

Marginal Zone Lymphoma



2022

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A six-word narrative about living with blood cancer from patients in our LLS Community

Stay strong and keep moving forward. Find the positive in every day. Be your own best patient advocate. Changed my life for the better. Accept, learn and focus on present. Learning to live a different life. Sudden and life changing—be positive. Waiting, worrying, anxiousness/happy I'm alive! Embrace a new normal each day. 5 years, 41 infusions, constant fatigue. Patience, positive attitude, hope and faith. Test to test, I will survive! Treatment, fatigue, treatment, fatigue and survival. Love life, live better every day. I don't look back only forward. So far, so good, live life. Meditation, mindfulness, wellness, faith, nutrition and optimism. Finding the joy while living with uncertainty. Watch, wait, treat, regroup, rest, re-energize. Blessed to be doing so well! Eye opening needed learning and healing. Feel great: uncertain travel plans annoying. Renewed faith, meditation, diet, mindfulness, gratitude. Watchful waiting can be watchful worrying. Scary, expensive, grateful, blessings, hope, faith. Thank god for stem cell transplants! Do not know what to expect. Extraordinarily grateful, I love my life. Diagnosed; frightened; tested; treating; waiting; hoping. I'm more generous, impatient less often. Embrace your treatment day after day. Live today, accept tomorrow, forget yesterday. Strength you never realized you had. Challenging to our hearts and minds. Life is what we make it. Live life in a beautiful way.



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- Thousands of patients and caregivers sharing experiences and information, with support from knowledgeable staff
- Accurate and cutting-edge disease updates
- The opportunity to participate in surveys that will help improve care

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Introduction

This book provides information about marginal zone lymphomas for patients and their families. Marginal zone lymphomas are a group of non-Hodgkin lymphomas that begin in a part of the lymph tissue called the “marginal zone.” They tend to be slow-growing lymphomas. There are three main subtypes of marginal zone lymphoma, based on whether it forms in the spleen, the lymph nodes or other lymphoid tissue outside the lymph nodes.

This book provides information about the diagnosis, staging and treatment of the three main subtypes of marginal zone lymphoma: extranodal, nodal and splenic. It also includes brief descriptions of normal blood, bone marrow and the lymphatic system, as well as a glossary of health terms related to marginal zone lymphoma.

Advances in the treatment of marginal zone lymphoma have resulted in improved remission rates, quality of life and survival for patients. This is due to new treatments that have been approved, and more are being studied in clinical trials.

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Lymphoma Basics

“Lymphoma” is the general name for many different types of cancer that start in the lymphatic system, the network of organs and tissues that protects the body against disease and infection and removes waste and toxins. The lymphatic system includes the lymph nodes, spleen, thymus, tonsils and bone marrow.

Lymphoma starts in a type of white blood cell called a “lymphocyte” in the lymphatic system. A mutation occurs in the DNA of a lymphocyte, which causes it to become an abnormal cancer cell (often called a “lymphoma cell”). The lymphoma cell divides again and again, making more and more abnormal cells. These abnormal cells eventually crowd out healthy cells and form tumors, generally in the lymph nodes or in the lymphatic tissue found in organs such as the stomach, intestines, skin or spleen. Lymphoma can develop in any part of the body where there are lymphocytes. While some lymphomas can be detected through routine bloodwork, most are diagnosed through the examination of a biopsy sample (lymphatic tissue examined under a microscope).

Lymphomas are grouped into two major categories: Hodgkin lymphoma and non-Hodgkin lymphoma. Hodgkin lymphomas contain Reed-Sternberg cells, which have a particular appearance when viewed under a microscope. They are unusually large, abnormal lymphocytes that may contain more than one nucleus. Non-Hodgkin lymphomas are a varied group of lymphomas that do not have the characteristic Reed-Sternberg cells seen in Hodgkin lymphoma.

There are more than 60 different subtypes of non-Hodgkin lymphoma. Non-Hodgkin lymphomas can start in any of the three types of lymphocytes: B lymphocytes (B cells), T lymphocytes (T cells) and natural killer (NK) cells. B cells make antibodies to fight infection; T cells help fight infections and attack cancer cells; and NK cells attack cancer cells and eliminate viruses. B-cell lymphomas are more common than T-cell and NK-cell lymphomas.

Specialists further classify non-Hodgkin lymphoma subtypes according to the rate of disease progression, either aggressive (fast growing) or indolent (slow growing). When indolent lymphomas are first diagnosed, most patients have fewer symptoms than patients with aggressive lymphoma subtypes. The appropriate treatment for each patient is determined based on whether they are diagnosed with an aggressive or indolent subtype, so getting an accurate diagnosis is very important. In some cases, indolent forms of non-Hodgkin lymphoma can transform into an aggressive form of the disease over time.

For more information about non-Hodgkin lymphoma, visit www.LLS.org/booklets to view the free LLS booklets *Non-Hodgkin Lymphoma* and *The Lymphoma Guide – Information for Patients and Caregivers*.

About Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is a rare, slow-growing subtype of non-Hodgkin lymphoma. It makes up about 7 percent of all non-Hodgkin lymphoma cases. In 2016, there were an estimated 7,460 patients with newly-diagnosed marginal zone lymphoma in the United States.

Marginal zone lymphomas develop in B lymphocytes (B cells), a type of white blood cell that is part of the immune system. While there are many types of B-cell cancers, marginal zone lymphomas specifically begin in a B cell in the marginal zone of lymphatic tissue.

Lymphatic tissue contains many lymphocytes and is part of the body's immune system, helping to protect the body from bacteria and other foreign organisms. This tissue can be found in the lymph nodes, the spleen and other parts of the body, such as the digestive, respiratory and urinary tracts.

Inside lymphatic tissue there are little round clumps, called lymphoid follicles, which contain mostly B cells. The area surrounding the lymphoid follicle center is called the mantle zone. Mantle cells are B cells within the mantle zone. Surrounding the mantle zone is the marginal zone. Marginal zone cells are B cells within the marginal zone of a lymphoid follicle. They appear small when viewed under a microscope.

Marginal zone lymphomas are cancers that form in B cells in the marginal zone. When a genetic mutation occurs in a B cell in the marginal zone, it may become a lymphoma cell—an abnormal cell that may grow and multiply out of control into many lymphoma cells. As these cells multiply, they can build up and form tumors. In some cases, they may also spread to other parts of the body.

The World Health Organization (WHO) classifies marginal zone lymphomas into three subtypes, depending on the site of involvement:

- Extranodal (MALT), which occurs in areas or organs outside the lymph nodes, such as the stomach, lungs, small intestine, salivary glands, thyroid, ocular adnexa (tissue around the eye) and skin
- Nodal, which occurs in the lymph nodes
- Splenic, which occurs primarily in the spleen

Marginal zone lymphomas occur primarily in adults. Approximately half of the people diagnosed with marginal zone lymphoma are over the age of 60 at the time of diagnosis.

While patients with marginal zone lymphoma generally have long survival times, the disease is often incurable. Relapse is common, sometimes occurring several times over many years. A small proportion of marginal zone lymphomas undergo transformation to diffuse large-B-cell lymphoma, a faster-growing lymphoma. Patients with transformed lymphoma are typically treated with regimens designed for diffuse large-B-cell lymphoma.

For the best outcome, patients are encouraged to seek treatment in a center with specialized doctors, called hematologist-oncologists, who have specific experience in the diagnosis and care of patients with lymphoma.

Extranodal Marginal Zone Lymphoma or MALT Lymphoma

Extranodal marginal zone lymphoma, also called “mucosa-associated lymphoid tissue (MALT) lymphoma,” can develop in a variety of organs. “Extranodal” means that it occurs outside the lymph nodes. This is the most common type of marginal zone lymphoma, accounting for approximately 60-70 percent of all cases of the disease. Typically MALT lymphomas stay in the area where they begin and do not become widespread. In some cases, however, they can spread to other parts of the body or transform into an aggressive form of B-cell lymphoma.

MALT lymphoma starts in “mucosa-associated lymphoid tissue” (MALT). “Mucosa” is the moist, inner lining of some organs and body cavities, such as the nose, mouth, lung, digestive tract and urinary tract. “Lymphoid tissue” is a group of lymphocytes. MALT is a collection of lymphocytes in the mucosa. MALT, which is rich in B cells, can form in the mucosa in response to inflammation to help protect the body from disease and infection. MALT lymphomas can develop if abnormal lymphocytes accumulate in the lymphoid tissue.

In many cases of MALT lymphoma, there is a chronic infection or autoimmune disorder that causes MALT to form. If a mutation occurs in one of the B cells in the marginal zone of the MALT tissue, it can become a lymphoma cell.

MALT lymphoma can develop almost anywhere in the body where there is lymphoid tissue, but it most often develops in the stomach. MALT lymphoma is normally divided into two groups:

- Gastric (stomach)
- Non-gastric, which can affect the lungs, salivary glands, breast, thyroid, salivary glands, lungs, skin, gut (bowel) or ocular adnexa (tissue around the eye)

Gastric MALT Lymphoma

Gastric MALT lymphoma develops in the stomach, the most common site for MALT lymphoma. It starts in B cells within the lymphoid tissue of the stomach’s inner lining (mucosa). This lymphoid tissue is not normally found in the stomach; it develops as a result of chronic inflammation that may be due to a chronic infection or an autoimmune condition.

Most gastric MALT lymphomas are lesions (areas of abnormal tissue) that typically grow slowly and do not usually spread to other areas in the body. Often, cases of gastric MALT are associated with a chronic infection of *H. pylori*, a type of bacteria that infects the stomach. It can damage the tissue in the stomach, causing ulcers (sores) on the inside lining of the stomach. Patients that test positive for *H. pylori* are treated with antibiotics to eradicate the infection, which can lead to a remission of the lymphoma in some patients.

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of a disease. A “sign” is a change in the body that a doctor sees in an exam or a test result. A “symptom” is a change in the body that a patient can see or feel. Signs and symptoms of gastric MALT may include:

- Heart burn and indigestion
- Abdominal pain
- Nausea
- Vomiting
- Loss of appetite
- Unexplained weight loss
- Gastric bleeding
- A mass or irregularity found during an endoscopy that is done for other medical reasons

Diagnosis

While certain signs and symptoms may suggest that a person has lymphoma, a series of tests are needed to confirm the diagnosis and the specific disease subtype of lymphoma. An accurate diagnosis helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

Talk to your doctor about:

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the results

Medical History and Physical Examination. If your doctor suspects that you may have lymphoma, he or she will ask about your health history and do a physical exam to look for signs of lymphoma. The doctor will examine you and pay special attention to your lymph nodes and other areas of the body that may be affected, including the skin, the spleen and the liver.

Upper Endoscopy. If you are having problems in your upper digestive tract, such as heartburn, feeling full quickly or coughing up or vomiting blood, your doctor may perform an upper endoscopy. This procedure is used to examine the upper digestive system and is done with an instrument called an “endoscope.” The endoscope is a long, thin, flexible tube with a light and small camera on the end.

The tube is put in through the mouth and then down the throat to examine the esophagus, stomach and small intestine. It allows the doctor to look at the wall of the digestive tract. If there are any suspicious areas that may be cancer, the doctor will perform a biopsy and remove samples of tissue so the cells can be examined.

