

# Understanding Lymphoma and Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL)



## Part 2 — Non-Hodgkin Lymphoma

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### Chapter 10: What is Non-Hodgkin Lymphoma

#### What Is Non-Hodgkin Lymphoma?

Non-Hodgkin lymphoma (NHL) is not a single disease but rather a large group of closely related cancers that come from abnormal (cancerous) lymphocytes. In the United States, NHL (including chronic lymphocytic leukemia [CLL] and small lymphocytic lymphoma [SLL]) is the seventh most common type of cancer.

The World Health Organization (WHO) classifies more than 80 types of NHL, and ongoing research continues to identify new types. While these various types share many common features (characteristics), certain characteristics set them apart from each other, including:

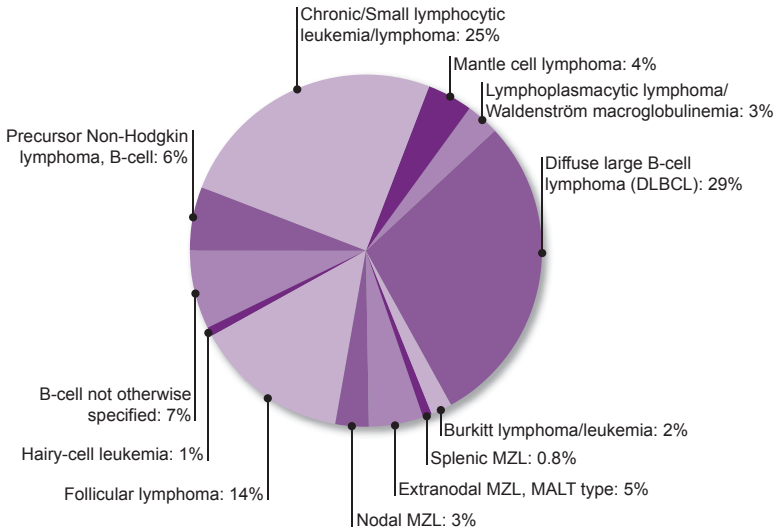
- How do cells appear when viewed under a microscope and what proteins appear on the surface of the cancer cells.
- How and where they grow in the body.
- How their growth and spread affects patients.
- How the disease should be treated.
- Likely outcome of treatment (curable vs not curable, but treatable).
- Genetic mutations (permanent change in the DNA [deoxyribonucleic acid]; the molecule that carries genetic information inside the cells) in the cells that make them become cancerous.

NHL is divided into the following two major groups (as well as some subgroups that are not discussed here):

- B-cell lymphomas — These lymphomas develop from abnormal B lymphocytes and are the most common, comprising about 85 percent of NHL in the United States.
- T/NK-cell lymphomas — These lymphomas develop from abnormal T lymphocytes or NK cells. They are less common and constitute up to 15 percent of patients with an NHL diagnosis.

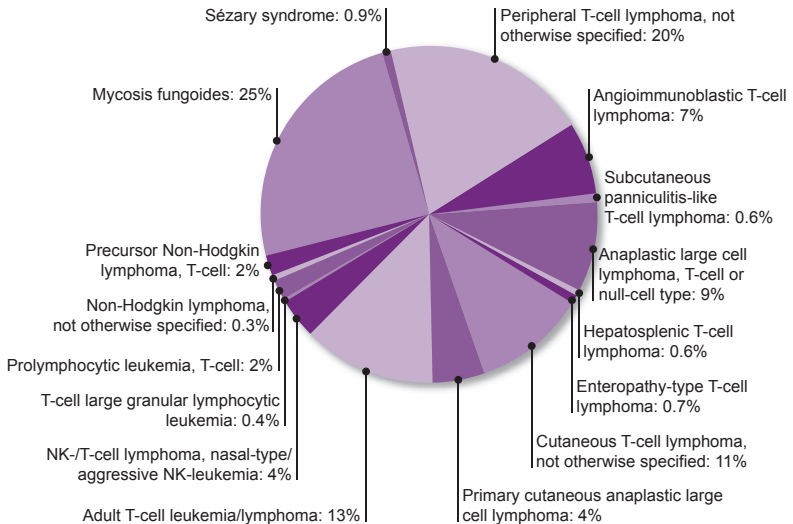
The following charts show how common or uncommon B- and T-cell NHLs are.

## RELATIVE FREQUENCIES OF B-CELL LYMPHOMAS IN THE UNITED STATES



Percentages are based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, 2008-2017. Some very rare types are not shown in the graph.

## RELATIVE FREQUENCIES OF T-CELL LYMPHOMAS IN THE UNITED STATES



Percentages are based on the National Cancer Institute's SEER data, 2008-2017. Some very rare types are not shown in the graph.

Another way to group NHL types is by how quickly they grow:

- *Indolent* (also called low-grade) lymphomas usually grow slowly and initially exhibit few symptoms. Indolent lymphomas are usually highly treatable. Patients can live a long time with these types of lymphomas because they tend to respond well to treatment and can remain in *remission* (disappearance of signs and symptoms) for many years or even decades. However, they are usually considered incurable because they can come back over time after the initial treatment. Some indolent lymphomas may transform (change) into aggressive lymphomas.
- *Aggressive* lymphomas grow and spread more quickly than indolent lymphomas. However, aggressive lymphomas can often be cured by treatments that kill rapidly dividing tumor cells.

The main types of indolent and aggressive NHLs are described in Table 10.1.

Pathologists (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) can tell the difference among the many different types of NHL by examining tissue, blood, and/or bone marrow (the spongy tissue inside the bones) samples under a microscope and by carrying out various laboratory tests. This information is critically important in deciding how to treat the disease in each patient.

**Table 10.1. Main Types of Indolent and Aggressive NHLs (Listed Alphabetically)**

Indolent NHLs	Aggressive NHLs
<ul style="list-style-type: none"> <li>■ Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).</li> <li>■ Follicular lymphoma (FL).</li> <li>■ Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM).</li> <li>■ Marginal zone lymphoma (MZL).</li> <li>■ Mycosis fungoides (MF) (subtype of cutaneous T-cell lymphoma).</li> </ul>	<ul style="list-style-type: none"> <li>■ Anaplastic large cell lymphoma (ALCL).</li> <li>■ Angioimmunoblastic T-cell lymphoma (AITL).</li> <li>■ Burkitt/Burkitt-like lymphomas.</li> <li>■ Diffuse large B-cell lymphoma (DLBCL)</li> <li>■ Lymphoblastic leukemia/lymphoma.</li> <li>■ Mantle cell lymphoma (MCL) (can also present as indolent).</li> <li>■ Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS).</li> <li>■ Primary mediastinal large B-cell lymphoma (PMBL) (subtype of DLBCL).</li> <li>■ Sézary syndrome (advanced subtype of cutaneous T-cell lymphoma).</li> <li>■ High-grade B-Cell Lymphoma (HGBCL).</li> </ul>

NHL, non-Hodgkin lymphoma.

While NHL subtypes are separated into two categories (indolent or aggressive), in some cases an indolent lymphoma may become aggressive. This is called *transformed lymphoma* and occurs when an indolent lymphoma turns into a more aggressive one—for example, when FL transforms into DLBCL. In this case, slow-growing cells (FL cells) might be mixed with a few faster-growing cells (DLBCL cells). If the number of fast-growing cells increases, the lymphoma can begin to behave more like an aggressive type (grows faster). For more information about transformed lymphomas please see *Transformed Lymphoma* Fact Sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

## Indolent B-Cell Lymphomas

### *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are types of NHL involving small lymphocytes that can be primarily in the bone marrow and blood (leukemia) or in the lymph nodes (lymphoma). While these used to be considered two separate diseases, recent research has shown that CLL and SLL are essentially the same disease. If the

malignant lymphocytes are found mainly in the lymph nodes, the disease is called SLL. If more than 5,000 malignant lymphocytes per microliter of blood are found in the bloodstream, then the disease is called CLL. Because they are essentially the same disease presenting in different parts of the body, the two terms are grouped together as CLL/SLL. The most common signs and symptoms of CLL/SLL are swollen lymph nodes, fatigue, shortness of breath, anemia, bruising easily, and frequent infections. However, many patients may not experience any signs or symptoms, so CLL/SLL is often discovered during routine blood tests and/or a physical examination. Half of CLL/SLL cases occur in people over the age of 68. Over time, CLL may occasionally progress to a more aggressive type of lymphoma, typically diffuse large B-cell lymphoma (DLBCL); this is called a Richter transformation (transformed lymphoma).

For a more detailed description of CLL/SLL, see Part 4 of this guide. Additional information about CLL is also available by viewing or reading our *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma* or the *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Follicular Lymphoma*

Follicular lymphoma (FL) is the second most common type of NHL diagnosed each year in the United States. Although it can affect people at any age, the average age at diagnosis is 60. FL usually appears in lymph nodes throughout the body, causing them to swell. Often one of the first signs is painless swelling in the neck, underarms, or groin caused by these enlarged lymph nodes. FL sometimes transforms into a more aggressive form of disease, like DLBCL or highgrade B-cell lymphoma (HGBCL).

