hepatitis C testing
PET/CT scan (preferred) or CT with contrast of chest, abdomen, and pelvis (C/A/P) if systemic therapy is planned
Bone marrow biopsy with aspirate
Evaluation to rule out extranodal primary sites since disease outside lymph nodes is common
Pregnancy test if chemotherapy or radiation therapy will be used
Possible: • Echocardiogram or multigated acquisition (MUGA) scan • Other imaging tests • Serum protein electrophoresis (SPEP) blood test • Discussion of fertility preservation

Stages 1 and 2 (limited)

Stage 1 or contiguous stage 2

In stage 1 MZL, disease is found in one lymph node. In contiguous stage 2, disease is found in lymph node groups next to one another.

For stage 1 or contiguous stage 2 disease, treatment options include:

- ISRT (preferred)
- ISRT with CD20-targeting monoclonal antibody (mAb) therapy. Chemotherapy might be added.
- CD20-targeting monoclonal antibody therapy (rituximab or obinutuzumab) with or without chemotherapy. Obinutuzumab is not used by itself as a single agent.

Non-contiguous stage 2

In stage 2 MZL, disease is found in two or more lymph node groups on the same side of the diaphragm, but the involved lymph nodes are not near each other. Treatment options include mAb therapy that targets CD20 with or without chemotherapy. Radiation therapy (RT) might be used. Observation might be an option in some cases.

Treatment response

For a complete response (CR) or partial response (PR), observation and follow-up care is recommended. ISRT might be given if you did not have it before. If you were treated with rituximab alone, then you might have maintenance therapy with rituximab.

For no response or disease progression, see treatment for Stages 3 and 4 (advanced) in the next section. Information on treatment for MZL that has transformed into diffuse large B-cell lymphoma can be found in *Chapter 8: Transformed MZL.*

Stages 3 and 4 (advanced)

In stage 3, disease is found in lymph nodes on both sides of the diaphragm or in lymph nodes above the diaphragm and in the spleen.

In stage 4, disease is found in various areas outside of the lymph nodes.

Surveillance

Your care team might wait until certain signs or symptoms appear before starting treatment. This is called active surveillance or observation. Visits with your doctor can range between every 3 to 12 months and usually involve blood tests, a physical exam, and an assessment of your symptoms. Imaging, such as CT or PET/CT scans, are not routinely performed and only reserved for when you develop symptoms.

When to begin treatment

Treatment will likely start when you have any of the following:

- B symptoms (such as fever, night sweats, fatigue, and weight loss) and other symptoms similar to follicular lymphoma (FL)
- Threatened end-organ function (refers to damage occurring in major organs fed by

the circulatory system such as the heart, kidneys, brain, and eyes)

- Low red blood cell count not related to NMZL
- Bulky disease
- Enlarged spleen (splenomegaly)
- Steady disease progression over at least 6 months

Treatment may include chemotherapy, immunotherapy, a clinical trial, or palliative involved-site radiation therapy (ISRT). ISRT treats cancer located in a small region or one area of your body.

First-line therapy

First-line systemic therapy is the first set of drug treatment given. For a list of first-line therapy options, **see Guide 10.**

Second-line therapy

Second-line therapy is the next set of drug treatment given if cancer progresses during or after systemic therapy. After 2 or more lines of systemic therapy, CAR T-cell therapy (axicabtagene ciloleucel) might be given. **See Guide 11.**

Guide 10
First-line therapy options: NMZL

Preferred options	• Bendamustine with rituximab • Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab
Other recommended	• Lenalidomide with rituximab • Rituximab
	For those who are older or unwell: • Chlorambucil with or without rituximab • Cyclophosphamide with or without rituximab

*An FDA-approved biosimilar might be used in place of rituximab.

Treatment response

For a complete response (CR) or partial response (PR), observation and follow-up care is recommended. ISRT might be given if you did not have it before. If you were treated with rituximab alone, then you might have maintenance therapy with rituximab.

For a partial response (PR), the following is recommended:

- Maintenance therapy for those treated with rituximab alone
- Observation
- If you have had 2 or more lines of systemic therapy, then CAR T-cell therapy (axicabtagene ciloleucel)

For no response or disease progression, you may have another biopsy and another round of systemic therapy with different agents (drugs) or a clinical trial could be considered. If you have had 2 or more lines systemic therapy, then CAR T-cell therapy (axicabtagene ciloleucel) might be given.

Guide 11
Second-line and next-line therapy options: NMZL

Preferred options	• Bendamustine with obinutuzumab or rituximab (not recommended if you had bendamustine before) • Acalabrutinib or zanubrutinib • Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab • Lenalidomide with rituximab
Other recommended	• Ibrutinib • Lenalidomide with obinutuzumab • Rituximab
	For those who are older or unwell: • Chlorambucil with or without rituximab • Cyclophosphamide with or without rituximab • Ibrutinib

*An FDA-approved biosimilar might be used in place of rituximab.