Cell Assessment. A hematopathologist examines the biopsy samples under a microscope to view the size, shape and type of cells. A hematopathologist is a doctor who has special training in identifying blood diseases. This specialist may also perform other tests with the sample, including:

- **Testing for *H. pylori*.** In this test, the tissue sample is examined under a microscope to look for *H. pylori* bacteria.
- **Flow Cytometry.** This lab test identifies the antigens, or proteins, on the surface and within cancer cells. Finding (or not finding) certain proteins can help the hematopathologist determine the type of lymphoma. The pattern of the surface proteins is called the “immunophenotype.”

Marginal zone lymphoma has a common pattern of proteins. The classical immunophenotype for marginal zone lymphoma is CD20+, CD5- and CD10-. This means that if a sample of lymphoma cells have the antigen CD20 but do not have CD5 or CD10 a person is diagnosed with marginal zone lymphoma. (CD is the abbreviation for “cluster of differentiation,” the term for these cell surface markers.)

- **Molecular Testing.** These tests look closely at the chromosomes and DNA in the lymphoma cells for specific chromosomal abnormalities and genetic mutations. These tests may be done to help diagnose some types of cancer and to help plan treatment.

It is recommended that the biopsy sample from the upper endoscopy be evaluated for a translocation involving chromosomes 11 and 18, abbreviated as t(11;18). A translocation is a genetic change in which a piece of one chromosome breaks off and attaches to another chromosome. Approximately 15 to 40 percent of patients with gastric MALT lymphoma have t(11;18). People with this translocation are less likely to respond to antibiotic therapy.

Staging

When a person is diagnosed with gastric MALT lymphoma, tests are done to determine the stage of the disease. Staging provides important information about how far the disease has spread in the body and helps in determining the best treatment.

Tests done to determine the stage of cancer may include:

Blood Tests. Blood tests can sometimes help determine how advanced the lymphoma is. These may include:

- Complete Blood Count (CBC). This test measures the number of red blood cells, white blood cells and platelets in the blood. Low blood cell counts may mean that the lymphoma has spread to the bone marrow and is affecting new blood cell formation.
- Comprehensive Metabolic Panel. This group of tests measures up to 14 chemicals in the blood. It gives important information about how well a person's kidneys, liver and other organs are working. Abnormal levels of these chemicals can be caused by cancer or other health problems.
- Lactate Dehydrogenase (LDH) Test. This test measures the level of LDH in the blood. LDH is a protein found in most cells. When a cell is damaged, LDH is released into the bloodstream. A high level of LDH in the blood can be caused by cancer and can be a sign that the cancer is widespread.
- Hepatitis Tests. Hepatitis is a disease of the liver. It can be caused by the hepatitis C and B viruses. All patients should be tested for hepatitis C because the virus has been associated with the development of marginal zone lymphoma. Hepatitis B testing should be performed on patients being considered for treatment with rituximab-containing regimens, because rituximab can cause hepatitis B to become active again.

Bone Marrow Aspiration and Biopsy. These two tests are used to collect and examine bone marrow, the spongy tissue found inside bones. They are generally done at the same visit, either at the doctor's office or in a hospital.

Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special, hollow needle is inserted through the hip bone and into the bone marrow to aspirate (remove) a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope.

Bone marrow aspiration and biopsy are done to show whether your bone marrow is healthy and making normal amounts of blood cells. But evaluation of the bone marrow may also be useful to see whether the lymphoma has spread to the bone marrow.

Imaging Tests. These tests create images (pictures) of the inside of the body. Various types of imaging tests such as computed tomography (CT) and positron-emission tomography (PET) scans can show where the lymphoma is located in the body and provide information that helps the doctor to determine the stage of the lymphoma.

Visit www.LLS.org/booklets to view the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

Staging System. In cancer staging, the Roman numerals I through IV (1-4) are used to represent the extent of cancer in the body. Stage I cancers are less advanced and often have a better prognosis. Higher-stage cancers are generally more widespread in the body and may require different or more intense treatment. Doctors use the findings from laboratory and imaging tests to determine the stage.

The Lugano staging system for gastric lymphomas, which is a modification of the older Ann Arbor system, is one of the more widely-used staging systems for gastric MALT lymphoma. See **Table 1** below for a description of the stages.

Table 1. Lugano Staging System for Gastric MALT Lymphomas

Stage I: The tumor is confined to the gastrointestinal tract. It can be a single primary lesion or multiple, non-contiguous lesions.

Stage II: The tumor extends into the abdomen. This is further subdivided based upon the location of nodal involvement.

- Stage II₁: Involvement of local nodes
- Stage II₂: Involvement of distant nodes
- Stage II₃: The tumor penetrates the serosa (outer lining of the abdomen and chest, including the stomach) to involve adjacent organs or tissues

Stage III: There is no stage III in this staging system.

Stage IV: There is extranodal involvement or accompanying supra-diaphragmatic (above the diaphragm) nodal involvement.

Rohatiner A, d'Amore F, Coiffier B, et al. Report on a workshop convened to discuss the pathological and staging classification of gastrointestinal tract lymphoma. *Annals of Oncology*. 1994;5(5):397-400.

Treatment

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you. See page 41 for more information on clinical trials.

The treatment approach for gastric MALT lymphoma depends on the stage of the disease and whether the patient is infected with *H. pylori* bacteria.

***H. pylori*-positive Stage I or Stage II₁ Disease.** *H. pylori* eradication therapy, which includes antibiotics, is recommended for all patients with stage I or

stage II disease who are infected with *H. pylori*. It is recommended whether or not their lymphoma cells have the chromosomal abnormality t(11;18), a mutation that makes it less likely for a patient to respond to antibiotic therapy. For more information about t(11;18), see page 8.

***H. pylori* Eradication Therapy.** For patients with early-stage gastric MALT lymphoma who test positive for *H. pylori*, antibiotics can be an effective first-line therapy and provide an excellent long-term outcome. Some studies have shown that gastric MALT lymphoma can be cured with just antibiotics. *H. pylori* eradication therapy generally consists of a proton pump inhibitor, along with a combination of antibiotics including clarithromycin and amoxicillin (or metronidazole for patients allergic to amoxicillin), given for 10 to 14 days.

Patients treated with *H. pylori* eradication therapy are evaluated after the completion of treatment to determine whether the *H. pylori* infection was successfully eradicated and whether the tumor has responded to treatment.

- At least four weeks after the completion of *H. pylori* eradication therapy, testing should be performed to confirm eradication of the infection. Up to 20 percent of patients will require a second *H. pylori* eradication therapy regimen to eliminate the bacterial infection completely.
- After successful eradication of the *H. pylori* infection, patients should undergo periodic upper endoscopy to evaluate for tumor response and monitor for signs of relapse, since MALT gastric lymphoma can recur. The National Comprehensive Cancer Network (NCCN) Guidelines recommend follow-up every 3 to 6 months for 5 years and then yearly, or as clinically indicated.

Approximately 20 to 30 percent of patients do not respond to *H. pylori* eradication therapy or are found to be in relapse during follow-up exams. In these cases, the doctor will take biopsy samples to confirm whether the patient has gastric MALT lymphoma or a more aggressive form of lymphoma, such as diffuse large B-cell lymphoma.

For patients with the chromosomal abnormality t(11;18) and with persistent lymphoma after antibiotic therapy, other available treatments include those listed below:

Radiation Therapy. This treatment uses high-energy x-rays to kill cancer cells. Radiation therapy can be very effective if the lymphoma is only affecting a few areas of the body. It is a preferred treatment approach in cases of localized disease after failure of antibiotic therapy for *H. pylori*.

Rituximab (Rituxan®). Rituximab, a type of monoclonal antibody therapy, is an option when antibiotic therapy has failed and radiation therapy is not medically recommended. It binds to a protein called CD20 on the lymphoma cells, helping the immune system to find and destroy the lymphoma cells.

After radiation therapy or rituximab, the NCCN Guidelines recommend follow-up care with upper endoscopy and biopsy every 3 to 6 months for 5 years and then yearly or as clinically indicated.

H. Pylori-negative Stage I or Stage II₁ Disease. For patients with stage I or stage II₁ disease who are not infected with *H. pylori*, treatments may include those listed below:

Radiation Therapy. This treatment uses high-energy x-rays to kill cancer cells. Radiation therapy can be very effective if the lymphoma is only affecting a few places in the body. Radiation therapy is a preferred technique in cases of localized disease.

Rituximab (Rituxan®). Rituximab is a type of monoclonal antibody therapy. It binds to a protein called CD20 on the lymphoma cells, helping the immune system to find and destroy them.

After radiation therapy or rituximab, the NCCN Guidelines recommend follow-up care with upper endoscopy and biopsy every 3 to 6 months for 5 years and then yearly or as clinically indicated.

Stage II_ε, II₂ or IV Disease. In patients with advanced disease who have an active *H. pylori* infection, treatment may begin with *H. pylori* eradication therapy (see page 11). Generally, patients are then observed until they develop symptoms. For patients without an active *H. pylori* infection, treatment may also be postponed until after symptoms appear.

Many doctors consider observation (the “watch-and-wait” approach), involving careful monitoring and follow-up care, to be an active form of therapy. This approach allows patients to avoid the side effects of treatment for as long as possible. Patients need to discuss with their doctors the potential benefits of the watch-and-wait approach versus starting chemoimmunotherapy and/or other therapies right after diagnosis.

Treatment usually needs to start when lymphoma-related symptoms appear. Not everyone with gastric MALT receives the same type of treatment. Choosing which treatment you receive is a very important decision. You and your doctor will tailor your treatment based on a number of different factors, such as the stage of your cancer, your age and overall health, and your personal preferences.

Current treatments for advanced-stage gastric MALT lymphoma may include chemoimmunotherapy. This type of treatment combines chemotherapy with immunotherapy. Chemotherapy uses various drugs to kill or slow the growth of cancer cells. Immunotherapy uses the body’s own immune system to find and kill cancer cells. Immunotherapy for marginal zone lymphoma often uses a monoclonal antibody drug called rituximab (Rituxan®). See **Table 2** on page 13 for a list of suggested first-line therapies for advanced-stage gastric MALT lymphoma, adapted from the NCCN Guidelines.

Table 2. Suggested First-Line Treatment Regimens

First-Line Therapy*	First-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + rituximab ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Lenalidomide + rituximab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimen</u></p> <ul style="list-style-type: none"> ○ Rituximab <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab

*Preferred and Other Recommended Regimens are listed in alphabetical order.

Abbreviation: ±, plus or minus (meaning with or without).

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, B-Cell Lymphomas. 2022.

See pages 44-47, for information on the drug classifications and approved indications for these therapies.

After completion of treatment, the NCCN Guidelines recommend follow-up care with upper endoscopy and biopsy every 3 to 6 months for 5 years and then yearly or as clinically indicated.

Treatment Options for Relapsed and Refractory Cases

Some patients with gastric MALT lymphoma do not respond to initial therapy. When this occurs, it is referred to as “refractory” disease. In other patients, the lymphoma comes back after it has been in remission. In these cases it is referred to as “relapsed” disease.

Many patients with relapsed or refractory gastric MALT lymphoma can obtain another period of remission with additional treatment. This approach can often control the lymphoma for many years. See **Table 3** on page 14 for a list of suggested treatments, adapted from the NCCN Guidelines, for relapsed and refractory cases of gastric MALT lymphoma.