For more information on FL, please visit LRF's website at [lymphoma.org/FL](http://lymphoma.org/FL), or view the *Follicular Lymphoma* and *Follicular Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia*

Lymphoplasmacytic lymphoma is an uncommon B-cell lymphoma, with about 1,000 to 1,500 people newly diagnosed in the United States each year. The term Waldenström macroglobulinemia (WM) is also used to describe this type of lymphoma specifically characterized by abnormally

high levels of a protein called macroglobulin or immunoglobulin M (IgM) in the blood, which causes the blood to thicken (hyperviscosity). The disease usually is more common in older adults and is mainly found in the bone marrow, although it can sometimes be found in the lymph nodes and spleen. Symptoms include fatigue, increased bleeding or bruising easily, headache, dizziness, vision changes, abdominal pain, and swollen lymph nodes.

For more information on WM, view the *Waldenström Macroglobulinemia* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Marginal Zone Lymphoma*

Marginal zone lymphoma (MZL) is a B-cell lymphoma that accounts for approximately 9 percent of all B-cell NHLs. The median age at diagnosis is 67 and it is more common in men. There are three categories of MZL based on location in the body, however, for many patients more than one of these areas are involved:

(1) Extranodal MZL (ENMZL; also called mucosa-associated lymphoid tissue [MALT]) occurs outside the lymphatic system (such as the skin or stomach) and is the most common form of MZL; (2) nodal MZL occurs within the lymph nodes; and (3) splenic MZL (SMZL) occurs mostly in the spleen, blood, and bone marrow.

Many people who develop ENMZL have a history of inflammation, infection, or autoimmune disorders. For example, chronic inflammation associated with *Helicobacter pylori* (*H. pylori*; a bacteria that can cause *gastritis* (inflammation in the stomach) and stomach ulcers (a break in the lining of the stomach)) may increase the risk of developing ENMZL of the stomach lining (also called gastric MALT).

Patients with SMZL may have an enlarged spleen. These lymphomas have been associated with hepatitis C virus (HCV) infection, and they may improve or even completely resolve after treatment for the HCV infection.

For more information on MZL, view the *Marginal Zone Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

## Indolent T-Cell Lymphomas

### *Cutaneous T-Cell Lymphoma*

Cutaneous T-cell lymphoma (CTCL) is a general term for a group of T-cell lymphomas that originate in the skin. The disease affects men more often than women and usually occurs in patients over 50 years old. Most forms of CTCL begin as indolent diseases and involve only skin symptoms, although some more aggressive forms of CTCL can involve the blood, lymph nodes, and other organs.

Mycosis fungoides is the most common type of CTCL. This type of lymphoma is indolent and usually progresses very slowly. Patients with mycosis fungoides may have various types of lesions, including:

- Patches, which are usually flat, possibly scaly, and look like a rash.
- Plaques, which are thicker, raised, usually itchy lesions that are often mistaken for eczema, psoriasis, or dermatitis.
- Tumors, which are raised bumps that may ulcerate (become an open sore).

Sézary syndrome, which is an aggressive form of CTCL in which there are abnormal T-cells circulating in the blood, is discussed on page 91.

Primary cutaneous anaplastic large cell lymphoma (ALCL) limited to the skin is an uncommon type of CTCL and tends to be very indolent. The characteristic features of primary cutaneous ALCL include the appearance of single or multiple raised, red skin lesions that do not go away, have a tendency to ulcerate, and may itch. These ALCL lesions are tumors, and they can appear on the skin on any part of the body, often grow very slowly, and may be present for a long time before being diagnosed. Only about 5 to 10 percent of the time does primary cutaneous ALCL spread beyond the skin to lymph nodes or organs. If this occurs, it is usually treated like systemic (throughout the body) ALCL.

For more information on CTCL, view the *Cutaneous Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).



## Aggressive B-Cell Lymphomas

### *Burkitt Lymphoma*

Burkitt lymphoma is a rare, highly aggressive B-cell NHL. There are three main types:

- Endemic Burkitt lymphoma is the most common type and is primarily found in Africa, where it is the most common childhood cancer. This type is rare outside of Africa. This type of lymphoma often starts as a tumor of the jaw or other facial bones.
- Sporadic Burkitt lymphoma occurs throughout the world. The sporadic form, seen in the United States, accounts for about one third of all childhood NHL. This type of lymphoma usually starts in the belly, causing a mass to develop in the abdomen.
- Immunodeficiency-related Burkitt lymphoma can occur in patients who have human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); in those who have inherited immune deficiencies; and in those who take immunosuppressive medications to prevent rejection after organ transplant.

The Epstein-Barr virus (EBV) has been linked to the development of endemic and some cases of sporadic Burkitt lymphoma. However, not all with a history of EBV will develop Burkitt lymphoma.

Symptoms include weight loss, loss of appetite, fatigue, fever, and night sweats. Burkitt lymphoma is potentially curable when treated aggressively.

For more information on Burkitt lymphoma, view the *Burkitt Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Diffuse Large B-Cell Lymphoma*

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in the United States, accounting for about 30 percent of patients with NHL. The frequency of DLBCL generally increases with age, and more than half of patients are over the age of 60 at diagnosis. The first sign of DLBCL is usually rapid swelling in the neck, underarms, or groin or abdominal pain and swelling caused by enlarged lymph nodes. Other

symptoms include night sweats, chills, unexplained fevers, and weight loss, a cluster of symptoms called B symptoms.

DLBCL can develop in the lymph nodes or outside the lymphatic system, and often spreads throughout the body. Each variant of DLBCL may need a different treatment. Despite being aggressive, some patients have no signs of the disease after initial treatment, and many are cured.

For more information on DLBCL, view the *Diffuse Large B-Cell Lymphoma* and the *Diffuse Large B-Cell Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Primary Mediastinal B-Cell Lymphoma*

Primary mediastinal B-cell lymphoma (PMBCL) is a form of DLBCL that appears in the thymus gland and is usually limited to the mediastinum (a compartment in the central part of the chest that includes the heart, thymus, esophagus, and trachea). Most patients are 30 to 40 years of age at diagnosis, and the disease is more common in women. Teenagers may also develop PMBCL. Symptoms include cough, chest pain, fever, weight loss, night sweats, shortness of breath, and superior vena cava syndrome, which is a swelling of the face and arms caused by compression of the major vein that delivers blood to the heart. Patients with PMBCL usually have a better prognosis than those with other subtypes of DLBCL, and most patients can be cured.

### *High-Grade B-Cell Lymphoma*

High-grade B-cell lymphoma is a type of aggressive B-cell NHL that has two subtypes. The first is DLBCL/HGBCL with *MYC* and *BCL2* rearrangements, which occur when parts of *genes* (small portions of DNA that determine a person's traits) switch places within chromosomes. Other HGBCLs that do not have *MYC* and *BCL2* rearrangements are called HGBCL-NOS (not otherwise specified). While its appearance under the microscope usually resembles DLBCL, HGBCL is a very aggressive type of lymphoma and requires intensive treatment. HGBCL can arise from indolent lymphomas, in a process called transformation. Molecular tests (such as fluorescence in situ hybridization [FISH]) that allow doctors to check for abnormalities under a microscope are used to confirm a diagnosis of HGBCL.

For more information on HGBCL, view the *High-Grade B-Cell Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Mantle Cell Lymphoma*

Mantle cell lymphoma (MCL) accounts for 3 to 5 percent of all patients with NHLs. This type of lymphoma more frequently happens in men, and the median age at diagnosis is 60. At the time of diagnosis, MCL is often present in several lymph nodes, in one or more organs (often the intestines), and in the bone marrow. In a small number of patients, MCL may follow an indolent course that does not require therapy initially. Most cases, however, are more aggressive and require treatment as an aggressive lymphoma.

For more information on MCL, please view the *Mantle Cell Lymphoma* and *Mantle Cell Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

## **Aggressive T-Cell Lymphomas**

### *Peripheral T-Cell Lymphoma*

Peripheral T-cell lymphoma (PTCL) is a group of T-cell lymphomas that account for over 50 percent of all cases of T-cell NHL in the United States. The most common subtypes include PTCL, not otherwise specified (PTCL- NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). PTCLs typically develop in tissues outside of the bone marrow (which is why they are called peripheral) such as the lymph nodes, spleen, gastrointestinal tract, and skin. Most are aggressive lymphomas. Some of these subtypes are described in more detail on the following pages.

For more information on all the subtypes of PTCL, visit LRF's website at [lymphoma.org/PTCL](http://lymphoma.org/PTCL), and view the *Peripheral T-Cell Lymphoma* fact sheet at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Anaplastic Large Cell Lymphoma*

Anaplastic large cell lymphoma (ALCL) is more common in younger people (children included), accounting for 2 percent of all NHLs and about 10-20 percent of all T-cell lymphomas. Initial symptoms of ALCL can

include fever, backache, painless swelling of lymph nodes, loss of appetite, and fatigue. ALCL occurs either systemically (throughout the body) or cutaneously (on the surface of the skin). Primary cutaneous ALCL is an indolent form of ALCL and is discussed on page 90. A rare type called breast implant associated ALCL can develop in women who have had silicone implants.