Follow-up care

After treatment, you will be monitored for signs and symptoms that cancer has returned. During this time, you will have a physical exam and lab tests every 3 to 6 months for 5 years and then every year afterward or as needed. You will also have CT scans with contrast no more than every 6 months. After 2 years, you will have a CT no more than once a year. Surveillance imaging is used for monitoring those without symptoms.

Key points

- Nodal marginal zone lymphoma (NMZL) forms in and is mostly limited to the lymph nodes. However, NMZL can be found outside of the lymph nodes in the bone marrow or blood.
- Treatment options include radiation therapy, chemotherapy, immunotherapy, or a clinical trial.
- Since NMZL is most often a slow-growing disease, your care team might wait until symptoms appear before starting treatment. This is called active surveillance, observation, or watch and wait.

Let us know what you think!

Please take a moment to complete an online survey about the NCCN Guidelines for Patients.

NCCN.org/patients/response

7
Splenic MZL

The spleen makes immune cells, filters the blood, stores blood cells, and removes old blood cells. Splenic marginal zone lymphoma (SMZL) is found in the blood, bone marrow, and spleen. The most common sign of SMZL is an enlarged spleen. Together, you and your care team will choose a treatment plan that is best for you.

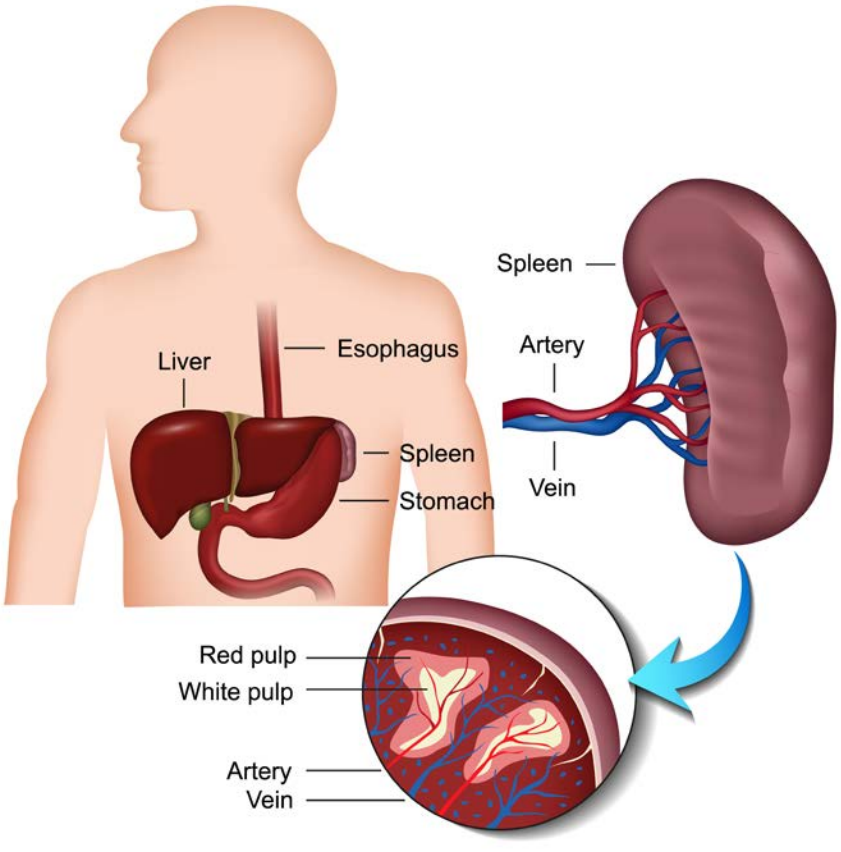
The spleen

The spleen is a fist-sized organ located on the left side of the body near the stomach, pancreas, and just under the diaphragm. The spleen filters your blood of antigens (proteins) and microorganisms, and removes any old, damaged, or worn-out red blood cells. The spleen also contains infection-fighting white blood cells and controls the level of blood cells (white blood cells, red blood cells, and platelets) in the body.

The spleen is made up of 2 types of tissues: red pulp, which filters the blood, and white pulp, which contains white blood cells that regulate inflammation and the body's response to infection.

The spleen

The spleen is made up of red and white pulp. Red pulp is a loose spongy tissue that contains lymphocytes, macrophages, granulocytes, and plasma cells. White pulp is all lymphatic (lymphoid) tissue. It contains white blood cells.



Red pulp

Red pulp gives the spleen its red color. It is a loose spongy tissue that contains white blood cells such as lymphocytes, macrophages, granulocytes, and plasma cells. The red pulp removes red blood cells—which carry oxygen—when they are old, damaged, or infected. It harvests the iron from the old red blood cells for recycling into new blood cells.

White pulp

White pulp is all lymphatic (lymphoid) tissue. It is called white because it looks whiter than the surrounding red pulp. White pulp of the spleen has 3 sections: the periarteriolar lymphatic sheath (PALS), the follicles, and the marginal zone. The marginal zone is where the distribution of blood flow between slow and fast transit pathways is controlled.

Marginal zone

The marginal zone is the region at the intersection of the red pulp and white pulp of the spleen. Cancer of the B cells in this zone affects the movement of blood through the spleen.