Table 3. Suggested Treatment Regimens for Relapsed/Refractory Disease

Second-Line and Subsequent Therapy*	Second-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + obinutuzumab (not recommended if treated with prior bendamustine) ○ Bendamustine + rituximab (not recommended if treated with prior bendamustine) ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab ○ Ibrutinib ○ Lenalidomide + rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab ○ Copanlisib (relapsed/refractory after 2 prior therapies) ○ CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab ○ Ibritumomab tiuxetan ○ Lenalidomide + obinutuzumab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Ibrutinib ○ Lenalidomide + rituximab ○ Rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20 mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab <p>*Preferred and Other Recommended Regimens are listed in alphabetical order. Abbreviations: mAB, monoclonal antibody; ±, plus or minus (with or without). NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology, B-Cell Lymphomas. 2022.</p> <p>See pages 44-47, for information on the drug classifications and the approved indications for these therapies.</p>

Treatment Outcomes

Some patients with gastric MALT lymphoma can be cured with *H. pylori* eradication therapy. Other patients achieve a remission but then relapse, sometimes several times over many years. But often, these relapses can be treated, and patients with MALT lymphomas have a relatively good prognosis, with a median survival of more than 10 years. Treatment outcomes can vary widely, however, so it is important to speak with your doctor about potential outcomes in your specific case.

It is also important to remember that survival statistics are only estimates and are based on patients diagnosed with gastric MALT lymphoma some time ago. Since the statistics were collected, new treatments have been approved and others are being studied in clinical trials. As a result, the outlook may be better for people diagnosed with this disease today.

Non-Gastric MALT Lymphoma

Non-gastric MALT lymphoma can develop in a variety of areas throughout the body. It can occur in the marginal zone of MALT tissue in the lungs, salivary glands, breast, thyroid, skin, liver, and tissue around the eye.

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of a disease. A “sign” is a change in the body that doctors see in an exam or a test result. A “symptom” is a change in the body that patients can see or feel.

Because MALT lymphomas are often slow-growing, patients may not have any symptoms at the time of diagnosis. The lymphoma may be discovered during medical tests for an unrelated issue.

In patients with symptoms, the symptoms occur in the part of the body where the lymphoma develops. For example:

- MALT lymphoma affecting the tear ducts or tissues around the eye may cause symptoms such as redness of the eye, swelling around the eye, eye irritation, double vision and/or a droopy eyelid.
- MALT lymphoma affecting the lungs may cause a cough, shortness of breath, coughing up blood or chest pain.
- MALT lymphoma affecting the salivary glands may cause swelling of the salivary glands in front of the ears, under the chin and/or in the mouth.
- MALT lymphoma affecting the skin may cause pink, red or purple lesions or lumps on the skin.
- MALT lymphoma affecting the thyroid gland may cause a lump at the front of the neck and/or symptoms of hypothyroidism (a deficiency of thyroid hormones that may cause fatigue, cold sensitivity, dry skin and unexplained weight gain).

Diagnosis

While certain signs and symptoms may suggest that a person has lymphoma, a series of tests are needed to confirm the diagnosis and the specific disease subtype. An accurate diagnosis helps the doctor to:

- Estimate how the disease will progress
- Determine the appropriate treatment

Talk to your doctor about:

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the results

Medical History and Physical Examination. If your doctor suspects that you may have lymphoma, he or she will ask about your health history and do a physical exam to look for signs of lymphoma. The doctor will examine you, paying special attention to your lymph nodes and other areas of the body that may be affected, including the skin, the spleen and the liver.

Biopsy. MALT lymphoma is typically diagnosed by a biopsy, a procedure to remove and examine a sample of tissue or cells. In cases of non-gastric MALT lymphoma, the sample is removed from the area in the body affected by the disease.

Cell Assessment. A hematopathologist examines the biopsy sample under a microscope to view the size, shape and type of cells. A hematopathologist is a doctor who has special training in identifying blood diseases. This specialist may also perform other tests on the sample including those listed below.

- **Flow Cytometry.** This lab test identifies the antigens, or proteins, on the surface and within cancer cells. Finding (or not finding) certain proteins can help the hematopathologist determine the type of lymphoma. The pattern of the surface proteins is called the “immunophenotype.”

Marginal zone lymphoma has a common pattern of proteins. The classical immunophenotype for marginal zone lymphoma is CD20+, CD5- and CD10-. This means that if a sample of lymphoma cells have the antigen CD20 but do not have CD5 or CD10 a person is diagnosed with marginal zone lymphoma. (CD is the abbreviation for “cluster of differentiation,” the term for these cell surface markers.)

Staging

When a person is diagnosed with MALT lymphoma, tests are done to determine the stage of the disease. Staging provides important information about how far the disease has spread in the body and helps determine the best treatment. These tests may include:

Blood Tests. Blood tests are helpful in treatment planning. They may include:

- Complete Blood Count (CBC). This test measures the number of red blood cells, white blood cells and platelets in the blood. Low blood cell counts may indicate that the lymphoma has spread to the bone marrow and is affecting new blood cell formation.

- **Comprehensive Metabolic Panel.** This is a group of tests that measure up to 14 chemicals in the blood. It gives important information about how well a person's kidneys, liver, and other organs are working. Abnormal levels of these chemicals can be caused by cancer or other health problems.
- **Lactate Dehydrogenase (LDH) Test.** This test measures the level of LDH in the blood. LDH is a protein found in most cells. When a cell is damaged, LDH is released in the bloodstream. A high level of LDH in the blood can be caused by cancer, and can also be a sign that the cancer is widespread.
- **Hepatitis Tests.** Hepatitis is a disease of the liver. It can be caused by the hepatitis C and B viruses. All patients should be tested for hepatitis C because the virus has been associated with the development of marginal zone lymphoma. Hepatitis B testing should be performed on patients being considered for treatment with rituximab-containing regimens, because if a patient has had hepatitis B, rituximab can cause hepatitis B to become active again.

Bone Marrow Aspiration and Biopsy. These two tests are used to collect and examine bone marrow, the spongy tissue found inside bones. They are generally done at the same visit, either at the doctor's office or in a hospital.

Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special, hollow needle is inserted through the hip bone and into the bone marrow to aspirate (remove) a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope.

In certain circumstances, evaluation of the bone marrow may be useful to see whether the lymphoma has spread to the bone marrow. This information helps the doctor evaluate the potential benefit of specific therapies.

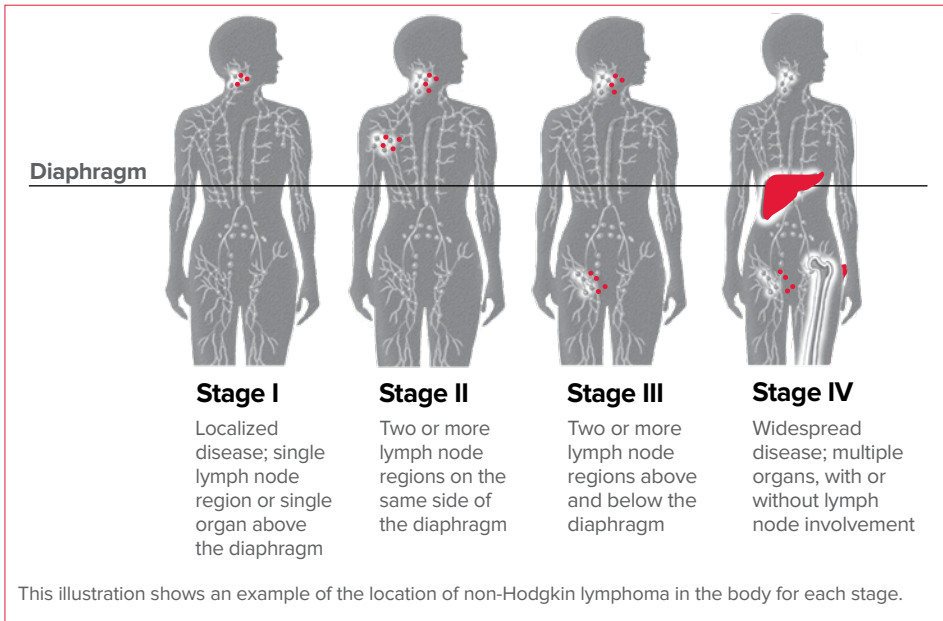
Imaging Tests. These tests create images (pictures) of the inside of the body. Various types of imaging tests such as computed tomography (CT) and positron-emission tomography (PET) scans can show where the lymphoma is located in the body and provide information that helps the doctor determine the stage of the lymphoma.

Visit www.LLS.org/booklets to view the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

Staging System. In cancer staging, the Roman numerals I through IV (1-4) are used to represent the extent of cancer in the body. Stage I cancers are less advanced and often have a better prognosis (projected outcome). Higher-stage cancers are generally more widespread in the body and may require different or more intense treatment. Doctors use the findings from laboratory and imaging tests to determine the stage.

The Lugano system, a modification of the older Ann Arbor system, is one of the more widely-used staging systems for non-Hodgkin lymphoma. See **Figure 1** below for a description of the stages.

Figure 1. Non-Hodgkin Lymphoma (NHL) Stages



Treatment

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you. See page 41 for more information on clinical trials.

The treatment approach for non-gastric MALT lymphoma depends on the stage of the disease.

Stage I or Stage II Disease. Current treatments for stage I and stage II disease may include the treatments listed below.

Radiation Therapy. This treatment uses high-energy x-rays to kill cancer cells. Radiation therapy can be very effective if the lymphoma is only affecting a few areas of the body. It is a preferred treatment approach in cases of localized disease.

Rituximab (Rituxan®). Rituximab, a type of monoclonal antibody therapy, is an option for select patients with stage I-II disease. It binds to a protein called CD20 on the lymphoma cells, helping the immune system find and destroy them.

Surgery. In patients with stage I-II disease, surgical removal of the lymphoma mass may be appropriate for certain extranodal sites of involvement, such as the lung, thyroid, colon, breast and small intestine. Observation is then recommended if there are no signs of residual disease following surgery.

Follow-up Care. The NCCN Guidelines recommend clinical follow-up including lab and imaging tests every 3 to 6 months for 5 years and then annually thereafter (or as clinically indicated). Localized disease recurrence may be treated with radiation therapy (if not previously received by the patient) or managed according to recommendations for advanced-stage disease (see Stage III or IV Disease, below).

Stage III or IV Disease. Current treatments for advanced-stage non-gastric MALT lymphoma may include chemoimmunotherapy. This type of treatment combines chemotherapy with immunotherapy. Chemotherapy uses various drugs to kill or slow the growth of cancer cells. Immunotherapy uses the body's own immune system to find and kill cancer cells. Immunotherapy for marginal zone lymphoma often uses a monoclonal antibody drug called rituximab (Rituxan®). See **Table 4** on page 21 for a list of suggested first-line therapies for advanced-stage non-gastric MALT lymphoma, adapted from the NCCN Guidelines.

Table 4. Suggested First-Line Treatment Regimens

First-Line Therapy*	First-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + rituximab ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Lenalidomide + rituximab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimen</u></p> <ul style="list-style-type: none"> ○ Rituximab <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab

*Preferred and Other Recommended Regimens are listed in alphabetical order.

Abbreviations: mAB, monoclonal antibody; ±, plus or minus (with or without).

NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. 2022

See pages 44-47, for information on the drug classifications and approved indications for these therapies.

Treatment Options for Relapsed and Refractory Cases

Some patients with non-gastric MALT lymphoma do not respond to initial therapy. When this occurs, it is referred to as “refractory” disease. In other patients, the lymphoma comes back after a remission. In these cases it is referred to as “relapsed” disease.