Patients with systemic ALCL are divided into two groups, depending on whether their cells contain an abnormal form of a protein called anaplastic lymphoma kinase (ALK). Systemic ALCL that is ALK positive, is more common in younger people, responds well to chemotherapy and may be curable. While ALK negative disease may initially respond to chemotherapy, it tends to relapse (disease returns after treatment) and often needs additional therapy such as stem cell transplantation (for more information, see the *Cellular Therapy* guide on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications)).

For more information on ALCL, visit LRF's website at [lymphoma.org/ALCL](http://lymphoma.org/ALCL), and view the *Anaplastic Large Cell Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Angioimmunoblastic T-Cell Lymphoma*

Angioimmunoblastic T-cell lymphoma (AITL) affects approximately seven percent of all patients with T-cell NHL in the United States. Most patients are middle-aged to elderly and are diagnosed at a median age of 65 years old with advanced-stage disease. Symptoms may include high fever, night sweats, skin rash, and some types of autoimmune disorders, such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). As a result of these autoimmune disorders, the body's immune system destroys its own red blood cells (in the case of AIHA) or platelets (in the case of ITP). Initially, AITL may be treated with steroids to relieve symptoms such as joint inflammation, joint pain, and skin rash.

For more information on AITL, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Peripheral T-Cell Lymphoma, Not Otherwise Specified*

Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) refers to a group of diseases that do not fit into any of the other PTCL subtypes. It is the second most common T-cell lymphoma, accounting for about 20 percent of all T-cell NHLs. It is also the most common subtype of PTCL. PTCL-NOS usually occurs in adults in their 60s. Although most patients with PTCL-NOS are diagnosed when their disease is still limited to the lymph nodes, sites outside the lymph nodes such as the liver, bone marrow, gastrointestinal tract, and skin may also be involved. This group of PTCLs is very aggressive, requires immediate treatment, and tends to relapse.

### *Sézary Syndrome*

Sézary syndrome is a rare form of CTCL that affects both the skin and the blood. Most cases occur in adults older than 60. The most common symptoms are swollen lymph nodes and a red, very itchy rash that covers large portions of the body. Other common signs and symptoms of Sézary syndrome include hair loss, thickened skin on the palms of the hands and soles of the feet, and abnormalities of the fingernails and toenails. Abnormal T-cells, called Sézary cells, can be found in both the skin and the blood.

For more information about Sézary syndrome, please view the *Cutaneous T-Cell Lymphoma* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

### *Lymphoblastic Lymphoma*

Lymphoblastic lymphoma is relatively rare and can originate from both B-cells and T-cells, but about 90 percent of all cases involve T-cells. T-cell lymphoblastic lymphoma cases represent about 30 percent of pediatric NHLs and tend to occur in males more often than females.

Lymphoblastic lymphoma is typically aggressive, and often occurs as a large mass in the chest. Experts suggest that lymphoblastic lymphoma and acute lymphoblastic leukemia (ALL) may come from the same type of cell and are different manifestations of the same disease. For this reason, lymphoblastic lymphoma is treated basically the same way as ALL. Symptoms include swollen lymph nodes, fever, night sweats,

unexplained weight loss, fatigue, and bruising easily. The complete remission (disappearance of signs and symptoms) rate after combination chemotherapy is usually very high.

### What Are the Signs and Symptoms of NHL?

Some patients with NHL do not have any obvious signs or symptoms of the disease. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 10.2, NHL may cause different signs and symptoms depending on the type of NHL and where it is located in the body. Keep in mind that many of these signs and symptoms are not specific to NHL and can be caused by other conditions.

**Table 10.2. Signs and Symptoms Commonly Found in Patients With NHL**

Sign or Symptom	Possible Reason
<ul style="list-style-type: none"><li>■ Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin. Lumps are usually not painful.</li></ul>	<ul style="list-style-type: none"><li>■ Lymph nodes, or “glands swell up due to lymphoma, They can also swell in response to an infection or injury.</li></ul>
<ul style="list-style-type: none"><li>■ Swollen, tender abdomen (“belly” or “stomach”)</li></ul>	<ul style="list-style-type: none"><li>■ Enlarged lymph nodes in the abdomen.</li><li>■ Accumulation (increase) of fluid in the abdomen.</li><li>■ Enlarged liver or spleen.</li></ul>

Sign or Symptom	Possible Reason
<ul style="list-style-type: none"> <li>■ Abdominal pain, nausea, vomiting, decreased appetite, or feeling full more easily</li> </ul>	<ul style="list-style-type: none"> <li>■ Enlarged lymph nodes or an enlarged spleen pressing on nearby normal structures (for example, the diaphragm [a muscle below the lungs that is essential for the breathing process], nerves, or spine).</li> <li>■ Enlarged spleen pressing on the stomach, which can make a person feel full after eating only a small amount of food.</li> <li>■ Pain in the spleen (an organ of the immune system that stores white blood cells and helps fight infections).</li> <li>■ Lymphoma in the intestine (or causing swelling near the intestine) possibly blocking bowel movements.</li> <li>■ Lymphoma of the stomach or abdominal lymph nodes.</li> </ul>
<ul style="list-style-type: none"> <li>■ Coughing, trouble breathing, or chest pain or pressure</li> </ul>	<ul style="list-style-type: none"> <li>■ Lymphoma in the chest, which may press on the windpipe or <i>bronchi</i> (tubes leading to the lungs).</li> <li>■ Fluid around the lungs (<i>pleural effusion</i>).</li> </ul>
<ul style="list-style-type: none"> <li>■ Headache, trouble thinking, weakness in extremities (legs or arms), personality changes, double or blurred vision, facial numbness, trouble speaking, or seizures (sudden, uncontrolled burst of electrical activity in the brain)</li> </ul>	<ul style="list-style-type: none"> <li>■ Lymphoma of the brain or spinal cord, or lymphoma originating in other parts of the body that has spread to or near the brain or spinal cord.</li> </ul>
<ul style="list-style-type: none"> <li>■ Rash or itchy red or purple lumps or nodules under the skin</li> </ul>	<ul style="list-style-type: none"> <li>■ Lymphoma of the skin.</li> </ul>
<ul style="list-style-type: none"> <li>■ “B symptoms,” including fever for no known reason, unexplained drastic weight loss, or drenching night sweats that soak clothing and sheets</li> </ul>	<ul style="list-style-type: none"> <li>■ Increased levels of inflammatory chemicals in the blood (molecules that initiate immune and inflammation responses called cytokines) that are released by lymphoma cells or by the immune system reacting to the lymphoma cells.</li> </ul>
<ul style="list-style-type: none"> <li>■ Severe or frequent infections</li> </ul>	<ul style="list-style-type: none"> <li>■ Reduced ability to fight infection because of decreased numbers of certain types of white blood cells or low levels of gamma globulins (antibodies).</li> </ul>

## Why Do Some People Develop NHL?

The reasons why certain people develop NHL are not understood. However, scientists have found that people with certain characteristics called “risk factors” have a slightly higher chance of developing NHL compared with people who do not have these risk factors. Having one or more NHL risk factors does not mean a person will definitely develop the disease. In fact, most people with the known risk factors never develop NHL, and many people diagnosed with NHL do not have any of these risk factors. However, there does seem to be a link between the risk factors described below and the development of NHL.

Known risk factors for NHL include:

- A weakened immune system caused by an inherited (passed from parent to child) immune disorder (inability to produce an adequate immune response); for example, hypogammaglobulinemia (Wiskott-Aldrich syndrome) or infection with human immunodeficiency virus (HIV; the virus that causes AIDS).
- An autoimmune disease (the immune system attacks the body’s own organs, tissues or cells; for example, Crohn’s disease, rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s syndrome, or psoriasis).
- Treatment for autoimmune diseases, especially with methotrexate and tumor necrosis factor (TNF)-inhibitor therapy as immunosuppression therapies.
- Treatment with certain drugs used after solid organ (such as the liver or kidney) transplantation.
- Infections with certain viruses (for example, human T-cell lymphotropic virus type 1 [HTLV-1], EBV or HCV).
- Infections with certain bacteria such as with *Helicobacter pylori*.
- Family history of lymphoma (first degree relative, like parent, child or sibling).
- Older age (like most cancers, NHL is much more common in adults older than 60, although NHL also occurs in children and younger adults).
- Male sex (for unknown reasons, NHL is slightly more common in men than in women).



- Exposure to certain chemicals (like benzene), herbicides (for example, Agent Orange) and pesticides, and some chemotherapy drugs used to treat other cancers or autoimmune diseases.
- Treatment with radiation therapy for other cancers, including NHL.

NHL cannot be caused by injury and cannot be caught by someone who has the disease. While parents, children, and siblings of patients with NHL have a slightly increased risk of developing this disease compared with the general population, there are not clearly identifiable genetic or hereditary factors that can predict this slightly increased risk. Therefore, routine screening for NHL among the immediate family members of patients with NHL is not recommended.

### What Are Prognostic Factors?

Favorable or good prognostic factors (characteristics that predict how well the patient will do) tend to be associated with better outcomes (like survival or good response to treatment), while unfavorable or poor prognostic factors tend to be associated with worse outcomes. Various prognostic indicators have been developed for different forms of NHL.