Testing

Splenic marginal zone lymphoma (SMZL) is the rarest type of marginal zone lymphoma. SMZL may be diagnosed by removal of the spleen (splenectomy), or by biopsy of the bone marrow and blood testing with imaging and other findings. SMZL immunophenotype is usually CD10-, CD5-, CD20+, CD23-/+, CD43-/+, and cyclin D1-, BCL2-, annexin A1, and CD103- (distinction from hairy cell leukemia) with expression of both IgM and IgD. *NOTCH2* and *KLF2* mutation status may be helpful to differentiate SMZL from other B-cell lymphoma subtypes.

Guide 12
Tests to diagnose SMZL

Needed	• Biopsy and hematopathology review • IHC panel: CD20, CD3, CD5, CD10, BCL2, kappa/ lambda, CD21 or CD23, cyclin D1, IgD, CD43, and annexin A1 with or without cell surface marker analysis by flow cytometry: kappa/ lambda, CD19, CD20, CD5, CD23, CD10, CD43, and CD103
In some cases	• Biomarker testing to detect: immunoglobulin (Ig) gene rearrangements and *MYD88* mutation status to differentiate between Waldenström macroglobulinemia (WM) and marginal zone lymphoma (MZL), *BRAF* mutation status to differentiate MZL from hairy cell leukemia (HCL), PCR for t(11;18) • Karyotype or FISH: chronic lymphocytic leukemia (CLL) panel; t(11;18); t(1;14); del(13q), del(7q) • FISH or PCR: t(14;18)

Tests used to diagnose SMZL are found in **Guide 12.**

Treatment

Tests used to plan treatment are found in **Guide 13.**

Observation

Treatment can sometimes wait if:

- You have no pain, discomfort, or other symptoms (asymptomatic),
- Your spleen is not enlarged (splenomegaly), and
- Your low red blood cell or platelet counts are not getting worse.

Enlarged spleen

If you have an enlarged spleen (splenomegaly), your blood will be tested for hepatitis C (HCV). If you test positive for HCV, HCV infection may be causing the SMZL. Anti-viral medicines used to treat HCV can also treat the SMZL. If you continue to have symptoms and low blood cell counts, then treatment with rituximab is preferred. Surgery to remove the spleen (splenectomy) is an option, but is rarely used. Pneumococcal, meningococcal, haemophilus influenza, and hepatitis B vaccinations should be given at least 2 weeks before a splenectomy.

Guide 13
Tests to plan treatment: SMZL

Biopsy and hematopathology review
Immunophenotyping with immunohistochemistry (IHC) and flow cytometry (FCM)
Physical exam with performance status (PS)
Complete blood count (CBC) with differential, lactate dehydrogenase (LDH), comprehensive metabolic panel (CMP), and hepatitis B and hepatitis C testing
CT with contrast of chest, abdomen, and pelvis (C/A/P)
Serum protein electrophoresis (SPEP) and/or immunoglobin (Ig) blood test
Pregnancy test if chemotherapy or radiation therapy will be used
Possible: • Bone marrow biopsy with or without aspirate • PET/CT scan • Other imaging tests • Other blood tests • Discussion of fertility preservation

You can live a normal, healthy life without a spleen. However, your care team will try other treatments before removing your spleen. If your spleen is removed, other organs, such as the liver, can take over many of the spleen's functions.

Follow-up care

After treatment, you will be monitored for the return of cancer. During this time, you will have a physical exam with lab and imaging tests every 3 to 6 months for 5 years and then every year afterward or as needed.

Recurrence

Recurrence is the return of cancer.

Treatment will likely start when you have any of the following:

- Symptoms such as belly (abdominal) discomfort, pain, low blood cell counts, or difficulty breathing
- Threatened end-organ function (refers to damage occurring in major organs fed by the circulatory system such as the heart, kidneys, brain, and eyes)
- Significant bulky disease
- Steady or rapid progression

Guide 14
First-line therapy options: SMZL

Preferred options	• Bendamustine with rituximab • Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab • Rituximab
Other recommended	• Lenalidomide with rituximab
	For those who are older or unwell: • Chlorambucil with or without rituximab • Cyclophosphamide with or without rituximab

*An FDA-approved biosimilar might be used in place of rituximab.

Treatment for recurrence may include systemic therapy or surgery to remove the spleen (splenectomy).

- If you did not have systemic therapy before, then you will be treated with first-line therapy. **See Guide 14.**
- If you were previously treated with rituximab, then you may be treated with second-line therapy. **See Guide 15.**

Did you know?

Chemotherapy, targeted therapy, and immunotherapy are types of systemic therapy.

Guide 15
Second-line and next-line therapy options: SMZL

Preferred options	• Bendamustine with obinutuzumab or rituximab (not recommended if you had bendamustine before) • Acalabrutinib or zanubrutinib • Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) with rituximab • Lenalidomide with rituximab
Other recommended	• Ibrutinib • Lenalidomide with obinutuzumab • Rituximab
	For those who are older or unwell: • Chlorambucil with or without rituximab • Cyclophosphamide with or without rituximab • Ibrutinib

*An FDA-approved biosimilar might be used in place of rituximab.