Many patients with relapsed or refractory non-gastric MALT lymphoma can obtain another period of remission with additional treatment. This approach can often control the lymphoma for many years. See **Table 5** on page 22 for a list of the suggested treatments for relapsed and refractory disease for non-gastric MALT lymphoma, adapted from the NCCN Guidelines.

Table 5. Suggested Treatment Regimens for Relapsed/Refractory Disease

Second-Line and Subsequent Therapy*	Second-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + obinutuzumab (not recommended if treated with prior bendamustine) ○ Bendamustine + rituximab (not recommended if treated with prior bendamustine) ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab ○ Ibrutinib ○ Lenalidomide + rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab ○ Copanlisib (relapsed/refractory after 2 prior therapies) ○ CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab ○ Ibritumomab tiuxetan ○ Lenalidomide + obinutuzumab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Ibrutinib ○ Lenalidomide + rituximab ○ Rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20 mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab <p>*Preferred and Other Recommended Regimens are listed in alphabetical order. Abbreviations: mAB, monoclonal antibody; ±, plus or minus (with or without). NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology, B-Cell Lymphomas. 2022.</p> <p>See pages 44-47, for information on the drug classifications and the approved indications for these therapies.</p>

Treatment Outcomes

Relapse is common in patients with non-gastric MALT lymphoma, sometimes occurring several times over many years, though these relapses can often be successfully treated. In general, patients with MALT lymphomas have a relatively good prognosis, with a median survival of more than 10 years. Treatment outcomes can vary widely, however, so it is important to speak with your doctor about the potential outcomes in your specific case.

It is also important to remember that survival statistics are only estimates and are based on patients diagnosed with non-gastric MALT some time ago. Since the statistics were collected, new treatments have been approved and more are being studied in clinical trials. As a result, the outlook may be better for people diagnosed with this disease today.

Nodal Marginal Zone Lymphoma

Nodal marginal zone lymphoma is a rare, slow-growing type of marginal zone lymphoma. It accounts for approximately 30 percent of all marginal zone lymphoma cases. It develops in B cells in the lymph nodes.

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of disease. A “sign” is a change in the body that the doctor sees in an exam or a test result. A “symptom” is a change in the body that the patient can see or feel. Most patients with nodal marginal zone lymphoma have no symptoms at diagnosis. The disease is often found during a routine exam or lab test.

Signs and symptoms of nodal marginal zone lymphoma may include:

- Swelling in one or more lymph nodes. The patient or doctor may be able to feel the swollen lymph node, or it may be discovered during tests done for another reason (for example, a routine mammogram or another test ordered for unrelated symptoms).
- Some people with nodal marginal zone lymphoma have what are known as “B symptoms.” These include:
 - Fever
 - Heavy night sweats
 - Unexplained weight loss

Diagnosis

While certain signs and symptoms may suggest that a person has lymphoma, a series of tests are needed to confirm the diagnosis and the specific subtype of lymphoma. An accurate diagnosis helps the doctor:

- Estimate how the disease will progress
- Determine when to begin treatment, and the appropriate treatment

Talk to your doctor about:

- The diagnostic tests that are being done
- What the results mean
- Getting copies of the results

Nodal marginal zone lymphoma is rare, and it can be difficult to differentiate it from advanced cases of MALT lymphoma or splenic lymphoma. So biopsy

samples should be examined by a “hematopathologist,” a doctor who has special training in identifying blood diseases by studying cells under a microscope and performing other specialized tests.

Medical History and Physical Examination. If your doctor suspects that you may have lymphoma, he or she will ask about your health history and do a physical exam to look for signs of lymphoma. The doctor will examine you, paying special attention to your lymph nodes and other areas of the body that may be affected, including the skin, the spleen and the liver.

Complete Blood Count (CBC). This test measures the number of red blood cells, white blood cells and platelets in the blood. Low blood cell counts may mean that the lymphoma has spread to the bone marrow and is affecting new blood cell formation. Patients with nodal marginal zone lymphoma may have low red blood cell and platelet counts.

Biopsy. You may need to undergo a biopsy to determine whether your signs and symptoms are due to lymphoma or another condition. A biopsy is a procedure to remove a sample of tissue or cells from the body so that it can be examined under a microscope. Nodal marginal zone lymphoma is diagnosed by removing either all or part of an involved lymph node and examining the tissue under a microscope to look for cancer cells.

To ensure that there is enough tissue to make an accurate diagnosis, the preferred method for the lymph node biopsy is usually excisional or incisional. In an excisional biopsy, the whole lymph node is removed. In an incisional biopsy, only part of the lymph node is removed. If the lymph node is just under the skin, the biopsy procedure is usually simple and can sometimes be done with a numbing medication (local anesthetic). If the lymph node is deep inside the chest or abdomen (stomach area), you may be sedated or receive general anesthesia.

A core needle biopsy may be necessary in certain situations, if the lymph node is too difficult to reach. In this method, a wide needle is used to remove a column of tissue from the lymph node. It is done with local anesthesia to numb the area. Another type of needle biopsy, called fine-needle aspiration, is generally not suitable for diagnosing lymphoma. This is because the long, thin needle that is used to draw out fluid and cells often does not collect enough cells to make an accurate diagnosis.

Cell Assessment. A hematopathologist examines the biopsy sample under a microscope to view the size, shape and type of cells. The hematopathologist may also perform other tests on the sample, including flow cytometry.

- **Flow Cytometry.** This lab test identifies the antigens, or proteins, on the surface and within cancer cells. Finding (or not finding) certain proteins can help the hematopathologist determine the type of lymphoma. The pattern of the surface proteins is called the “immunophenotype.”

Marginal zone lymphoma has a common pattern of proteins. The classical immunophenotype for marginal zone lymphoma is CD20+, CD5- and CD10-. This means that if a sample of lymphoma cells have the antigen CD20 but do not have CD5 or CD10 a person is diagnosed with marginal zone lymphoma. (CD is the abbreviation for “cluster of differentiation,” the term for these cell surface markers.)

Visit www.LLS.org/booklets to view the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

Staging

After a cancer diagnosis of lymphoma, tests are done to determine the stage of the disease. Staging provides important information about the extent of cancer in the body and how the patient will respond to treatment.

Staging Tests. Tests used to gather information for staging include:

Blood Tests. Blood tests can sometimes help determine how advanced the lymphoma is. They may include:

- **Comprehensive Metabolic Panel.** This is a group of tests that measure up to 14 chemicals in the blood. It gives important information about how well a person’s kidneys, liver and other organs are working. Abnormal levels of these chemicals can be caused by cancer or other health problems.
- **Lactate Dehydrogenase (LDH) Test.** This test measures the level of LDH in the blood. LDH is a protein found in most cells. When a cell is damaged, LDH is released in the bloodstream. A high level of LDH in the blood can be caused by cancer and can be a sign that the cancer is widespread.
- **Hepatitis Tests.** Hepatitis is a disease of the liver. It can be caused by the hepatitis C and B viruses. All patients should be tested for hepatitis C because the virus has been associated with the development of marginal zone lymphoma. Hepatitis B testing should be performed on patients being considered for treatment with rituximab-containing regimens, because rituximab can cause hepatitis B to become active again.

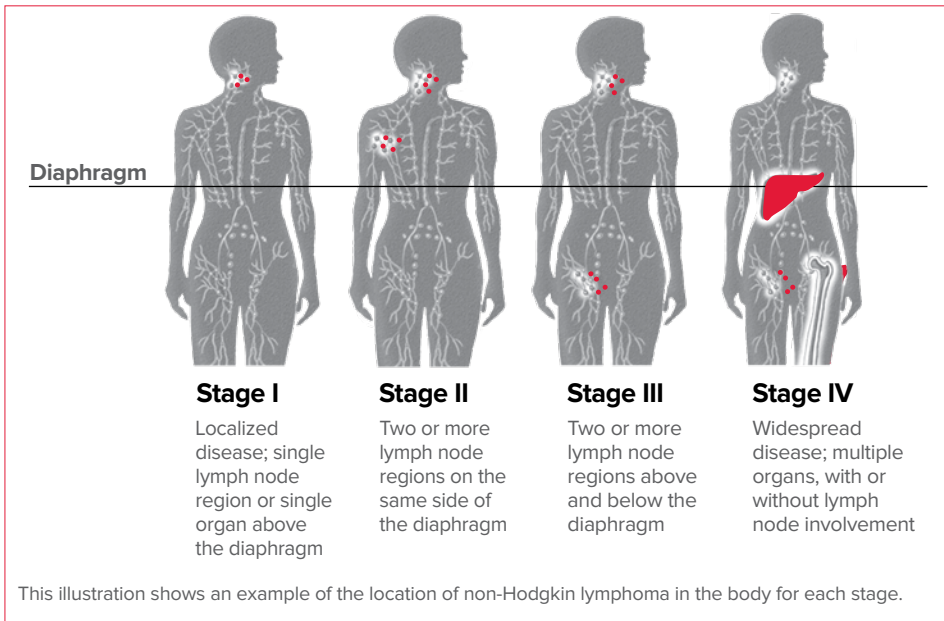
Imaging Tests. These tests create images (pictures) of the inside of the body. Various types of imaging tests such as computed tomography (CT) and positron-emission tomography (PET) scans can show where the lymphoma is located in the body and provide information that helps the doctor determine the stage of the lymphoma.

Visit www.LLS.org/booklets to view the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

Staging System. In cancer staging, the Roman numerals I through IV (1-4) are used to represent the extent of cancer in the body. Stage I cancers are less advanced and often have a better prognosis. Higher-stage cancers are generally more widespread in the body and may require different or more intense treatment.

The Lugano system, a modification of the older Ann Arbor system, is one of the more widely-used staging systems for non-Hodgkin lymphoma. See **Figure 2** below for description of the stages.

Figure 2. Non-Hodgkin Lymphoma (NHL) Stages



Treatment

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you. See page 41 for more information on clinical trials.

The treatment approach for nodal marginal zone lymphoma depends on the stage of the disease.

Stage I or Stage II Disease. Treatment options in stage I or II include:

Watch-and-Wait Approach. For patients who have no symptoms, the doctor may recommend a period of observation, called “watch and wait.” Many doctors consider observation, involving careful monitoring and follow-up care, to be an active form of therapy. This approach allows the patient to avoid the side effects of treatment for as long as possible. Patients need to discuss with their doctors the potential benefits of the watch-and-wait approach versus other treatment options. Treatment should start once patient begins to exhibit lymphoma-related symptoms or there are signs of disease progression based on lab tests.

Radiation Therapy. This treatment uses high-energy x-rays to kill cancer cells. Radiation therapy can be very effective if the lymphoma is only affecting a few areas of the body. For patients with nodal marginal zone lymphoma that is limited to a single lymph node region, radiation therapy has the potential to cure the lymphoma.

Rituximab (Rituxan®). Rituximab, with or without chemotherapy, may be recommended. Rituximab is a type of monoclonal antibody therapy. It binds to a protein called CD20 on the lymphoma cells, helping the immune system find and destroy them.

Follow-Up Care. The NCCN Guidelines recommend clinical follow-up including lab and imaging tests every 3 to 6 months for the first 5 years after the completion of therapy, and then annually thereafter (or as clinically indicated). Patients with disease not responding to radiation therapy or rituximab should be treated with regimens for stage III or IV disease (see below).

Stage III or Stage IV Disease. Standard treatments usually do not cure patients with stage III or IV nodal marginal zone lymphoma. While most patients can achieve a remission, repeated relapses are common. Treatment for these patients focuses on alleviating symptoms and improving quality of life.