### What Is the International Prognostic Index?

The International Prognostic Index (IPI) was first developed for aggressive lymphomas such as DLBCL. The IPI is based on five factors represented by the acronym APLES: age, performance status (PS; measurement of level of body function and capacity for self-care), lactate dehydrogenase (LDH; protein that rises in the blood in case of fast-growing NHL) level, number of extranodal sites (lymphoma cells located outside of the lymph nodes), and stage (as shown in Table 10.3 below). The IPI score assigns 1 point for the presence of each negative prognosis factor, which adds up to make a final score (from 0 to 5). Risk groups are based on the final score and are categorized as low risk (0/1), low-intermediate risk (2), high-intermediate risk (3) and high risk (4/5). Updated versions of this score include the revised IPI (R-IPI) and the National Comprehensive Cancer Network IPI (NCCN-IPI). Other prognostic indicators have been developed for specific NHL subtypes. The Follicular Lymphoma International Prognostic Index (FLIPI) is based on the original IPI but excludes PS and adds hemoglobin

(protein present in red blood cells that transports oxygen) level as a risk factor. Other indicators have been developed for MCL and MZL.

**Table 10.3. International Prognostic Index for Diffuse Large B-cell Lymphoma and NHL**

Factor	Better Prognostic Factors	Worse Prognostic Factors
Age	60 years or younger	Older than 60 years
Performance Status (PS)	ECOG score ≤ 1 (Patient able to function normally)	ECOG score ≥ 2 (Patient needs help with daily activities)
Lactate Dehydrogenase (LDH) Level	Normal	Above upper limit of normal
Extranodal Sites	Lymphoma is only in the lymph nodes or in only one area outside of the lymph nodes	Lymphoma is in two or more organs outside of the lymph nodes
Stage	I or II	III or IV

**What Is Relapsed or Refractory NHL?**

In some patients who receive treatment, NHL can relapse (come back after treatment) or become refractory (disease does not respond to treatment). There are many treatment options for patients with relapsed or refractory NHL. Exactly what type of treatment is best for individual patients with relapsed or refractory NHL depends on such factors as the subtype of NHL, the patient’s age and overall health, the extent and location of disease, the type of previous therapies received, and the length of response to previous therapies.

Many of the therapies for newly diagnosed NHL can be effective in patients with relapsed or refractory NHL. Many treatment centers will also consider using autologous or allogeneic stem cell transplantation for patients with relapsed or refractory NHL, especially aggressive NHL, depending on the patient’s age, overall health, and other characteristics (see page 59 in Chapter 7 in Part 1 of this guide for further information on stem cell transplantation).

Patients who do not go into complete remission (CR, no signs or symptoms of disease) following treatment or who do not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions when newly diagnosed, and some choose to do so if their disease relapses or is considered refractory.

While clinical trials can be a good option for patients at all stages of disease, they are often especially useful for patients with relapsed or refractory NHL, because many of the novel therapeutic agents (new drugs) most recently approved by the U.S. Food and Drug Administration (FDA; organization responsible for the approval of drugs and making sure that drugs are safe and effective) and those being investigated in clinical trials are used specifically for these patients. Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapter 8 in Part 1 further describes clinical trials and some of the options currently under investigation.

## Part 2 — Non-Hodgkin Lymphoma

### Chapter 11: Treatments for Non-Hodgkin Lymphoma

This chapter reviews the most common therapies currently used in the treatment of NHL. Keep in mind that new therapies may have been approved by the FDA since this guide was published. Read Chapter 12 to learn more about emerging treatments under investigation.

There are important differences between different types of NHL, and a treatment that works for one type of NHL may not necessarily be the best treatment choice for another type. There are also small but important differences in the lymphoma cells found in different patients diagnosed with the same type of NHL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

#### What Types of Treatments Are Used in Patients With NHL?

There are four general types of approaches and treatments for patients with NHL:

- *Active surveillance*, also known as *watchful waiting* (observation with no treatment given), in which the patient is closely monitored to see if/when treatment should be started.
- Drug therapy, including one or more of the following types of drugs:
  - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply). Most patients with lymphoma receive combination chemotherapy (two or more drugs) instead of a single drug (monotherapy). The most common chemotherapy regimens are detailed in Table 11.1.
  - Immunotherapy, which helps the body's immune system attack lymphoma cells (monoclonal antibodies, antibody-drug conjugates [antibody combined with treatment drug], bispecific antibodies, immune checkpoint inhibitors, immunomodulatory drugs and radioimmunotherapy).

- Targeted therapies, which affect special characteristics or internal workings of lymphoma cells. These drugs may kill, slow down, stop the growth of cancer cells or help the immune system fight against cancer cells.
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells.
- Cellular therapy (such as stem cell transplantation and chimeric antigen receptor [CAR] T-cell therapy).

Each of these types of therapies is described in detail in this chapter. Treatment side effects are detailed in Part 5 of this guide (pages 180-207).

## Active Surveillance

With the active surveillance approach (watchful waiting), patients' health and disease are monitored, but they do not receive any anti-lymphoma treatments. For more information about active surveillance see Chapter 7 in Part 1 of this guide.

This approach is used in patients with indolent, non-aggressive NHLs (i.e., FL, MZL, or SLL) who have no significant symptoms and would not yet benefit from treatment. Patients with non-aggressive disease continue to remain untreated if they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or of significant concern. This approach may be used after the initial diagnosis of NHL or after relapse, depending on the situation, but once a patient's disease demonstrates a need for therapy, a treatment course would begin. Active surveillance may also be used for advanced NHL without indications for treatment. As there are a number of reasons that your team may recommend initiation of treatment, it is important to report any new or ongoing symptoms or other medical concerns during follow-up visits with your oncology team.

Although active surveillance or watchful waiting may not be what a patient is expecting after the diagnosis of a lymphoma, many patients can safely delay initiation of treatment for long periods of time. As a result, it is important to discuss with your physicians what concerns you may have related to active surveillance so that these can be addressed.

Active surveillance most often is not a treatment option for patients with aggressive NHL or Hodgkin lymphoma (HL). Usually, treatment for these patients should start as soon as possible after diagnosis.

## Chemotherapy

For the treatment of some B-cell lymphomas, a standard combination chemotherapy regimen is known as CHOP, which includes the drugs cyclophosphamide (Cytosan, Neosar), doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS), vincristine (Oncovin and others), and prednisone (Deltasone and others). CHOP has been administered for more than 25 years in patients with lymphoma. In some cases, your team may recommend a modified version of CHOP based on your age, other medical conditions, or factors associated with your specific lymphoma case.

In the vast majority of cases of B-cell NHL, doctors add a fifth agent, an anti-CD20 monoclonal antibody (an engineered molecule that is not considered a chemotherapy) called rituximab (Rituxan), to this combination to create R-CHOP. Many of the chemotherapy treatment regimens in Table 11.1 are combined with rituximab (Rituxan) to treat B-cell NHL. In these cases, the treatment regimens have an “R” added to their name (not shown in the table). Rituximab is discussed in greater detail on page 106.

Sometimes other chemotherapy regimens and anti-CD20 antibodies (such as obinutuzumab [Gazyva]) are used. Some of these alternative regimens are shown in Table 11.1.

For T-cell lymphomas, CHOP is the most frequently used frontline (initial) treatment, but CHOEP or CHP, with the antibody-drug conjugate (a monoclonal antibody attached to a chemotherapy drug) brentuximab vedotin (Adcetris), may also be used.

Table 11.1 lists the common chemotherapy drugs and regimens used for NHL. This list is subject to change as the FDA approves new lymphoma treatments.

**Table 11.1. Common Chemotherapy Regimens For NHL**

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
B	■ Bendamustine (Treanda, Bendeka)	IV infusion
BV	■ Brentuximab vedotin (Adcetris)	IV infusion
C	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion or oral tablets
CDOP	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion
	■ Liposomal doxorubicin (Doxil)	IV infusion
	■ Vincristine (Oncovin and others)	IV infusion
	■ Prednisone (Deltasone and others)	Oral tablets
CEOP	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion
	■ Vincristine (Oncovin and others)	IV infusion
	■ Prednisone (Deltasone and others)	Oral tablets
	■ Epirubicin (Ellence)	IV infusion
CEPP	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion
	■ Etoposide (VePesid, Toposar, Etopophos)	IV infusion or oral capsules
	■ Prednisone (Deltasone and others)	Oral tablets
	■ Procarbazine (Mutalane)	Oral capsules
CHOP	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion
	■ Doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS)	IV infusion
	■ Vincristine (Oncovin and others)	IV infusion
	■ Prednisone (Deltasone and others)	Oral tablets
CHOEP	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion
	■ Doxorubicin (Adriamycin)	IV infusion
	■ Vincristine (Oncovin and others)	IV infusion
	■ Etoposide (VePesid, Toposar, Etopophos)	IV infusion or oral capsules
	■ Prednisone (Deltasone and others)	Oral tablets
CHP	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion
	■ Doxorubicin (Adriamycin)	IV infusion
	■ Prednisone (Deltasone and others)	Oral tablets