Key points

- The spleen is the largest lymphatic organ. It makes immune cells, filters the blood, stores blood cells, and removes old blood cells.
- Splenic marginal zone lymphoma (SMZL) is found in the blood, bone marrow, and marginal zone of the spleen.
- Treatment can sometimes wait until you have symptoms, an enlarged spleen, and a worsening low red blood cell, white blood cell, or platelet count.
- If you test positive for hepatitis C, then it will be treated.
- After treatment, you will be monitored for recurrence, the return of cancer. Recurrence is treated with systemic therapy, surgery to remove the spleen (splenectomy), or involved-site radiation therapy (ISRT).

We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer.

Take our survey to let us know what we got right and what we could do better.

NCCN.org/patients/feedback

8
Transformed MZL

Marginal zone lymphoma (MZL) can transform into diffuse large B-cell lymphoma (DLBCL). This means your slow-growing MZL has turned into a large-celled, fast-growing lymphoma. Together, you and your care team will choose a treatment plan that is best for you.

Overview

Marginal zone lymphoma (MZL) can transform into diffuse large B-cell lymphoma (DLBCL). This can occur before, during, or after treatment. In DLBCL, fast-dividing cells are commonly found in lymph nodes, spleen, liver, bone marrow, or other tissues and organs.

Certain gene rearrangements can be found in DLBCL. In gene rearrangements, part of a gene has broken off and attached to another gene.

- *MYC, BCL2,* and *BCL6* gene rearrangements are commonly found in DLBCL.
- Fluorescence in situ hybridization (FISH) will be done to look for gene rearrangements.

For more information, read the *NCCN Guidelines for Patients: Diffuse Large B-Cell Lymphomas,* available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

After little or no therapy

If MZL changed into DLBCL after little or no treatment, then it will be treated with a chemoimmunotherapy such as RCHOP or Pola-R-CHP. Radiation therapy might be given. Involved-site radiation therapy (ISRT) treats cancer located in a small region or one area of your body. The goal of treatment is remission.

- RCHOP consists of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
- Pola-R-CHP consists of polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Other possible chemoimmunotherapy options include:

- DA-EPOCH is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab.
- RCDOP is rituximab, cyclophosphamide, liposomal doxorubicin (Doxil), vincristine, and prednisone.
- RCEOP is rituximab, cyclophosphamide, etoposide, vincristine, and prednisone.
- RGCVP is rituximab, gemcitabine (Gemzar or Infugem), cyclophosphamide, vincristine, and prednisone.

Treatment response

After treatment, you will have imaging and lab tests to see if any cancer remains.

- In a complete response (CR) or complete remission, no cancer remains. Observation or a clinical trial are options. If disease relapses, you will have a biopsy before starting treatment.
- If a partial response (PR), then you will be given a different chemoimmunotherapy.
- If your disease did not respond to treatment or has progressed, then you will be given a different chemoimmunotherapy.

After multiple lines of therapy

If MZL changed into DLBCL after multiple lines of therapy, then the treatment recommendations include:

- Clinical trial
- Systemic therapy. Options are based on what you were treated with before, your unique situation, and other factors. A type of radiation therapy called involved-site radiation therapy (ISRT) might be added to treat cancer located in a small region or one area of your body.
- ISRT alone
- Best supportive care

Guide 16
Systemic therapy options: HCT planned

Preferred options	Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) if you did not have it before
	If previously treated with anthracycline-based regimen such as doxorubicin • Dexamethasone and cytarabine (DHA) with carboplatin, cisplatin, or oxaliplatin (platinum-based chemotherapy). Rituximab might be added. • Gemcitabine, dexamethasone, and cisplatin (GDP) or (gemcitabine, dexamethasone, and carboplatin). Rituximab might be added. • Ifosfamide, carboplatin, and etoposide (ICE). Rituximab might be added.

*An FDA-approved biosimilar might be used in place of rituximab.

The goal of treatment is remission. If an HCT is being considered, it is usually decided early in treatment planning because having an HCT will affect future treatment options. Certain treatments are not recommended before or after an HCT. For example, HCT is not recommended after CAR T-cell therapy. However, bispecific monoclonal antibody therapy can be given after HCT or CAR T-cell therapy.

Systemic therapy options are based on if an HCT is planned.

- If an HCT is planned, **see Guide 16.**
- If an HCT is not planned, **see Guide 17.**

If cancer returns or does not respond to treatment, another systemic therapy will be given. After multiple lines of systemic therapy, CAR T-cell therapy or bispecific monoclonal antibody therapy might be given.

CAR T-cell therapy options include the following:

- Lisocabtagene maraleucel (Breyanzi)
- Axicabtagene ciloleucel (Yescarta)
- Tisagenlecleucel (Kymriah).