Treatment options in stage III or IV include the methods listed below.

Watch-and-Wait Approach. For patients who have no symptoms, the doctor may recommend a period of observation, called “watch and wait.” Many doctors consider observation, involving careful monitoring and follow-up care, to be an active form of therapy. This approach allows the patient to avoid the side effects of treatment for as long as possible. Patients need to discuss with their doctors the potential benefits of the watch-and-wait approach versus other treatment options. Treatment should start once patient begins to exhibit lymphoma-related symptoms or there are signs of disease progression based on lab tests.

Chemoimmunotherapy. Current treatments for advanced-stage nodal marginal zone lymphoma may include chemoimmunotherapy. This type of treatment combines chemotherapy with immunotherapy. Chemotherapy uses various drugs

to kill or slow the growth of cancer cells. Immunotherapy uses the body’s own immune system to find and kill cancer cells. Immunotherapy for marginal zone lymphoma often uses a monoclonal antibody drug called rituximab (Rituxan®). See **Table 6** below for a list of suggested first-line therapies for advanced-stage nodal marginal zone lymphoma, adapted from the NCCN Guidelines.

Table 6. Suggested First-Line Treatment Regimens

First-Line Therapy*	First-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + rituximab ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Lenalidomide + rituximab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimen</u></p> <ul style="list-style-type: none"> ○ Rituximab <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab

*Preferred and Other Recommended Regimens are listed in alphabetical order.
 Abbreviations: mAB, monoclonal antibody; ±, plus or minus (with or without).
 NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. 2022

See pages 44-47, for information on the drug classifications and approved indications for these therapies.

Treatment Options for Relapsed and Refractory Cases

Some patients with lymphoma do not respond to initial therapy. When this occurs, it is referred to as “refractory” disease. In other patients, the lymphoma comes back after a remission. In these cases, it is referred to as “relapsed” disease.

Many patients with relapsed or refractory nodal marginal zone lymphoma can obtain another period of remission with additional treatment. See **Table 7** on page 30 for a list of suggested treatments for relapsed and refractory cases of nodal marginal zone lymphoma, adapted from the NCCN Guidelines.

Table 7. Suggested Treatment Regimens for Relapsed/Refractory Disease

Second-Line and Subsequent Therapy*	Second-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + obinutuzumab (not recommended if treated with prior bendamustine) ○ Bendamustine + rituximab (not recommended if treated with prior bendamustine) ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab ○ Ibrutinib ○ Lenalidomide + rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab ○ Copanlisib (relapsed/refractory after 2 prior therapies) ○ CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab ○ Ibritumomab tiuxetan ○ Lenalidomide + obinutuzumab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Ibrutinib ○ Lenalidomide + rituximab ○ Rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20 mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab <p>*Preferred and Other Recommended Regimens are listed in alphabetical order. Abbreviations: mAB, monoclonal antibody; ±, plus or minus (with or without). NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology. B-Cell Lymphomas. 2022.</p> <p>See pages 44-47, for information on the drug classifications and the approved indications for these therapies.</p>

Stem Cell Transplantation. Stem cell transplantation may be considered as a treatment option for select patients with refractory or relapsed nodal marginal zone lymphoma.

The goal of stem cell transplantation is to cure the patient's cancer with very high doses of chemotherapy. Although administering such high doses of chemotherapy drugs can kill more lymphoma cells, it can also severely damage the stem cells in the bone marrow and cause dangerously low blood cell counts. This may result in anemia, serious infections and uncontrolled bleeding. Stem cell transplantation allows doctors to give higher doses of chemotherapy than can typically be given. This is because, after the intensive therapy, the patient receives an infusion of stem cells to replace those destroyed by the chemotherapy.

The main types of stem cell transplantation are:

- Autologous, in which a patient's own stem cells are collected before chemotherapy, stored, and then returned to the patient's body after completing chemotherapy.
- Allogeneic, in which a patient receives stem cells from a matched or partially matched donor, either related or unrelated to the patient.

For indolent lymphomas, including some types of marginal zone lymphomas, autologous stem cell transplantation is primarily used to treat patients who have relapsed. Allogeneic transplantation may be considered in some cases, particularly for younger patients whose cancer is more aggressive or has high-risk features.

Stem cell transplantation can cause serious side effects that can be life-threatening. So, it may not be a treatment option for most patients with nodal marginal zone lymphoma. The risks and benefits of transplantation must always be considered, and the decision to undergo a transplant should be discussed with the doctor. The doctor will consider many factors, including the patient's age, general health, certain prognostic factors, previous treatments, and whether the patient has a well-matched donor.

For more information on stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Treatment Outcomes

Standard treatments usually do not cure patients with nodal marginal zone lymphoma. While remissions can be achieved, relapses are common, sometimes occurring several times over many years. However, these relapses can often be successfully treated. Overall survival, at five years after diagnosis, ranges from 55 percent to 80 percent. Treatment outcomes can vary widely, however, so it is important to discuss with your doctor the potential outcomes in your specific case.

It is also important to remember that survival statistics are only estimates and are based on patients diagnosed with nodal marginal zone lymphoma some time ago. Since the statistics were collected, new treatments have been approved and more are being studied in clinical trials. As a result, the outlook may be better for people diagnosed with this disease today.

Splenic Marginal Zone Lymphoma

Splenic marginal zone lymphoma is a rare, slow-growing type of non-Hodgkin lymphoma that occurs most often in the spleen and bone marrow, and sometimes the blood. It accounts for about 9 percent of all marginal zone lymphoma cases diagnosed each year in the United States. Splenic marginal zone lymphoma is uncommon before the age of 50. The median age at diagnosis is 65 to 70 years.

The spleen is a soft, spongy organ above the stomach and under the ribs on the left side, about the size of a fist. It is part of the lymphatic system, and it performs several critical functions including:

- Filtering out and destroying old, damaged blood cells
- Storing red blood cells and platelets
- Producing lymphocytes (a type of white blood cell) that fight infection and disease

The cause of splenic marginal zone lymphoma is unknown in most cases. It is more common in people who have been infected with hepatitis C virus or who have an autoimmune condition.

Signs and Symptoms

Signs and symptoms are changes in the body that may indicate the presence of disease. A “sign” is a change that doctors see during an exam or in a test result. A “symptom” is a change that patients can see or feel.

Splenic marginal zone lymphoma develops slowly and may not cause symptoms for many years. It may be discovered during a physical exam when the doctor notices that the spleen is larger than it should be, or during a blood test. Many patients have no symptoms at the time of diagnosis.

In most patients, splenic marginal zone lymphoma causes an enlarged spleen. This is called “splenomegaly.” Symptoms of an enlarged spleen include:

- Pain in the left upper abdomen that may spread to the left shoulder
- Feeling full after eating only a small amount (from the enlarged spleen pressing on the stomach)
- Decreased appetite
- Unexplained weight loss

Splenic marginal zone lymphoma often spreads to the bone marrow, the soft tissue inside of certain bones. The bone marrow is where new blood cells are made. If cancer spreads to the bone marrow, cancer cells can crowd out the body’s healthy blood cells, causing low red blood cell and platelet counts.

As a result, patients may not have enough healthy blood cells and often have symptoms related to low blood cell counts.

Symptoms of anemia (low red blood cell count) include:

- Fatigue
- Shortness of breath during normal physical activities
- Dizziness, particularly upon standing quickly
- Pale complexion
- Palpitations (racing heart)

Symptoms of thrombocytopenia (low platelet count) include:

- Bruising easily
- Prolonged bleeding from minor cuts
- Frequent or severe nosebleeds
- Bleeding gums

Diagnosis

If patients have signs or symptoms of lymphoma, they may need to undergo a biopsy to determine whether the signs and symptoms are from lymphoma or another condition. A biopsy is a procedure to remove a sample of cells from the body so that it can be examined under a microscope. A definitive diagnosis of splenic marginal zone lymphoma would require a splenectomy (surgery to remove the spleen). This is rarely done though, due to the health risks of removing the spleen. Most cases of splenic marginal zone lymphoma are diagnosed with blood and bone marrow tests.

Complete Blood Count (CBC). This test measures the number of red blood cells, white blood cells and platelets in the blood. Patients with splenic marginal zone lymphoma usually have lymphocytosis, a high white blood cell count, at the time of diagnosis. It often results from the immune system working to fight off an infection or other disease. Additionally, patients often have low red blood cell and platelet counts.

Comprehensive Metabolic Panel. This is a group of tests that measure up to 14 chemicals in the blood. It gives important information about how well a person's kidneys, liver and other organs are working. Abnormal levels of these chemicals can be caused by cancer or other health problems.

Lactate Dehydrogenase (LDH) Test. This test measures the level of LDH in the blood. LDH is a protein found in most cells. When a cell is damaged, LDH is released in the bloodstream. A high level of LDH in the blood can be caused by

cancer and also can be a sign that the cancer is widespread.

Hepatitis Tests. Hepatitis is a disease of the liver. It can be caused by the hepatitis C and B viruses. All patients should be tested for hepatitis C because the virus has been associated with the development of marginal zone lymphoma. Hepatitis B testing should be performed on patients being considered for treatment with rituximab-containing regimens, because rituximab can cause hepatitis B to become active again.

Bone Marrow Aspiration and Biopsy. These two tests are used to collect and examine bone marrow, the spongy tissue found inside bones to look for lymphoma cells in the bone marrow. These tests are generally done at the same visit, either at the doctor's office or in a hospital.

Bone marrow has both a solid and a liquid component. For a bone marrow aspiration, a special, hollow needle is inserted through the hip bone and into the bone marrow to aspirate (remove) a liquid sample of cells. For a bone marrow biopsy, a wider needle is used to remove a sample of solid bone that contains bone marrow. Both samples are sent to the lab where they are examined under a microscope.

In certain circumstances, evaluation of the bone marrow may be useful to see whether the lymphoma has spread to the bone marrow.

Cell Assessment. A hematopathologist examines the blood and bone samples under a microscope to view the size, shape and type of cells. A hematopathologist is a doctor who has special training in identifying blood diseases. This specialist may also perform other tests with the samples, including flow cytometry and cytogenetic analysis.

- **Flow Cytometry.** This lab test identifies the antigens, or proteins, on the surface and within the cancer cells. Finding (or not finding) certain proteins can help the hematopathologist determine the type of lymphoma. The pattern of the surface proteins is called the “immunophenotype.”

Marginal zone lymphoma has a common pattern of proteins. The classical immunophenotype for marginal zone lymphoma is CD20+, CD5- and CD10-. This means that if a sample of lymphoma cells have the antigen CD20 but do not have CD5 or CD10 a person is diagnosed with marginal zone lymphoma. (CD is the abbreviation for “cluster of differentiation,” the term for these cell surface markers.)

- **Cytogenetic Analysis.** This is done to look for abnormal changes in the chromosomes of the lymphoma cells. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each pair of chromosomes is a certain size, shape and structure. In some cases of lymphoma, the chromosomes of the lymphoma cells have abnormal changes that can be seen under a microscope, such as an extra chromosome, a deletion or a translocation.

The lymphoma cells in the sample are allowed to grow in the laboratory, and prior to examination, a special stain is applied. The sample is then examined under a microscope and photographed to show the arrangement of the chromosomes, called a “karyotype.” The karyotype shows if there are any abnormal changes in the size, shape, structure or number of chromosomes in the lymphoma cells. Many patients with splenic marginal zone lymphoma have an abnormal karyotype, often with complex chromosomal changes. A “complex karyotype” is defined by the presence of three or more unrelated chromosomal abnormalities that occur in more than one cell.