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
CODOXM-IVAC	<ul style="list-style-type: none"> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> <li>■ Vincristine (Oncovin and others)</li> <li>■ Liposomal doxorubicin (Doxil)</li> <li>■ Cytarabine/high-dose Ara-C (Cytosar-U, Tarabine PFS)</li> <li>■ Methotrexate (Mexate and others)</li> <li>■ Ifosfamide (Ifex)</li> <li>■ Etoposide (VePesid, Toposar, Etopophos)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral capsules</p>
CVP (COP)	<ul style="list-style-type: none"> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> <li>■ Vincristine (Oncovin and others)</li> <li>■ Prednisone (Deltasone and others)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets</p>
DHAP	<ul style="list-style-type: none"> <li>■ Dexamethasone (Decadron and others)</li> <li>■ Cytarabine/high-dose Ara-C</li> <li>■ Cisplatin (Platinol, Platinol-AQ)</li> </ul>	<p>Oral tablets or IV infusion</p> <p>IV infusion</p> <p>IV infusion</p>
DHAX	<ul style="list-style-type: none"> <li>■ Dexamethasone (Decadron and others)</li> <li>■ Cytarabine (Cytosar)</li> <li>■ Oxaliplatin (Eloxatin)</li> </ul>	<p>Oral tablets or IV infusion</p> <p>IV infusion</p> <p>IV infusion</p>
DICE	<ul style="list-style-type: none"> <li>■ Dexamethasone (Decadron and others)</li> <li>■ Ifosfamide (Ifex)</li> <li>■ Cisplatin (Platinol)</li> <li>■ Etoposide/VP16 (VePesid, Toposar, Etopophos)</li> </ul>	<p>Oral tablets or IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral capsules</p>
EPOCH	<ul style="list-style-type: none"> <li>■ Etoposide/VP16 (VePesid, Toposar, Etopophos)</li> <li>■ Prednisone (Deltasone and others)</li> <li>■ Vincristine (Oncovin and others)</li> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> <li>■ Doxorubicin/hydroxy daunorubicin (Adriamycin/Adriamycin PFS)</li> </ul>	<p>IV infusion or oral capsules</p> <p>Oral tablets</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p>



Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
ESHAP	<ul style="list-style-type: none"> <li>■ Etoposide/VP16 (VePesid, Toposar, Etopophos)</li> <li>■ Methylprednisolone (Medrol and others)</li> <li>■ Cytarabine/high-dose Ara-C (Platinol, Platinol-AQ)</li> <li>■ Cisplatin (Platinol)</li> </ul>	<p>IV infusion or oral capsules</p> <p>Oral tablets</p> <p>IV infusion</p> <p>IV infusion</p>
F	<ul style="list-style-type: none"> <li>■ Fludarabine (Fludara)</li> </ul>	IV infusion
FC	<ul style="list-style-type: none"> <li>■ Fludarabine (Fludara)</li> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p>
FND	<ul style="list-style-type: none"> <li>■ Fludarabine (Fludara)</li> <li>■ Mitoxantrone (Novantrone)</li> <li>■ Dexamethasone (Decadron and others)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets or IV Infusion</p>
G	<ul style="list-style-type: none"> <li>■ Gemcitabine (Gemzar)</li> </ul>	IV infusion
GCVF	<ul style="list-style-type: none"> <li>■ Gemcitabine (Gemzar)</li> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> <li>■ Vincristine (Oncovin and others)</li> <li>■ Prednisolone (Orapred ODT)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>Oral tablet</p>
GDP	<ul style="list-style-type: none"> <li>■ Gemcitabine (Gemzar)</li> <li>■ Dexamethasone (Decadron and others)</li> <li>■ Cisplatin (Platinol)</li> </ul>	<p>IV infusion</p> <p>Oral tablets or IV infusion</p> <p>IV infusion</p>
GemOX	<ul style="list-style-type: none"> <li>■ Gemcitabine (Gemzar)</li> <li>■ Oxaliplatin (Eloxatin)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p>
HDMP	<ul style="list-style-type: none"> <li>■ High-dose methylprednisolone (Solu-Medrol)</li> </ul>	IV infusion or IM injection
HD MTX and HD Ara-C	<ul style="list-style-type: none"> <li>■ High-dose methotrexate (Mexate and others)</li> <li>■ Cytarabine/high-dose Ara-C</li> </ul>	<p>IV infusion, IM injection, or Oral tablets</p> <p>IV infusion</p>

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
HyperCVAD/ MTX-Ara-C	<ul style="list-style-type: none"> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> <li>■ Vincristine (Oncovin and others)</li> <li>■ Doxorubicin/hydroxydaunorubicin (Adriamycin/Adriamycin PFS)</li> <li>■ Dexamethasone (Decadron and others)</li> <li>■ Methotrexate (Mexate and others)</li> <li>■ Cytarabine/high-dose Ara-C (Platinol, Platinol-AQ)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets or IV infusion</p> <p>IV infusion, IM injection, or oral tablets</p> <p>IV infusion</p>
ICE	<ul style="list-style-type: none"> <li>■ Ifosfamide (Ifex)</li> <li>■ Carboplatin (Paraplatin)</li> <li>■ Etoposide/VP16 (VePesid, Toposar, Etopophos)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral capsules</p>
O	<ul style="list-style-type: none"> <li>■ Obinutuzumab (Gazyvaro)</li> </ul>	IV infusion
P	<ul style="list-style-type: none"> <li>■ Pralatrexate (Folotyn)</li> </ul>	IV infusion
Pola-R-CHP	<ul style="list-style-type: none"> <li>■ Polatuzumab vedotin-piiq (Polivy)</li> <li>■ Rituximab (Rituxan)</li> <li>■ Cyclophosphamide (Cytoxan, Neosar)</li> <li>■ Doxorubicin (Doxil)</li> <li>■ Prednisone (Deltasone and others)</li> </ul>	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets</p>
R	<ul style="list-style-type: none"> <li>■ Rituximab (Rituxan, Rituxan Hycela)</li> </ul>	IV infusion or subcutaneous injection
SMILE	<ul style="list-style-type: none"> <li>■ Methotrexate (Mexate and others)</li> <li>■ Leucovorin/Levoleucovorin (Wellcovorin)</li> <li>■ Ifosfamide (Ifex)</li> <li>■ Mesna (Mesnex)</li> <li>■ Dexamethasone (Decadron and others)</li> <li>■ Etoposide/VP16 (VePesid, Toposar, Etopophos)</li> <li>■ Pegaspargase (Oncaspar)</li> </ul>	<p>IV infusion, IM injection, or oral tablets</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral tablets</p> <p>Oral tablets or IV infusion</p> <p>IV infusion or oral capsules</p> <p>IV infusion or IM injection</p>

IV, intravenous; IM, intramuscular

## What Other Types of Drugs Are Used to Treat Patients With NHL?

In addition to chemotherapy, there are many types of other drugs used to treat NHL. These can be divided into two main categories: immunotherapy and targeted therapies. Most of these drugs have been developed relatively recently, and ongoing studies are continually testing new drugs in these categories.

### Immunotherapy

Currently used FDA-approved immunotherapies for NHL can be subdivided into six types:

- The monoclonal antibodies rituximab (Rituxan), obinutuzumab (Gazyva), ofatumumab (Arzerra), tafasitamab-cxix (Monjuvi), and mogamulizumab-kpkc (Poteligeo).
- The antibody-drug conjugates (ADCs) brentuximab vedotin (Adcetris), polatuzumab vedotin-piiq (Polivy), and loncastuximab tesirine-lpyl (Zynlonta).
- The bispecific antibodies epcoritamab (Epkincy), mosunetuzumab (Lunsumio), and glofitamab-gxbm (Columvi).
- The immune checkpoint inhibitor pembrolizumab (Keytruda).
- The immunomodulatory drug (IMiD) lenalidomide (Revlimid).
- The radioimmunotherapy ibritumomab tiuxetan (Zevalin).

For detailed information about treatment see Chapter 7 in Part 1 of this guide, and the *Immunotherapy and Other Targeted Therapies* fact sheet on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications). Approved immunotherapies for NHL are described below.

### Monoclonal antibodies

Rituximab (Rituxan), obinutuzumab (Gazyva), and ofatumumab (Arzerra) are directed against different parts of CD20, an antigen (marker) that is almost universally present on the surface of B-cells.

Tafasitamab-cxix (Monjuvi) binds to the CD19 antigen on B lymphocytes to promote cell death. Some cancer cells have large amounts of PD-L1 protein, which helps them “hide” from immune cells, and the anti-PD1

immune checkpoint inhibitors like pembrolizumab (Keytruda) are used in these unique lymphoma subtypes. Mogamulizumab-kpkc (Poteligeo) is a monoclonal antibody that disrupts lymphocyte movements through the body.