Bispecific monoclonal antibody therapy options include:

- Epcoritamab-bysp (Epkinly)
- Glofitamab-gxbm (Columvi)

Guide 17
Systemic therapy options: HCT not planned

Preferred options	Cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (RCHOP) if you did not have it before
	If previously treated with anthracycline-based regimen such as doxorubicin • Polatuzumab vedotin-piiq. Bendamustine and/or rituximab might be added. • Tafasitamab-cxix and lenalidomide
Other recommended	• Cyclophosphamide, etoposide, vincristine, prednisone (CEOP). Rituximab might be added. • Gemcitabine, dexamethasone, and cisplatin (GDP) or (gemcitabine, dexamethasone, and carboplatin). Rituximab might be added. • Gemcitabine and oxaliplatin (GemOx). Rituximab might be added. • Loncastuximab tesirine-lpyl

*An FDA-approved biosimilar might be used in place of rituximab.

Treatment response

After treatment, you will have imaging (PET/CT scan) and lab tests to see if any cancer remains.

Complete response

In a complete response (CR) or complete remission no cancer remains. You might enter observation. An autologous (self) hematopoietic cell transplant (HCT) or an allogeneic (donor) HCT are options in some cases. ISRT might be added if you did not have it before and cancer is located in a small region or one area of your body. After treatment, you will enter surveillance and be monitored for relapse.

Partial response

In a partial response (PR), treatment options are based on the types of treatment you had before. Options listed below depend on your individual situation:

- CAR T-cell therapy (preferred, if not given before)
- Allogeneic HCT in some cases. ISRT might be added if not given before and an HCT is not planned.
- ISRT (if not given before and disease is located in a small region or one area of your body)
- Observation with follow-up tests

Chemoimmunotherapy regimen examples

- ✓ **RCHOP** is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
- ✓ **Pola-R-CHP** is polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Relapse

If disease relapses, you may have a biopsy before treatment. Treatment might include a clinical trial, a systemic therapy not used before, ISRT (if not given before and disease is located in a small region or one area of your body), CAR T-cell therapy, bispecific antibody therapy, or best supportive care. In best supportive care, the focus is improving quality of life and relieving discomfort.

No response or disease progresses

When disease progresses during treatment or does not respond to treatment, treatment might include a clinical trial, a systemic therapy not used before, ISRT (if not given before and disease is located in a small region or one area of your body), CAR T-cell therapy, bispecific antibody therapy, or best supportive care.

Key points

- Marginal zone lymphoma (MZL) can transform into diffuse large B-cell lymphoma (DLBCL). This means your slow-dividing MZL has turned into a fast-dividing lymphoma.
- The goal of treatment is remission.
- If MZL changed into DLBCL after little or no treatment, then it will be treated with a chemoimmunotherapy such as RCHOP or Pola-R-CHP. Radiation therapy might be given.
- If MZL changed into DLBCL after multiple lines of therapy, then the treatment recommendations include a clinical trial, systemic therapy, radiation therapy, or best supportive care.
- A hematopoietic cell transplant (HCT) might be an option in some cases after multiple lines of systemic therapy. If an HCT is being considered, it is usually decided early in treatment planning.
- The order of treatment matters. HCT is not an option after CAR T-cell therapy or bispecific antibody therapy.
- Bispecific antibody therapy is an option after HCT or CAR T-cell therapy.

9
Making treatment decisions

It's important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your care team.

It's your choice

In shared decision-making, you and your care team share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your care team.

Treatment decisions are very personal. What is important to you may not be important to someone else.Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments
- Your feelings about pain or side effects
- Cost of treatment, travel to treatment centers, and time away from school or work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your care team. If you take the time to build a relationship with your care team, it will help you feel supported when considering options and making treatment decisions.

Second opinion

It is normal to want to start treatment as soon as possible. While cancer can't be ignored, there is time to have another doctor review your test results and suggest a treatment plan. This is called getting a second opinion, and it's a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

Support groups

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn't have support groups for people with cancer, check out the websites listed in this book.

Questions to ask

Possible questions to ask your care team are listed on the following pages. Feel free to use these questions or come up with your own.

Questions about testing and diagnosis

1. What subtype and stage of marginal zone lymphoma do I have?
2. What does the cancer subtype and stage mean in terms of length of survival and quality of life?
3. Is there a cancer center or hospital nearby that specializes in my subtype of marginal zone lymphoma?
4. What tests will I have? How often will they be repeated?
5. Will my insurance pay for this test?
6. How soon will I know the results and who will explain them to me?
7. What will you do to make me comfortable during testing?
8. How will my biopsy be performed? What else might be done at this time?
9. How often will I have blood tests?
10. How long will it take to get these test results?

Questions about your care team's experience

1. What is your experience treating marginal zone lymphoma? What else do you treat?
2. What is the experience of those on your team?
3. I would like a second opinion. Is there someone you can recommend?
4. I would like another pathologist or hematopathologist to review my blood samples. Is there someone you recommend?
5. How many people like me have you treated?
6. Will you be consulting with experts to discuss my care? Whom will you consult?
7. How many procedures like the one you're suggesting have you done?
8. Is this treatment a major part of your practice?
9. How often is a complication expected? What are the complications?
10. Who will manage my day-to-day care?