Imaging Tests. These tests create images (pictures) of the inside of the body. Various types of imaging tests such as computed tomography (CT) and positron-emission tomography (PET) scans can show where the lymphoma is in the body.

Visit www.LLS.org/booklets to view the free LLS booklets *Understanding Lab and Imaging Tests* and *Understanding Genetics*.

Treatment

New treatments may have been approved since this book was printed. Check www.LLS.org/DrugUpdates or call (800) 955-4572.

Before you begin treatment, you and your doctor will discuss your treatment options. One option may be a clinical trial. Like all treatment options, clinical trials have possible risks and benefits. By considering all of your treatment options, including clinical trials, you will be taking an active role in a very important decision that affects you. See page 41 for more information on clinical trials.

Treatment options depend on whether or not the patient has lymphoma symptoms at the time of diagnosis.

Asymptomatic Patients (Patients who have no symptoms of lymphoma).

Splenic marginal zone lymphoma is typically slow-growing. Not all newly diagnosed patients need immediate treatment. Patients may not need treatment for the lymphoma unless they begin to have symptoms.

Treatment for Hepatitis C. For patients infected with the hepatitis C virus, the doctor may recommend anti-viral treatment. Newer treatments for hepatitis C are less intensive and more effective than those used in the past. Treatment for hepatitis C may help decrease white blood cell counts and splenomegaly (enlarged spleen). Sometimes treating hepatitis C virus can also treat the lymphoma.

Watch-and-Wait Approach. For patients who have no symptoms, the doctor may recommend a period of observation, called “watch and wait.” Many doctors consider observation, involving careful monitoring and follow-up care, to be an active form of therapy. This approach allows the patient to avoid the side effects

of treatment for as long as possible. Patients need to speak with their doctors about the potential benefits of the watch-and-wait approach, versus other treatment options.

Symptomatic Patients. Treatment for lymphoma should start once patients begin to exhibit lymphoma-related symptoms or there are signs that the disease has progressed based on lab tests. Treatment should also start once patients have splenomegaly and one or more of the following signs or symptoms:

- Local symptoms related to splenomegaly, such as a sense of fullness or discomfort in the left upper abdomen, a feeling of pain in the left shoulder, or early satiety (feeling full after eating only a small amount of food)
- Low blood cell counts due to extensive infiltration of lymphoma cells in the bone marrow

Rituximab (Rituxan®). Single-agent rituximab therapy is recommended for patients with minimal or moderate symptoms (or symptoms of splenomegaly, weight loss, early satiety or abdominal pain). Rituximab is a type of monoclonal antibody therapy. It binds to a protein called CD20 on the lymphoma cells, helping the immune system to find and destroy them.

Splenectomy. The doctor may recommend a splenectomy, an operation to remove the spleen, if a patient has severe symptoms due to an enlarged spleen that do not respond to rituximab therapy. Symptoms of enlarged spleen including abdominal pain, early satiety with weight loss, and/or low blood cell counts due to splenic sequestration, can be relieved quickly by a splenectomy. (Splenic sequestration happens when a large volume of blood is trapped in the spleen.) Splenectomy is also indicated when splenic marginal cell lymphoma is suspected to have transformed into diffuse large B cell lymphoma, a faster-growing type of lymphoma, within the spleen.

After the spleen is removed, the body is less able to fight infection, so it is important to take precautions to reduce the risk of infection. This includes receiving pneumococcal and meningococcal vaccinations at least two weeks before the splenectomy. Vaccination against *Haemophilus influenzae* type b (HiB), should also be considered at that time. After the operation, long-term antibiotic therapy may also be recommended.

Follow-up Care. Patients should be monitored on a regular basis following treatment. The NCCN Guidelines recommend follow-up (including blood tests, bone marrow tests and imaging tests as clinically indicated) every 3 to 6 months for 5 years, and then every year or as clinically indicated thereafter.

Treatment Options for Relapsed and Refractory Disease

Some patients with lymphoma do not respond to initial therapy. When this occurs, it is referred to as “refractory” disease. In other patients, the lymphoma comes back after a remission. In these cases, it is referred to as “relapsed” disease.

It is common for splenic marginal zone lymphoma to relapse after treatment. Patients can usually obtain another period of remission with additional treatment. This approach can often control the lymphoma for many years. See **Table 8** on page 39 for a list of suggested treatments for relapsed and refractory splenic marginal zone lymphoma, adapted from the NCCN Guidelines.

Table 8. Suggested Treatment Regimens for Relapsed/Refractory Disease

Second-Line and Subsequent Therapy*	Second-Line Therapy for Elderly or Infirm (Frail)*
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Bendamustine + obinutuzumab (not recommended if treated with prior bendamustine) ○ Bendamustine + rituximab (not recommended if treated with prior bendamustine) ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab ○ CVP (cyclophosphamide, vincristine, prednisone) + rituximab ○ Ibrutinib ○ Lenalidomide + rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20-mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + obinutuzumab ○ Copanlisib (relapsed/refractory after 2 prior therapies) ○ CVP (cyclophosphamide, vincristine, prednisone) + obinutuzumab ○ Ibritumomab tiuxetan ○ Lenalidomide + obinutuzumab ○ Rituximab 	<p>(if doctor believes patient cannot tolerate any therapies listed on left)</p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> ○ Ibrutinib ○ Lenalidomide + rituximab ○ Rituximab ○ Zanubrutinib (relapsed/refractory after at least one prior anti-CD20 mAB-based regimen) <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> ○ Chlorambucil ± rituximab ○ Cyclophosphamide ± rituximab <p>*Preferred and Other Recommended Regimens are listed in alphabetical order. Abbreviations: mAB, monoclonal antibody; ±, plus or minus (with or without). NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology, B-Cell Lymphomas. 2022.</p> <p>See pages 44-47, for information on the drug classifications and the approved indications for these therapies.</p>

Treatment Outcomes

Splenic marginal zone lymphoma is generally indolent, meaning it is slow growing. Treatment is often successful, but relapses are common, and then more treatment is needed to keep it under control. Patients may have periods when they feel well and do not need treatment, followed by periods when their symptoms get worse and they require more treatment.

Most people with splenic marginal zone lymphoma live for many years, with a median overall survival of more than 10 years. In up to 5 to 10 percent of cases, the disease progresses to diffuse large B-cell lymphoma, which often decreases the survival time. Treatment outcomes can vary widely, however, so it is important to speak with your doctor about the potential outcomes in your specific case.

It is also important to remember that survival statistics are only estimates and are based on patients diagnosed with splenic marginal zone lymphoma some time ago. Since the statistics were collected, new treatments have been approved and more are being developed in clinical trials. As a result, the outlook may be better for people diagnosed with this disease today.

Clinical Trials for Blood Cancers

Every new cancer drug goes through a series of carefully controlled research studies before it can become part of standard cancer care. These research studies are called clinical trials and they are used to find better ways to care for and treat people with cancer.

In the United States, the FDA (Food and Drug Administration) requires that all new drugs and other treatments be tested in clinical trials before they can be approved. At any given time, there are thousands of cancer clinical trials taking place. Doctors and researchers are always looking for new and better ways to treat cancer.

Researchers use cancer clinical trials to study new ways to:

- Treat cancer using
 - A new drug
 - A drug that is already approved to treat a different kind of cancer
 - A new combination of drugs
 - A new way of giving a drug (orally, as a pill, intravenously [IV], etc)
- Manage cancer symptoms and ease treatment side effects
- Find and diagnose cancer
- Keep cancer from coming back after treatment
- Manage long-term side effects

By taking part in a clinical trial, patients can see doctors who are experts in their disease. They can gain access to new, cutting-edge therapies and provide helpful information for future patients. The treatments and information we have today are due in large part to patients who are willing to join clinical trials. Anyone interested in being part of a clinical trial should talk to their hematologist-oncologist about whether a clinical trial might be right for them. During this conversation it may help to:

- Have a list of questions to ask about the risks and benefits of each trial (visit www.LLS.org/WhatToAsk for lists of suggested questions).
- Ask a family member or friend to go with you to your doctor visit—both for support and to take notes.

Clinical trials can be difficult to navigate and figure out, but The Leukemia & Lymphoma Society is here to help. Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find potential clinical trials, overcome the barriers to enrollment and provide support throughout the entire clinical trial

process. Our Clinical Trial Nurse Navigators are registered nurses who are experts in blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Talk with you about your treatment goals
- Help you to understand the clinical-trial process, including your rights as a patient
- Ask you for details about your diagnosis (such as past treatments, treatment responses, and your cancer genetic profile), your current health and your medical history, because these might impact whether you can take part in certain clinical trials
- Help you to understand how your finances, insurance coverage, support network, and ability and willingness to travel might impact your choice of clinical trials
- Guide you and help you in your efforts to find and enroll in a clinical trial, including connecting you with trial sites
- Help you deal with any problems you might have as you enroll in a trial
- Support you throughout the clinical trial process

Please call an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/CTSC for more information about clinical trials and the Clinical Trial Support Center at LLS.

Also, visit www.LLS.org/booklets to view *Understanding Clinical Trials for Blood Cancers*.

Treatment Side Effects

Cancer treatments can cause side effects. These are problems that occur when treatment affects healthy tissues or organs. People are affected by cancer treatments in different ways. Side effects depend on many factors, including the type and dosage of the treatment, as well as the patient's age and their other medical conditions.

Each treatment or drug has different possible side effects. Your healthcare team should give you information about the possible side effects of your treatments. Side-effect management is important. If you have any concerns about potential side effects, talk to the members of your treatment team to get help.

Most side effects can be managed without compromising the effectiveness of your treatment. In fact, aggressive management of side effects often leads to better treatment outcomes. Most side effects are temporary and go away when treatment is completed. However, some side effects are long-term and may appear years after the treatment has been completed. Late side effects may

include development of another type of cancer, heart disease and low levels of thyroid hormones (hypothyroidism).

See the free LLS series *Side Effects Management (filter for Side Effect Management)* at www.LLS.org/booklets for more information.

Follow-Up Care

Your medical care does not stop once active treatment has finished. Your doctor will continue to make sure that your lymphoma has not returned, manage side effects and monitor you for late effects of treatment. This is called follow-up care.

Monitoring for Recurrence. After a patient completes treatment and is in remission, follow-up tests are done to check how well the treatment worked and to look for signs of relapse. Tests are also done to see how well the patient's organs are working.

Patients undergo frequent follow-up tests during the first 5 years after treatment. Testing and check-ups may be required less often as times goes on, but scheduled follow-up visits should continue indefinitely.