*Rituximab (Rituxan), Rituximab and Hyaluronidase Human (Rituxan Hycela), Rituximab-abbs (Truxima), and Rituximab-pvvr (Ruxience)*

Rituximab (Rituxan) is the most commonly used antibody for B-cell NHL. In 1997, rituximab became the first monoclonal antibody approved by the FDA for the treatment of patients with lymphoma. As of 2022, rituximab is approved by the FDA for treatment of adult patients with NHL in the following settings:

- Previously untreated follicular CD20-positive B-cell NHL in combination with first-line chemotherapy, and in patients achieving a complete (no signs of lymphoma after treatment) or partial remission (tumor responded to treatment and shrunk to less than one-half of its original size), as single-agent maintenance therapy (ongoing treatment of patients whose disease has responded well to treatment).
- Non-progressing (including stable disease) low-grade CD20-positive B-cell NHL as a single agent after first-line chemotherapy (commonly R-CVP [rituximab, cyclophosphamide, vincristine, prednisone], R-CHOP [rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone] or BR [bendamustine and rituximab]).
- Relapsed or refractory low-grade or follicular CD20-positive B-cell NHL as a single agent.
- Previously untreated CD20-positive DLBCL in combination with CHOP or other anthracycline-based chemotherapy regimens.

Rituximab (Rituxan) is also approved for pediatric patients over 6 months with previously untreated, CD20-positive mature B-cell NHL, including DLBCL, BL or Burkitt-like lymphoma (high grade B-cell lymphoma, NOS), in combination with chemotherapy.

The original form of rituximab (Rituxan) is given as an IV infusion, and the schedule varies depending on the type of combination regimen used. When combined with chemotherapy, rituximab is usually given during the

first day of each chemotherapy cycle (regular treatment schedule that consists of treatment periods followed by a rest period).

A subcutaneous form (injection just below the skin) of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved by the FDA in 2017 for the treatment of adult patients with NHL in the following settings:

- Relapsed or refractory FL as a single agent.
- Previously untreated FL in combination with first line chemotherapy and in patients achieving a complete or partial remission, as single-agent maintenance therapy.
- Non-progressing (including stable disease) FL as a single agent after first line CVP chemotherapy.
- Previously untreated DLBCL in combination with CHOP chemotherapy or other anthracycline-based chemotherapy regimens.

Subcutaneous administration allows the drug to be given in a shorter period of time. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of rituximab by IV infusion. Dosing of subcutaneous rituximab varies depending on the type of lymphoma being treated.

Rituximab-abbs (Truxima), a *biosimilar*, is a biologic therapy that is modeled after an existing biologic therapy or reference (an already approved drug with a similar effect in the body) product that has already been approved by the FDA. Biosimilar therapy is expected to be just as effective as its reference product with the potential benefit of reducing the cost of treatment. Rituximab-abbs (Truxima), approved by the FDA in 2018, and rituximab-pvvr (Ruxience), approved by the FDA in 2019, are biosimilars to rituximab (Rituxan) for use in patients with untreated, relapsed or refractory, or non-progressing CD20- positive B-cell NHL. Rituximab-abbs and rituximab-pvvr are delivered intravenously.

### *Obinutuzumab (Gazyva)*

Obinutuzumab (Gazyva) was first approved by the FDA in 2013 and is indicated for use in the following situations:

- In combination with bendamustine (Treanda, Bendeka) followed by monotherapy for the treatment of patients with FL that has relapsed after, or is refractory to, a regimen containing rituximab (Rituxan).
- In combination with chemotherapy followed by monotherapy for the treatment of adult patients achieving at least a partial remission for the treatment of previously untreated stage II bulky, stage III, or stage IV FL.

Obinutuzumab (Gazyva) is also being investigated in other types of NHL. In patients with FL, obinutuzumab (Gazyva) is given as an IV infusion in six 28-day treatment cycles in combination with bendamustine (Treanda), six 21-day cycles (in combination with CHOP, followed by 2 additional 21-day cycles of obinutuzumab [Gazyva] alone) or eight 21-day cycles in combination with CVP.

### *Mogamulizumab-kpkc (Poteligeo)*

Mogamulizumab-kpkc was approved by the FDA in 2018 for the treatment of relapsed or refractory mycosis fungoides or Sézary syndrome (a type of T-cell NHL) in adult patients after at least one prior *systemic* (throughout the body) therapy. Mogamulizumab-kpkc blocks the C-C chemokine receptor type 4 (CCR4) receptor resulting in cell death of the targeted T-cells. It is delivered intravenously once a week for the first 28-day cycle and then once every two weeks for each subsequent cycle.

### *Tafasitamab-cxix (Monjuvi)*

Tafasitamab-cxix was approved by the FDA in 2020 to be used in combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL, NOS (including DLBCL arising from low grade lymphoma) who are not eligible for stem cell transplantation. Tafasitamab-cxix binds to CD19 that is expressed on B-cells—including neoplastic B lymphocytes—and promotes cell *lysis* (the breakdown of cells) resulting in cell death. Tafasitamab-cxix is delivered intravenously 5 times during the first 28-day cycle of treatment, 4 times during the second and third 28-day cycles of treatment, and on days 1 and 15 of each subsequent 28-day cycle.

## Antibody-Drug Conjugates

An antibody-drug conjugate is a chemotherapy drug attached to a monoclonal antibody. The three antibody-drug conjugates approved for use in NHL are described below:

### *Brentuximab Vedotin (Adcetris)*

Brentuximab vedotin (Adcetris) is a combination of a small molecule, monomethyl auristatin E (MMAE or vedotin), attached to a monoclonal antibody against CD30 (brentuximab). The monoclonal antibody part of this drug is like a “guided missile” that is directed against and attaches to lymphoma cells that express the CD30 antigen. Once the monoclonal antibody is attached to the lymphoma cell, it is taken inside the cell (internalized). MMAE is then released, where it attacks the inner parts of the cell and causes it to stop multiplying and die.

As of 2018, Brentuximab vedotin (Adcetris) is approved by the FDA for the treatment of adult patients with NHL in the following situations:

- Systemic (throughout the body) ALCL after failure of at least one previous combination chemotherapy regimen.
- Previously untreated systemic ALCL or other CD30-expressing PTCL, including AITL and PTCL – NOS, in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) chemotherapy.
- Primary cutaneous ALCL or CD30-expressing mycosis fungoides.

Brentuximab vedotin (Adcetris) is given as an IV infusion once every three weeks.

### *Polatuzumab vedotin-piiq (Polivy)*

Polatuzumab vedotin-piiq (Polivy) is a combination of the small molecule drug monomethyl auristatin E (MMAE or vedotin) attached to a monoclonal antibody targeting CD79b (polatuzumab), a component (piece) of the NHL B-cell receptor. After the antibody binds CD79b, it is internalized and MMAE is released to kill the cancer cell by blocking cell division.

Polatuzumab vedotin-piiq (Polivy) was approved by the FDA in 2019 for the treatment of adult patients with:

- Relapsed or refractory DLBCL and DLBCL-not otherwise specified (NOS), after at least two prior therapies, in combination with bendamustine (Treanda) and a rituximab product.
- Previously untreated DLBCL, DLBCL-NOS or high-grade B-cell lymphoma (HGBCL) and who have an IPI score of 2 or greater, in combination with R-CHP.

Polatuzumab vedotin-piiq (Polivy) is given as an IV infusion once every 21 days in combination with bendamustine (Treanda) and a rituximab product. Premedication (prior treatment) with an antihistamine and fever reducer is recommended to prevent infusion-related reactions (like fever, chills, flushing and muscle pain).

### *Loncastuximab tesirine-lpyl (Zynlonta)*

Loncastuximab tesirine-lpyl (Zynlonta) is a conjugate of a small molecule called tesirine (or SG3199, an anti-cancer agent) with a monoclonal antibody (loncastuximab) targeting CD19, a protein expressed at the surface of NHL B-cells. Upon binding to CD19, the conjugate is internalized and tesirine is released inside the B-cell, where it binds to the DNA and leads to cell death.

Loncastuximab tesirine-lpyl was approved by the FDA in 2021 for the treatment of adult patients with relapsed or refractory DLBCL-NOS, DLBCL arising from low-grade lymphoma, and HGBCL, after at least two or more lines of systemic therapy. It is given as an IV infusion once every 3 weeks. Premedication with dexamethasone is recommended to prevent reactions such as edema (swelling) and effusions (accumulation of fluid in the body).

## **Bispecific Antibodies**

Bispecific antibodies (bsAbs) approved to treat NHL work by linking cancer cells to cells from the immune system that fight cancer. These bsAbs combine regions that bind to CD20 on malignant B-cells and CD3 on cancer-fighting T-cells. For this reason, they are also called “T-cell engagers”.



This group of drugs may be valuable therapeutic alternatives for patients with relapsed/refractory NHL who have not responded to or are not eligible cellular therapy.

### *Epcoritamab (Epkiny)*

Epcoritamab (Epkiny) is a T-cell engaging bsAb that binds to the CD3 and CD20. It is indicated for the treatment of adult patients with relapsed or refractory DLBCL, DLBCL-NOS, including DLBCL arising from indolent lymphoma (transformed lymphoma), and HGBCL after two or more lines of systemic therapy. Epcoritamab is administered by subcutaneous injection weekly for the first 3 cycles, followed by every 2 weeks for cycles 4-9 and then once every 4 weeks. Each cycle is 28 days.