Questions about options

1. What will happen if I do nothing?
2. How do my age, overall health, and other factors affect my options?
3. Which option is proven to work best for my cancer, age, overall health, and other factors?
4. What if I am pregnant or am planning to get pregnant soon?
5. What are the possible complications and side effects? Are any life-threatening?
6. What can be done to prevent or relieve the side effects of treatment?
7. Am I a candidate for a clinical trial? Can I join a clinical trial at any time?
8. What decisions must be made today?
9. Is there a social worker or someone who can help me decide about treatment?
10. Is there a hospital or treatment center you can recommend for treatment?

Questions about treatment

1. Which treatment(s) do you recommend and why?
2. Does the order of treatment matter?
3. When will I start treatment?
4. How long will treatment likely take?
5. What should I expect from treatment?
6. What will you do to make me comfortable during treatment?
7. How much will my insurance pay for treatment?
8. Are there programs to help me pay for treatment?
9. What are the chances my cancer will return after treatment?
10. What are my chances of developing a different cancer later in life?

Questions about radiation therapy

1. What type of radiation therapy (RT) will I have?
2. What will you target?
3. What is the goal of this RT?
4. How many treatment sessions will I require? Can you do a shorter course of RT?
5. Do you offer this type of RT here? If not, can you refer me to someone who does?
6. What side effects can I expect from RT?
7. Should I eat or drink before RT?
8. Will I be given medicine to help me relax during RT?
9. What should I wear?

Questions about surgery

1. What will be removed during surgery?
2. What kind of surgery will I have?
3. Will I have more than one surgery?
4. Does my cancer involve any veins, arteries, or nerves and how might this affect surgery?
5. What is the chance that this surgery will shorten my life?
6. Will I have a scar and where will it be located?
7. How can I prepare for surgery?
8. How long will recovery take and what should I expect?
9. How much pain will I be in? What will be done to manage my pain?
10. What treatment will I have before, during, or after surgery?

Questions about side effects

1. What are the side effects of treatment?
2. How are these side effects treated?
3. How long will these side effects last?
4. What side effects should I watch for that could be life-threatening?
5. When should I call my care team?
6. What should I do on weekends and other non-office hours?
7. What emergency department or ER should I go to?
8. Will my treatment team be able to communicate with the ER team?
9. What medicines can I take to prevent or relieve side effects?
10. What can I do to help with pain and other side effects?

Questions about clinical trials

1. What clinical trials are available for my type and stage of cancer?
2. What are the treatments used in the clinical trial?
3. What does the treatment do?
4. Has the treatment been used before? Has it been used for other types of cancer?
5. What are the risks and benefits of this treatment?
6. What side effects should I expect? How will the side effects be controlled?
7. How long will I be in the clinical trial?
8. Will I be able to get other treatments if this doesn't work?
9. How will you know the treatment is working?
10. Will the clinical trial cost me anything? If so, how much?

Questions about hematopoietic cell transplants

1. Which type of transplant is an option for me?
2. What do I need to do to prepare?
3. What are the risks to me and/or the donor?
4. How will the transplant affect my prognosis?
5. How will a transplant affect the quality and length of my life?
6. What should I expect from a transplant?
7. How long should I expect to be in the hospital?
8. How will I feel before, during, and after the transplant?
9. How many transplants has this center done for my subtype of marginal zone lymphoma?
10. What is my risk of developing graft-versus-host disease (GVHD)?

Questions about resources and support

1. Who can I talk to about help with housing, food, and other basic needs?
2. What help is available for transportation, childcare, and home care?
3. How much will I have to pay for treatment?
4. What help is available to pay for medicines and other treatment?
5. What other services are available to me and my caregivers?
6. How can I connect with others and build a support system?
7. How can I find in-person or online support?
8. Who can help me with my concerns about missing work or school?
9. Who can I talk to if I don't feel safe at home, at work, or in my neighborhood?
10. How can I get help to stop smoking or vaping?

Resources

Be the Match
bethematch.org/one-on-one

Blood & Marrow Transplant Information Network
bmtinfonet.org

Lymphoma Research Foundation
lymphoma.org

MedlinePlus
medlineplus.gov

National Bone Marrow Transplant Link (nbmtLINK)
nbmtlink.org

National Cancer Institute (NCI)
cancer.gov/types/lymphoma/patient/adult-nhl-treatment-pdq

National Coalition for Cancer Survivorship
canceradvocacy.org

The Leukemia & Lymphoma Society
LLS.org/PatientSupport

Triage Cancer
triagecancer.org

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and help make the
NCCN Guidelines for Patients
better for everyone!**

NCCN.org/patients/comments

Notes

Words to know

allogeneic hematopoietic cell transplant (allogenic HCT)
A cancer treatment that replaces abnormal blood stem cells with healthy donor cells.

autologous hematopoietic cell transplant (autologous HCT)
A cancer treatment that destroys your bone marrow then rebuilds it with your healthy stem cells. Also called high-dose therapy with autologous stem cell rescue (HDT/ASCR). The high-dose therapy is used to eradicate the disease and stem cell rescue is needed because of the toxic effects of the treatment.