People who have been treated for marginal zone lymphoma are encouraged to:

- Maintain regular follow-up appointments with their hematologist-oncologists. Their doctors will monitor them for signs of relapse and will also be able to detect any treatment side effects or the onset of other medical problems.
- Keep a record of their cancer diagnosis, treatment and follow-up care needs. This record, often called a “survivorship care plan,” should be provided to patients in writing so they can share it with any new healthcare providers they see. Ask the doctor for this information. The plan should include the following information:
 - List of all healthcare providers
 - Diagnosis summary with specifics such as subtype and/or genetic markers
 - Treatment summary with specifics such as the names, dates, and dosages of chemotherapy or other drugs, the area treated with radiation therapy, surgery and/or transplantation information, as well as treatment response and side effects
 - Maintenance treatment information, if applicable
 - List of possible late effects
 - Schedule for ongoing monitoring with recommended tests, frequency and coordinating provider
 - Health and wellness recommendations, such as nutrition, exercise and other disease screenings

- Receive periodic screening and monitoring for other types of cancer, including skin, gastrointestinal, kidney, blood, bladder, prostate, breast, lung, head and neck cancer, if they received treatments that increase the risk of developing a second cancer.
- Seek medical and psychosocial support for fatigue, depression and other long-term effects, if needed.
- Consider ways to reduce their risks for cancer, such as quitting smoking, protecting their skin from prolonged sun exposure, and exercising.

Vaccines. Patients with non-Hodgkin lymphoma are advised to receive certain vaccines, including those for pneumococcal pneumonia and influenza, once they have finished treatment. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Patients should not be given vaccines that use live organisms or those with high viral loads, such as the herpes zoster (shingles) vaccine. However, they can receive Shingrix® because it uses an inactivated form of the virus.

Current COVID-19 vaccines are also recommended. Speak to your doctor for more information.

Drugs Used to Treat Marginal Zone Lymphoma

Below are some drugs used in the treatment of marginal zone lymphoma.

Monoclonal Antibody Therapy. Antibodies are proteins made by the immune system to help fight infections. Monoclonal antibodies are proteins made in the laboratory and are designed to attack a specific target on cancer cells. For example, some monoclonal antibody therapies for marginal zone lymphoma target the antigen CD20 found on the surface of B cells, including lymphoma cells. Once they are attached to the CD20 antigen, the treatments work by helping the immune system identify and destroy the cancer cells.

- **Rituximab (Rituxan®)** is a CD20-directed cytolytic antibody indicated for the treatment of adult patients with non-Hodgkin lymphoma. It is given as an infusion into a vein.

Bruton Tyrosine Kinase (BTK) Inhibitors. Human cells have many different kinases. Kinases are proteins in cells that normally relay signals that tell cells to grow, divide and survive. The BTK protein transmits important chemical signals that instruct B cells to mature and produce antibodies.

BTK is central to B-cell receptor signaling. It is present in all B-cells, and low-level activation is necessary for normal B-cell growth and survival. Certain B-cell cancers, including marginal zone lymphoma, are dependent on BTK for survival. A mutation in the BTK gene causes the BTK pathway to become overactive, which results in the proliferation (multiplication or increase in number) of the cancer cells. Drugs that block this overactive pathway are called BTK inhibitors.

In addition, BTK inhibitors help release the lymphoma cells from the bone marrow, lymph nodes, spleen or other areas in which they are hidden in a protective microenvironment where they can hide from the immune system. Release from the protective microenvironment potentially helps the immune system find and destroy these lymphoma cells.

These drugs are long-term therapies which is a very different type of approach from chemotherapy.

- **Ibrutinib (Imbruvica®)** is a BTK inhibitor indicated for the treatment of adult patients with marginal zone lymphoma who require systemic therapy and have received at least one prior anti-CD20-based therapy. It is taken by mouth.
- **Zanubrutinib (Brukinsa®)** is a next-generation BTK inhibitor indicated for the treatment of adult patients with relapsed or refractory marginal zone lymphoma who have received at least one anti-CD20-based regimen. It is taken by mouth.

PI3K Inhibitors. Phosphoinositide 3-kinases (PI3Ks) are a group of proteins that are an important part of the B-cell receptor pathway. They transmit signals in cells that help control cell growth. Some lymphoma cells have higher-than-normal levels of PI3K, which causes them to multiply. PI3K inhibitors block the signaling pathways that cause the lymphoma cells to grow and divide.

- **Copanlisib (Aliqopa®)** is indicated for the treatment of adult patients with relapsed follicular lymphoma. While this drug is not FDA-approved to treat marginal zone lymphoma, it is commonly used as an “off-label” treatment for patients with relapsed or refractory marginal zone lymphoma who have received at least two prior therapies. “Off-label” prescribing is when a doctor gives a drug that is FDA approved to treat one condition for another condition.

Immunomodulatory Drugs. Immunomodulatory drugs act in multiple ways to kill lymphoma cells. They also affect other cells in the bone marrow, including immune cells. These drugs induce a cancer suppressor response directed by the immune system.

- **Lenalidomide (Revlimid®)** is a thalidomide analogue indicated for the treatment of adult patients with previously treated marginal zone lymphoma, in combination with rituximab. It is taken by mouth.

Chemotherapy. Chemotherapy drugs kill fast-growing cells throughout the body, including both cancer cells and normal, healthy cells. Different types of chemotherapy drugs work in different ways to eliminate lymphoma cells or stop new lymphoma cells from forming. As a result, more than one chemotherapy drug is used to attack the cancer from different angles and prevent drug resistance. For patients with advanced disease or relapsed or refractory marginal zone lymphoma, the doctor may recommend chemoimmunotherapy, which is chemotherapy combined with an immunotherapy drug, such as rituximab. Below are some of the chemotherapy drugs that are often used to treat marginal zone lymphoma:

- **Bendamustine (Bendeka® , Treanda®)** is an alkylating drug indicated for treatment of patients with indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen. It is given by injection.
- **Chlorambucil (Leukeran®)** is indicated in the treatment of non-Hodgkin lymphoma.
- **Cyclophosphamide (Cytosan®)** is an alkylating drug indicated for treatment of malignant lymphomas.
- **Doxorubicin (Adriamycin®)** is an anthracycline topoisomerase inhibitor indicated for the treatment of non-Hodgkin lymphoma.
- **Vincristine (Oncovin®)** is used in combination with other chemotherapy drugs to treat certain types of non-Hodgkin lymphoma.

Corticosteroids. Corticosteroids are a class of drugs that are used to reduce inflammation, swelling and pain. In high doses, they can kill lymphoma and leukemia cells.

- **Prednisone** is an anti-inflammatory medication used with other chemotherapy drugs to treat lymphoma.

Radioimmunotherapy. This type of therapy consists of a monoclonal antibody that works by targeting CD20 on B cells. In the laboratory, a radioactive substance is attached to the antibody. When the antibody attaches to the CD20 antigens on B cells, radiation is delivered directly to the targeted cells, killing them and nearby cells. Stem cells in the bone do not have the antigen CD20. This allows healthy B cells to regenerate after treatment.

- **Ibritumomab Tiuxetan (Zevalin®)** is a CD20-directed radiotherapeutic antibody administered as part of the Zevalin therapeutic regimen, indicated for the treatment of adult patients with relapsed or refractory low-grade B-cell non-Hodgkin lymphoma.

Additional Drugs Used in the Treatment of Marginal Zone Lymphoma

Sometimes, other drugs are used “off label” during later lines of therapy. This

means they are FDA-approved to treat other types of blood cancer, but they have not been approved for marginal zone lymphoma.

Obinutuzumab (Gazyva®) is a CD20-directed cytolytic antibody approved for the treatment of follicular lymphoma and chronic lymphocytic leukemia. While this drug is not FDA-approved to treat marginal zone lymphoma, it is commonly used as an off-label treatment for it.

Normal Blood and Bone Marrow

Blood. Blood is the liquid that flows through a person's arteries and veins. It carries oxygen and nutrients throughout the body. It also carries away waste products. Blood is composed of plasma and cells.

Plasma. Plasma is largely made up of water, in which many chemicals are dissolved. These chemicals each have a special role. They include:

- Proteins
 - Albumin, the most common blood protein
 - Blood-clotting proteins (coagulation factors) made by the liver
 - Erythropoietin, a protein made by the kidneys that stimulates red blood cell production
 - Immunoglobulins, proteins that help the body fight infection
- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B12
- Electrolytes, such as calcium, potassium and sodium

Blood cells. Blood cells are formed in the bone marrow, a spongy tissue where blood cells grow and develop. Blood cells start as stem cells. The process of stem cells maturing into blood cells is called "hematopoiesis." The blood cells are suspended in the plasma. See **Figure 3** on page 48.

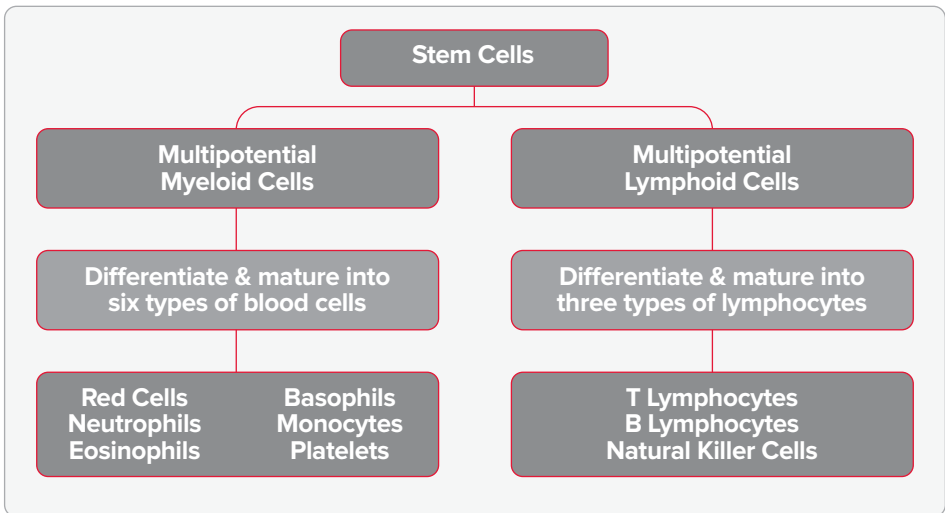
Once the stem cell is created, it will develop into one of the three types of blood cells:

1. Red blood cells (the cells that carry oxygen)
 - These make up a little less than half of the body's total blood volume.
 - They are filled with hemoglobin, the protein that picks up oxygen from the lungs and takes it around the body. It binds with carbon dioxide (CO₂) and removes it from the cells and then brings it back to the lungs. When a person exhales (breathes out), the CO₂ is removed from the lungs.

2. Platelets (cells that help blood to clot)
 - These are small cells (one-tenth the size of red blood cells).
 - They help stop bleeding from an injury or cut.
 - They stick to the torn surface of the vessel, clump together and plug up the bleeding site. They form a clot with the help of proteins, such as fibrin, and electrolytes, such as calcium.

3. White blood cells (WBCs). These are the cells that fight infections. They include:
 - Neutrophils and monocytes. These cells, called “phagocytes,” ingest and destroy bacteria and fungi. Unlike red blood cells and platelets, neutrophils and monocytes can leave the bloodstream and enter tissues to attack invading organisms and fight off infection.
 - Eosinophils and basophils. These WBCs respond to allergens or parasites.
 - Lymphocytes. These WBCs, found mostly in the lymph nodes, spleen and lymphatic channels, are a key part of the immune system. Some enter the bloodstream. There are three major types of lymphocytes:
 - T lymphocytes (T cells)
 - B lymphocytes (B cells)
 - Natural killer cells (NK cells)

Figure 3. Blood Cell & Lymphocyte Development



Bone Marrow. In healthy people, stem cells in the bone marrow produce new blood cells continuously. When blood cells are fully developed, they enter the bloodstream as blood passes through the marrow and then circulate throughout the body.

In babies, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have blood-forming marrow. In adults, marrow is only found in the spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull.