### *Mosunetuzumab (Lunsumio)*

Mosunetuzumab (Lunsumio) is a T-cell engaging bsAb that binds to CD3 and CD20. It is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. Mosunetuzumab is given weekly as an IV infusion for the first cycle and then every 3 weeks in 21-day cycles for 8-17 cycles based on response.

### *Glofitamab-gxbm (Columvi)*

Glofitamab (Columvi) is a bsAb that binds CD20 and CD3. It is indicated for the treatment of adult patients with relapsed or refractory DLBCL, DLBCL-NOS or large B-cell lymphoma (LBCL) arising from FL, after two or more lines of systemic therapy. Glofitamab is given by IV infusion on days 8 and 15 of cycle 1. Before initiating glofitamab, all patients receive pretreatment with obinutuzumab on day 1 of the cycle. From cycle 2, it is administered every 3 weeks for a maximum of 12 cycles.

## **Immune checkpoint inhibitors**

An immune checkpoint inhibitor binds to PD-1 or PD-L1, located on the surface of the lymphoma cell, and prevents it from escaping the body's immune response. Only one immune checkpoint inhibitor is approved for use in NHL, as described on the next page.

### *Pembrolizumab (Keytruda)*

In 2018, pembrolizumab (Keytruda) was approved by the FDA for treatment of primary mediastinal large B-cell lymphoma (PMBCL) in adult and pediatric patients with refractory or relapsed disease following two or more prior lines of therapy. Urgent reductive surgery (therapy that reduces the number of cancer cells) is rarely performed in PMBCL, but in those cases treatment with pembrolizumab (Keytruda) is not recommended.

Pembrolizumab is a checkpoint inhibitor that blocks the PD-1 receptor on T-cells to allow the immune system to better identify and attack lymphoma cells. Pembrolizumab is given as an IV infusion every 3 or 6 weeks (for adults) or every 3 weeks (for children).

### **Immunomodulatory Drugs**

Immunomodulatory drugs have many ways of working against cancer cells. They cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate the immune system to help destroy cancer cells. The only immunomodulatory drug (IMiD) approved for use in NHL is lenalidomine (Revlimid).

### *Lenalidomide (Revlimid)*

Lenalidomide (Revlimid) is a novel therapeutic agent that inhibits the growth and causes the death of some types of malignant blood cells. For this reason, lenalidomide is FDA approved for treatment of adult patients with NHL in the following situations:

- Patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade).
- Previously treated FL and MZL in combination with a rituximab product.
- In combination with tafasitamab for patients with relapsed or refractory DLBCL
- Lenalidomide comes as an oral tablet. It is given once a day for three weeks of a four-week cycle.

## Radioimmunotherapy

Radioimmunotherapy (RIT) consists of a radioactive *isotope* (molecule) attached to a monoclonal antibody. The monoclonal antibody recognizes and attaches to antigens on lymphoma cells, thereby exposing them to radiation. The only currently available RIT that is FDA-approved for lymphoma is ibritumomab tiuxetan (Zevalin).

### *Ibritumomab Tiuxetan (Zevalin)*

Ibritumomab tiuxetan consists of three parts: the CD20-targeted monoclonal antibody ibritumomab, a radioactive isotope called yttrium-90 (Y90), and tiuxetan, a molecule that links them together. The ibritumomab component of the drug binds to CD20-positive NHL B-cells. Once bound, the radiation from the Y90 damage the cell, triggering its destruction. Y90 ibritumomab tiuxetan was first approved by the FDA in 2002 and is indicated for the treatment of:

- Relapsed or refractory low-grade or follicular B-cell NHL.
- Previously untreated follicular NHL in patients who have achieved partial or complete responses to first line chemotherapy.

Ibritumomab tiuxetan is given through an IV injection in combination with rituximab (Rituxan). Treatment time is very short. Radioimmunotherapy treatment requires two infusions given about one week apart.

## Targeted Therapies

This term refers to drugs that target molecules that cancer cells use to survive, multiply, and spread in the body. To learn more about targeted therapies, please view Chapter 7 of this guide (page 57).

FDA-approved targeted therapies used in the treatment of NHL include:

- Histone deacetylase (HDAC) inhibitors belinostat (Beleodaq), romidepsin (Istodax), and vorinostat (Zolinza).
- The proteasome inhibitor bortezomib (Velcade).
- The Bruton tyrosine kinase (BTK) inhibitors: acalabrutinib (Calquence), ibrutinib (Imbruvica), zanubrutinib (Brukinsa), and pirtobrutinib (Jaypirca).
- The tyrosine kinase inhibitor crizotinib (Xalkori).

- The enhancer of zeste homolog 2 (EZH2) inhibitor tazemetostat (Tazverik).
- The nuclear export inhibitor selinexor (Xpovio).
- The retinoid X receptor (RXR) activator bexarotene (Targretin).

### *Belinostat (Beleodaq)*

Belinostat (Beleodaq) is a HDAC inhibitor, approved to treat adult patients with relapsed or refractory PTCL. It is given as an IV infusion on the first five days of a 21-day treatment cycle.

### *Romidepsin (Istodax)*

Romidepsin (Istodax) is an HDAC inhibitor approved for the treatment of CTCL in adult patients who have received at least one prior systemic therapy. It is given as an IV infusion over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.

### *Vorinostat (Zolinza)*

Vorinostat (Zolinza) is an HDAC inhibitor approved for treatment of patients with CTCL whose disease has progressed or has not responded to other therapies, or for whom the disease has persisted or returned after two systemic therapies. Vorinostat (Zolinza) is given as a tablet once daily with food.

### *Bortezomib (Velcade)*

Bortezomib (Velcade) is a proteasome inhibitor, a class of drugs that cause an abnormal build-up of proteins in a cancerous cell, resulting in cell death. Bortezomib (Velcade) is approved for the treatment of adult patients with MCL. It is given by IV infusion twice weekly for two weeks, followed by 10-day rest period every 3 weeks.

### *Acalabrutinib (Calquence)*

Acalabrutinib (Calquence) inhibits the BTK signaling protein to block the growth and survival of cancerous B-cells in some types of NHL. It is approved for the treatment of adult patients with MCL who have received at least one prior therapy. It comes in capsules that are taken twice daily and should be swallowed whole with water.

### *Ibrutinib (Imbruvica)*

Ibrutinib (Imbruvica) inhibits the signaling protein BTK to block the growth and survival of the cancerous B-cells in some types of NHL. Ibrutinib (Imbruvica) is approved for the treatment of adult patients with WM, as a single agent or in combination with rituximab (Rituxan). It is also approved in adult and pediatric patients aged 1 year or older with chronic graft versus host disease (GVHD, where the graft attacks the patient's healthy cells) after failure of one or more lines of systemic therapy.

Ibrutinib (Imbruvica) comes in capsules and tablets that should be swallowed whole with a glass of water once daily.

### *Zanubrutinib (Brukinsa)*

Zanubrutinib (Brukinsa) inhibits the BTK signaling protein to block the growth and survival of the cancerous B-cells in some types of NHL. It is approved for the treatment of adult patients with MCL who have received at least one prior therapy, WM, and relapsed or refractory MZL who have received at least one anti-CD20-based regimen. It is taken as an oral tablet once or twice a day with water.

### *Pirtobrutinib (Jaypirca)*

Pirtobrutinib (Jaypirca) inhibits the BTK signaling protein to block the growth and survival of cancerous B-cells in some types of NHL. Pirtobrutinib (Jaypirca) is indicated for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor. It is taken as an oral tablet once a day with water.

### *Crizotinib (Xalkori)*

Crizotinib (Xalkori) is a multi-kinase inhibitor, including anaplastic lymphoma kinase (ALK), which promotes the growth of some forms of NHL. By inhibiting ALK, it stops the proliferation (multiplication) and induces the death of ALK-positive NHL cells. Crizotinib (Xalkori) is approved for the treatment of pediatric patients (over 1 year of age) and young adults with relapsed or refractory systemic ALCL that is ALK-positive. It is taken as an oral tablet twice a day.

### *Tazemetostat (Tazverik)*

Tazemetostat (Tazverik) inhibits the EZH2 enzyme to decrease overgrowth of cancer cells. It is approved for the treatment of adult patients with relapsed or refractory FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least two prior systemic therapies, and for adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options. It is taken as an oral tablet twice a day.

### *Selinexor (Xpovio)*

Selinexor (Xpovio) blocks the movement of several proteins inside the cell promoting anti-cancer activity and prevent uncontrolled growth of cancer cells. It is approved for the treatment of adult patients with relapsed or refractory DLBCL-NOS, including DLBCL arising from FL, after at least 2 lines of systemic therapy. Selinexor (Xpovio) is taken as a tablet on days 1 and 3 each week with anti-nausea medicines.

### *Bexarotene (Targretin)*

Bexarotene (Targretin) activates retinoid X that regulates (controls) cell division and multiplication, preventing tumor growth. Bexarotene (Targretin) has two different forms of administration - gel and capsules. The gel is indicated for the topical treatment of cutaneous lesions of patients with refractory or persistent disease after other therapies, or who have not tolerated other therapies for CTCL. A generous amount of gel should be applied over the surface of each lesion using a clean washed finger. Bexarotene (Targretin) capsules are indicated for the treatment of cutaneous manifestations (skin symptoms) of CTCL in patients who are refractory to at least one prior systemic therapy. Capsules should be taken as a single oral daily dose with a meal.