best supportive care
Treatment to improve quality of life and relieve discomfort.

biomarker testing
A lab test of any molecule in your body that can be measured to assess your health. Also called molecular testing.

biopsy
A procedure that removes fluid or tissue samples to be tested for a disease.

biosimilar
A drug that is almost an identical drug made by another company. It has been approved by the U.S. Food and Drug Administration (FDA) and must be used in the exact same way and at the same dose as the other drug.

bone marrow
The sponge-like tissue in the center of most bones.

bone marrow aspiration
A procedure that removes a liquid bone marrow sample to test for a disease.

bone marrow biopsy
A procedure that removes bone and solid bone marrow samples to test for a disease.

chromosome
The structures within cells that contain coded instructions for cell behavior.

clinical trial
A type of research that assesses health tests or treatments.

complete response (CR)
No signs of lymphoma are found. Also called complete remission.

computed tomography (CT)
A test that uses x-rays from many angles to make a picture of the insides of the body.

contrast
A substance put into your body to make clearer pictures during imaging tests.

deoxyribonucleic acid (DNA)
A chain of chemicals in cells that contains coded instructions for making and controlling cells.

endoscope
A thin, long tube fitted with tools that is guided down the mouth.

flow cytometry (FCM)
A lab test of substances on the surface of cells to identify the type of cells present.

fluorescence in situ hybridization (FISH)
A lab test that uses special dyes to look for abnormal chromosomes and genes.

gastroenterologist
A doctor who's an expert in digestive diseases. This system contains organs that break down food for the body to use.

gastrointestinal (GI) tract
The group of organs through which food passes after being eaten. Also called digestive tract. It includes the esophagus, stomach, small intestine, colon, and rectum. The innermost layer of the GI tract is called the mucosa.

gene
A set of coded instructions in cells for making new cells and controlling how cells behave.

H. pylori
A type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with *H. pylori* infections may be more likely to develop cancer in the stomach, including extranodal marginal zone lymphoma (EMZL). Also called *Helicobacter pylori*.

hematopathologist
A doctor who specializes in the study of blood diseases and cancers using a microscope.

hematopoietic cell transplant (HCT)
A cancer treatment that replaces abnormal blood stem cells with healthy cells.

histology
The study of tissues and cells under a microscope.

human leukocyte antigen (HLA)
A cell protein by which your body knows its own cells from foreign cells.

imaging test
A test that makes pictures (images) of the insides of the body.

immune system
The body's natural defense against infection and disease.

immunohistochemistry (IHC)
A lab test of cancer cells to find specific cell traits involved in abnormal cell growth.

immunophenotyping
A lab test that detects the type of cells present based on the cells' surface proteins.

induction
The first treatment that is given to greatly reduce the amount of cancer.

involved-site radiation therapy (ISRT)
Uses radiation therapy to treat cancer located in a small region or one area of your body.

karyotype
Lab test that makes a map of chromosomes to find defects.

lactate dehydrogenase (LDH)
A protein in blood that helps to make energy in cells.

lymph
A clear fluid containing white blood cells.

lymph node
A small, bean-shaped disease-fighting structure.

lymphadenopathy
Lymph nodes that are abnormal in size or consistency.

lymphatic system
Germ-fighting network of tissues and organs that includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels. Part of the immune system.

lymphedema
Swelling in the body due to a buildup of fluid called lymph.

lymphocyte
A type of white blood cell that is part of the immune system.

lymphoid
Referring to a type of white blood cell called a lymphocyte.

magnetic resonance imaging (MRI)
A test that uses radio waves and powerful magnets to make pictures of the insides of the body.

maintenance
The phase of treatment used over a long period to prevent cancer from returning.

monitoring
A period of testing for changes in cancer status.

mutation
An abnormal change in the instructions within cells for making and controlling cells.

partial response (PR)
Lymphoma is still present but has reduced in size.

pathologist
A doctor who's an expert in testing cells and tissue to find disease.

peripheral blood (PB)
Blood that circulates throughout the body.

platelet (PLT)
A type of blood cell that helps control bleeding. Also called thrombocyte.

polymerase chain reaction (PCR)
A lab process in which copies of a DNA part are made.

positron emission tomography (PET)
A test that uses radioactive material to see the shape and function of body parts.

prognosis
The likely course a disease will take.

radiation therapy (RT)
A treatment that uses high-energy rays.

recovery
A period of time without treatment to allow blood cell counts to return to normal.

recurrence
The return of cancer after a cancer-free period.

red blood cell (RBC)
A type of blood cell that carries oxygen from the lungs to the rest of the body. Also called an erythrocyte.

refractory cancer
A cancer that does not improve with treatment.

relapse
The return or worsening of cancer after a period of improvement.

remission
Minor or no signs of disease.

side effect
An unhealthy or unpleasant physical or emotional response to treatment.

spleen
An organ that is part of the lymphatic system. The spleen makes lymphocytes, filters the blood, stores blood cells, and destroys old blood cells. It is located on the left side of the abdomen near the stomach.

splenectomy
Surgery to remove the spleen.

supportive care
Treatment for the symptoms or health conditions caused by cancer or cancer treatment. Also sometimes called palliative care or best supportive care.

translocation
A switching of parts between two chromosomes.

tumor lysis syndrome (TLS)
A rare condition caused when waste released by dead cells is not quickly cleared out of your body.

white blood cell (WBC)
A type of blood cell that helps fight infections in the body. Also called a leukocyte.