Hematopoietic stem cells are found in the marrow. These stem cells are important because they can be used for transplants. Some stem cells enter the bloodstream and circulate. Doctors know how to stimulate the growth of these cells in the marrow and make them migrate into the bloodstream. Then a special technique called “apheresis” is used to separate them from the circulating blood so they can be collected and stored. Stem cells from the placenta and the umbilical cord of a newborn infant can also be harvested and used for future transplantation.

The Lymphatic System

The bone marrow is really two organs in one. It is (1) the organ that forms blood cells, and (2) the organ that forms lymphocytes, which make up part of the immune system.

The marrow bone produces three main types of lymphocytes. They are:

- B lymphocytes (B cells), which make antibodies in response to foreign antigens, especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for other white blood cells to recognize the antibody and pull it into the cell (ingest it) along with its attached microbe. The white blood cell then kills and ingests the microbe.
- Natural killer (NK) cells, which have granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus.

The lymphocytes circulate through channels called “lymphatics,” which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system, such as the skin, spleen, tonsils and adenoids, intestinal lining, and (in young people) the thymus.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions and to make the most of the knowledge and skills of the members of your healthcare team.

For Help and Information

Consult With an Information Specialist. Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information.

- Call: (800) 955-4572 (Monday through Friday, from 9 am to 9 pm ET)
- Email and Live Chat: www.LLS.org/InformationSpecialists

Clinical Trial Support Center. Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. When appropriate, patients and caregivers can work with Clinical Trial Nurse Navigators who will help find a clinical trial according to their needs and personally assist them throughout the entire clinical trial process. Visit www.LLS.org/CTSC for more information.

One-on-One Nutrition Consultations. Access free one-on-one nutrition consultations provided by a registered dietitian with experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit www.LLS.org/nutrition to schedule a consultation or for more information.

Free Information Booklets. LLS offers free education and support booklets that can be either read online or ordered. Please visit www.LLS.org/booklets for more information.

Telephone/Web Education Programs. LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit www.LLS.org/programs for more information.

Financial Assistance. LLS offers financial assistance to individuals with blood cancer. Please visit www.LLS.org/finances for more information.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. Please call or visit our website for more information.

- Call: (877) 557-2672
- Visit: www.LLS.org/copay

Free Mobile Apps

- LLS Health Manager™ – Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit www.LLS.org/HealthManager to download for free.
- LLS Coloring For Kids™ – Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit www.LLS.org/ColoringApp to download for free.

Podcast. *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit www.LLS.org/TheBloodline for more information and to subscribe.

Suggested Reading. LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit www.LLS.org/SuggestedReading to find out more.

Continuing Education. LLS offers free continuing education programs for healthcare professionals. Please visit www.LLS.org/ProfessionalEd for more information.

Community Resources and Networking

LLS Community. The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Please visit www.LLS.org/community to join.

Weekly Online Chats. Moderated online chats can provide support and help cancer patients reach out and share information. Please visit www.LLS.org/chat to join.

LLS Chapters. LLS offers community support and services in the United States and Canada, including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact the nearest chapter, please call or visit our website.

- Call: (800) 955-4572
- Visit: www.LLS.org/ChapterFind

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit www.LLS.org/ResourceDirectory to obtain our directory.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. Please call or visit our website for more information.

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy

Additional Help for Specific Populations

Información en español (LLS Information in Spanish). Please visit www.LLS.org/espanol for more information.

Language Services. Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

Information for Veterans. Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please call the VA or visit the webpage.

- Call: (800) 749-8387
- Visit: www.publichealth.va.gov/exposures/AgentOrange

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks who were subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were either in the NYC disaster area, or who lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please call the WTC Health Program or visit their webpage.

- Call: (888) 982-4748
- Visit: www.cdc.gov/wtc/faq.html

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please call the National Institute of Mental Health (NIMH) or visit their website.

- Call: (866) 615-6464
- Visit: www.nimh.nih.gov and enter “depression” in the search box

Health Terms

Aggressive Lymphoma. Lymphoma that grows and spreads quickly and typically causes severe symptoms.

Alkylating Agent. A type of cancer drug that interferes with the DNA in cancer cells and inhibits their growth.

Allogeneic Stem Cell Transplantation. A treatment that uses stem cells from a healthy donor to restore a patient's bone marrow that is damaged or diseased after receiving high doses of chemotherapy and/or radiation therapy. **See the free LLS book *Blood and Marrow Stem Cell Transplantation*.**

Anemia. A condition in which the number of red blood cells is below normal, reducing the blood's ability to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath.

Antigen. Any substance that causes the body to make an immune response against that substance. Antigens include toxins, bacteria and viruses. Cancer cells also have antigens on them that can cause an immune response.

Autologous Stem Cell Transplantation. A treatment in which stem cells are removed from a patient, stored and then returned to the patient's body after intensive cancer treatment. **See the free LLS book *Blood and Marrow Stem Cell Transplantation*.**

Biopsy. A procedure to remove a sample of cells or tissue from the body for examination by a pathologist. The pathologist may examine the sample under a microscope or perform other tests on the cells or tissue.

Blood Cells. There are three major types of blood cells: 1) red blood cells that carry oxygen; 2) white blood cells that fight infections; and 3) platelets that help stop bleeding.

Bone Marrow. The spongy tissue in the hollow, central cavity of bones where blood cells form.

Bone Marrow Aspiration. A procedure in which a liquid sample of bone marrow is removed for examination. The sample is usually taken from the patient's hip bone, using a special needle, after a medication is given to numb the area. Bone marrow aspiration and bone marrow biopsy can be done in a doctor's office or in a hospital and are usually done at the same visit.

Bone Marrow Biopsy. A procedure in which a sample of bone containing bone marrow is removed for examination. The sample is usually taken from the hip bone, using a special hollow needle, after medication is given to numb the skin and tissue in that area. Bone marrow aspiration and bone marrow biopsy can be done in a doctor's office or in a hospital and are usually done at the same visit.

Complete Blood Count (CBC). A laboratory test that measures the number of red blood cells, white blood cells and platelets in the blood. It also measures the amount of hemoglobin (the substance in the blood that carries oxygen) and the hematocrit (the amount of whole blood that is made up of red blood cells).

Computed Tomography (CT) Scan. A procedure in which a series of x-ray images is processed with a computer to create 3-dimensional (3-D) views of tissues and organs in the body.

DNA. Abbreviation for deoxyribonucleic acid, the molecules inside cells that carry genetic information. DNA is passed to new cells during the process of cell division. A change or mutation in the DNA can lead to cell death, changes in the cell function and, in some cases, cancer.

Extranodal. Refers to an area or organ outside of the lymph nodes.

FDA. The abbreviation used to refer to the United States Food and Drug Administration. The FDA is responsible for assuring the safety, effectiveness and security of drugs, medical devices and the nation's food supply.

First-Line Therapy. The first treatment given for a disease.

Follicular Lymphoma. A type of B-cell non-Hodgkin lymphoma that is usually slow-growing. The abnormal B cells usually grow in clumps called "follicles" inside the lymph nodes.

Hematopathologist. A doctor who has special training in identifying blood diseases by examining blood, bone marrow, lymph and other tissue samples under a microscope and performing tests to determine if the blood cells are normal or not.

Hepatitis. Disease of the liver causing inflammation. Viruses called hepatitis A, hepatitis B and hepatitis C are the most common causes of the disease. Hepatitis B and hepatitis C can cause cirrhosis (scarring of the liver), liver failure and liver cancer. Symptoms of hepatitis include an enlarged liver, fever, nausea, vomiting, abdominal pain and dark urine.

H. pylori. Bacteria 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 mucosa-associated lymphoid tissue (MALT) lymphoma.

Imaging Test. A test that makes images (pictures) of areas inside the body. Imaging tests use different forms of energy, such as x-rays, radio waves and ultrasound. They may be used to help diagnose cancer, plan treatment or find out how well treatment is working.

Immune System. A complex network of cells, tissues and organs that work together to defend the body against infections and other diseases.

Immunophenotyping. A laboratory test that detects the presence of markers, called “antigens,” on white blood cells. Normal white blood cells have antigen patterns that are unique to specific cell types and stages of development. Abnormal cells seen in leukemias and lymphomas also have specific antigen patterns that can be used to identify them. This test can help diagnose specific types of leukemia and lymphoma.

Immunotherapy. A type of therapy that uses the body’s immune system to destroy cancer cells.

Indolent Lymphoma. Lymphoma that typically grows and spreads slowly with few symptoms.

Lymphatic System. The tissue and organs that make, store and carry lymphocytes (a type of white blood cells) that fight infections and other diseases.

Lymph Node. A bean-sized structure that is part of the body’s immune system. Lymph nodes are distributed throughout the body. They contain lymphocytes (a type of white blood cells) that help the body fight infections and other diseases. In patients with lymphoma and some types of lymphocytic leukemia, the cancerous lymphocytes multiply and cause the lymph nodes to become enlarged.

Lymphocyte. A type of white blood cell that is essential to the body's immune system. There are three major types of lymphocytes: B lymphocytes (B cells), which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes (T cells), which have several functions, including assisting B lymphocytes to make antibodies; and natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Malignant. Cancerous. Malignant cells can spread throughout the body and invade other tissues.

Monoclonal Antibody. A type of synthetic protein that can bind to substances in the body, including cancer cells. Monoclonal antibodies are used in cancer treatment to target cancer cells; they can be used alone or modified and attached to chemotherapy drugs.

Mucosa. The moist tissue that lines certain parts inside the body, including the nose, mouth, lungs, digestive tract and urinary tract. Glands in the mucosa make mucus (thick, slippery fluid).

Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma. A type of marginal zone lymphoma that occurs outside the lymph nodes in mucosal tissue in areas such as the stomach, small intestine, salivary gland, lungs, thyroid and the area around the eyes.

Off-Label. The legal use of a prescription drug to treat a disease when it has not been approved by the FDA for that disease.

Oncologist. A doctor who has special training in diagnosing and treating cancer.

Pathologist. A doctor who has special training in identifying diseases by examining cells and tissue samples under a microscope.

Positron Emission Tomography (PET) Scan. A procedure in which a small amount of radioactive glucose (sugar) is injected into a vein, and then a scanner is used to create detailed computerized pictures of areas where the glucose is being absorbed in the body. Cancer cells appear brighter in the pictures because they absorb more glucose than normal cells do. This helps locate cancer cells in the body.

Proton Pump Inhibitor. Medication that works by reducing the amount of acid made in the stomach.

Radiation Therapy. The use of x-rays and other forms of radiation to kill cancer cells and shrink tumors.

Refractory. The term used to describe a disease that does not go into remission or improve substantially after treatment.

Relapse. The return of a disease after a period of improvement.

Second-Line Therapy. Treatment that is given when the first treatment does not work or stops working.

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

Splenomegaly. An enlarged spleen.

Staging. The use of exams and tests to determine if and how far a cancer has spread throughout the body. Staging provides important information for treatment planning.

Stem Cell Transplantation. See Allogeneic Stem Cell Transplantation and Autologous Stem Cell Transplantation.

Systemic Therapy. Treatment with drugs that travel through the bloodstream to reach cells all over the body.

Thrombocytopenia. A condition in which the number of platelets in the blood is below normal.

Upper Endoscopy. A procedure using an endoscope to examine the upper digestive system. An endoscope is a thin, tube-like instrument with a light and a lens for viewing. In an upper endoscopy, the doctor guides the endoscope through the mouth and down into the esophagus and stomach.

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