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas, Version 1.2024. It was adapted, reviewed, and published with help from the following people:

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Abramson Cancer Center
at the University of Pennsylvania
Philadelphia, Pennsylvania
800.789.7366 • pennmedicine.org/cancer

Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio
UH Seidman Cancer Center
800.641.2422 • uhhospitals.org/services/cancer-services
CC Taussig Cancer Institute
866.223.8100 • my.clevelandclinic.org/departments/cancer
Case CCC
216.844.8797 • case.edu/cancer

City of Hope National Medical Center
Duarte, California
800.826.4673 • cityofhope.org

Dana-Farber/Brigham and Women's Cancer Center |
Mass General Cancer Center
Boston, Massachusetts
617.732.5500 • youhaveus.org
617.726.5130 • massgeneral.org/cancer-center

Duke Cancer Institute
Durham, North Carolina
888.275.3853 • dukecancerinstitute.org

Fox Chase Cancer Center
Philadelphia, Pennsylvania
888.369.2427 • foxchase.org

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska
402.559.5600 • unmc.edu/cancercenter

Fred Hutchinson Cancer Center
Seattle, Washington
206.667.5000 • fredhutch.org

Huntsman Cancer Institute at the University of Utah
Salt Lake City, Utah
800.824.2073 • healthcare.utah.edu/huntsmancancerinstitute

Indiana University Melvin and Bren Simon
Comprehensive Cancer Center
Indianapolis, Indiana
888.600.4822 • www.cancer.iu.edu

Mayo Clinic Comprehensive Cancer Center
Phoenix/Scottsdale, Arizona
Jacksonville, Florida
Rochester, Minnesota
480.301.8000 • Arizona
904.953.0853 • Florida
507.538.3270 • Minnesota
mayoclinic.org/cancercenter

Memorial Sloan Kettering Cancer Center
New York, New York
800.525.2225 • mskcc.org

Moffitt Cancer Center
Tampa, Florida
888.663.3488 • moffitt.org

O'Neal Comprehensive Cancer Center at UAB
Birmingham, Alabama
800.822.0933 • uab.edu/onealcancercenter

Robert H. Lurie Comprehensive Cancer Center
of Northwestern University
Chicago, Illinois
866.587.4322 • cancer.northwestern.edu

Roswell Park Comprehensive Cancer Center
Buffalo, New York
877.275.7724 • roswellpark.org

Siteman Cancer Center at Barnes-Jewish Hospital
and Washington University School of Medicine
St. Louis, Missouri
800.600.3606 • siteman.wustl.edu

St. Jude Children's Research Hospital/
The University of Tennessee Health Science Center
Memphis, Tennessee
866.278.5833 • stjude.org
901.448.5500 • uthsc.edu

Stanford Cancer Institute
Stanford, California
877.668.7535 • cancer.stanford.edu

The Ohio State University Comprehensive Cancer Center -
James Cancer Hospital and Solove Research Institute
Columbus, Ohio
800.293.5066 • cancer.osu.edu

The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins
Baltimore, Maryland
410.955.8964
www.hopkinskimmelcancercenter.org

The UChicago Medicine Comprehensive Cancer Center
Chicago, Illinois
773.702.1000 • uchicagomedicine.org/cancer

The University of Texas MD Anderson Cancer Center
Houston, Texas
844.269.5922 • mdanderson.org

UC Davis Comprehensive Cancer Center
Sacramento, California
916.734.5959 • 800.770.9261
health.ucdavis.edu/cancer

UC San Diego Moores Cancer Center
La Jolla, California
858.822.6100 • cancer.ucsd.edu

UCLA Jonsson Comprehensive Cancer Center
Los Angeles, California
310.825.5268 • cancer.ucla.edu

UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, California
800.689.8273 • cancer.ucsf.edu

University of Colorado Cancer Center
Aurora, Colorado
720.848.0300 • coloradocancercenter.org

University of Michigan Rogel Cancer Center
Ann Arbor, Michigan
800.865.1125 • rogelcancercenter.org

University of Wisconsin Carbone Cancer Center
Madison, Wisconsin
608.265.1700 • uwhealth.org/cancer

UT Southwestern Simmons
Comprehensive Cancer Center
Dallas, Texas
214.648.3111 • utsouthwestern.edu/simmons

Vanderbilt-Ingram Cancer Center
Nashville, Tennessee
877.936.8422 • vicc.org

Yale Cancer Center/Smilow Cancer Hospital
New Haven, Connecticut
855.4.SMILOW • yalecancercenter.org

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