## **Radiation Therapy**

Radiation therapy (also called radiotherapy) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. The term is generally used to describe external-beam radiotherapy, in which a radiation beam is delivered from a machine. For detailed information about radiation therapy, see Chapter 7 in Part 1 of this guide. The most common types of radiation therapy and delivery methods used for NHL are described below.

### *Image-Guided Radiation Therapy (IGRT)/Tomography*

This technique uses repeated imaging scans to monitor changes in tumor size and location throughout the radiation treatment. Imaging scans include computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) scans. The aim is to direct radiation to the areas affected by the cancer, sparing healthy tissues.

### *Three-Dimensional Conformal Radiation Therapy (3D-CRT)*

Very sophisticated computer software and advanced machines deliver radiation to a precisely shaped area of the body.

### *Electron Beam Radiation*

A machine sends electrons (negatively charged particles) directly to the area where the lymphoma was found and sometimes to nearby lymph nodes.

### *Proton Therapy*

Uses positively charged particles called protons delivered by an external beam. This can reduce the radiation exposure of nearby healthy tissues, allowing higher doses to be delivered to the tumor. It may be useful to treat tumors near places that are difficult to treat (e.g., heart, lungs, or esophagus).

### *Total Skin Electron Beam Therapy*

A weak radiation beam that only penetrates the outer layers of the skin is directed to the entire surface of the body.

### *Photopheresis or Extracorporeal Photochemotherapy*

A fraction of the patient's blood is removed from the body, treated with a chemical that makes lymphocytes more likely to die when exposed to ultraviolet radiation, and re-infused back into the patient.

## **Cellular Therapy**

Cellular therapy is the introduction of autologous (from the patient) or allogeneic (from a donor) healthy human cells into the patient's body for medical purposes to replace or repair damaged tissue and/or cells. Allogeneic transplants require immunosuppressant therapy (drugs that

prevent the immune system from attacking healthy cells and tissues) to reduce the risk of rejection of the transplanted cells (“graft”) and GVHD.

Both stem cell transplantation and CAR T-cell therapy are forms of cellular therapy, and many of the steps in the procedures are similar. While both procedures require prior chemotherapy, the regimen used in CAR T-cell therapy is associated with fewer side effects. Further information on Cellular Therapy is described in Chapter 7.

## CAR T-Cell Therapy

CAR T-cells are a special type of cellular immunotherapy that uses patient’s T-cells that were modified to help fight cancer. For more information on CAR T-cell therapy see Chapter 7 in Part 1 of this guide (page 57) and the *Cellular Therapy* guide on LRF’s website at [lymphoma.org/publications](http://lymphoma.org/publications). CAR T-cell therapies approved to treat NHL are described below.

### *Axicabtagene Ciloleuce* (Yescarta)

Axicabtagene ciloleuce (Yescarta) is a CAR T-cell therapy directed to the CD19 antigen, which is present on almost all B lymphoma cells, making it an ideal target for cellular therapy. It is approved for the treatment of adult patients with:

- Large B-cell lymphoma that is refractory to first line chemoimmunotherapy or that relapses within 12 months of first line chemoimmunotherapy
- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL-NOS, PMBCL, HGBCL, and DLBCL arising from FL.
- Relapsed or refractory FL after two or more lines of systemic therapy (efficacy observed in early studies is being confirmed in larger studies called confirmatory clinical trials).

Axicabtagene ciloleuce (Yescarta) is for autologous use only and is given through central venous access over 30 minutes. Dosing is based on the number of CAR-positive viable T-cells, and the patient’s weight.



### *Tisagenlecleucel (Kymriah)*

Tisagenlecleucel (Kymriah) is also directed against CD19. It is for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL-NOS, HGBCL, and DLBCL arising from FL, and relapsed or refractory FL after two or more lines of systemic therapy. Tisagenlecleucel (Kymriah) is for autologous use only and is given as a single-dose by IV infusion.

### *Brexucabtagene Autoleucel (Tecartus)*

Brexucabtagene autoleucel (Tecartus) is a CAR T-cell therapy directed against the CD19 antigen. It is approved for the treatment of adult patients with relapsed or refractory MCL. Brexucabtagene autoleucel (Tecartus) is for autologous use only and is given through central venous access (a catheter introduced inserted into a vein in the neck, chest, arm or groin) over 30 minutes. Dosing is based on the number of CAR-positive viable T-cells, and the patient's weight.

### *Lisocabtagene maraleucel (Breyanzi)*

Lisocabtagene maraleucel (Breyanzi) is a CAR T-cell therapy directed against the CD19 antigen. It is approved for the treatment of adult patients with large B-cell lymphoma including DLBCL-NOS (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL grade 3B, who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.
- Relapsed or refractory disease to first-line chemoimmunotherapy or are not eligible for stem cell transplantation due to comorbidities (other existing diseases) or age.
- Relapsed or refractory disease after two or more lines of systemic therapy.

Lisocabtagene maraleucel (Breyanzi) is for autologous use only and is given as single dose by IV infusion. Dosing is based on the number of CAR-positive viable (alive and healthy) T-cells.

## Stem Cell Transplantation

A stem cell transplant adds new stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells. In deciding if transplantation is a good option, doctors consider the patient's health status, age, medical history, cancer stage, and responses to previous therapy.

There are three types of stem cell transplantation that differ based on the source of the stem cells: *autologous*, *allogeneic* and *syngeneic*.

### *Autologous Stem Cell Transplant*

In an autologous stem cell transplant, patients are their own donor. Autologous stem cell transplantation is used in patients with cancers that are responding to chemotherapy. The ability to transplant the patient's own stem cells (autologous stem cell transplant) allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success.

### *Allogeneic Stem Cell Transplant*

In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood (blood collected from the umbilical cord at birth).

### *Syngeneic Stem Cell Transplant*

In a syngeneic stem cell transplant, the donor is the patient's identical twin.

For additional information about the process of stem cell transplantation, please view Chapter 7 of this guide (page 59) and the *Understanding Cellular Therapy* guide on LRF's website at [lymphoma.org/publications](http://lymphoma.org/publications).

## Part 2 — Non-Hodgkin Lymphoma

### Chapter 12: Clinical Trials and Advances in Treatment of Patients with Non-Hodgkin Lymphoma

#### Overview of Clinical Trials

Drugs that are not yet approved for sale by the FDA are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase (before testing in humans). The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development. The most common way for a patient to receive an investigational drug is through a clinical trial.

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial.

Clinical trials are not a “last resort” for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for NHL must be tested this way before patients can use them in the future. Participating in a clinical trial can help to improve the treatment options for NHL patients for many years to come. Patients with all stages of NHL can participate in clinical trials, whether at the time of initial diagnosis or at relapse.

To find out more about getting access to investigational drugs and clinical trials, visit the National Cancer Institute’s (NCI’s) website at [www.cancer.gov](http://www.cancer.gov) and search for “access to investigational drugs.” Alternatively, visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) to search for trials using a particular drug or to find clinical trials nearby. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline

“Clinical Trials Information Service” (call (800) 500-9976 or email [helpline@lymphoma.org](mailto:helpline@lymphoma.org)) for additional information and recent updates.

See Chapter 8 of this guide (page 69) for more general information about the topics below:

- What is a clinical trial?
- Why is a placebo (a substance that contains no medicine and/or has no effect) sometimes used in Phase III trials?
- Should I participate in a clinical trial?
- What is informed consent in a clinical trial?
- What is the cost of participating in a clinical trial?

## Advances in Treatment of Patients With NHL

Doctors and scientists around the world are working hard to improve currently available treatment options and find better and safer drugs to treat patients with NHL. Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease.

Today’s science is moving very quickly. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline/ Clinical Trials Information Service for additional information and recent updates.

For a detailed description of currently approved treatment options, please see Chapter 11 (pages 98-120).

## Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences (the order by which drugs are given) of existing drugs. The goal is to develop treatment regimens that are better at eradicating NHL cells while leaving healthy cells alone, decreasing the chance of side effects. Researchers are also investigating the best way to use imaging techniques (for example, positron emission tomography [PET]) to evaluate responses to therapy and to determine future doses.

## Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or eliminating GVHD in allogeneic transplants in which donor cells recognize the normal organs of the patient as foreign and attack them; improving ways to remove all lymphoma cells from stem cell samples drawn from the patient's bone marrow and used for autologous transplants; and developing more effective regimens for reduced-intensity (use of lower doses of chemotherapy and radiation) stem cell transplantation.

## Immunotherapy

### *Monoclonal Antibodies*

The success of the monoclonal antibody rituximab (Rituxan) inspired researchers to develop other monoclonal antibodies to treat patients with various types of NHL, such as the receptor tyrosine kinase-like Orphan Receptor 1 (ROR1) inhibitor cirmtuzumab for MCL and MZL. Another example of a type of monoclonal antibody being developed for treatment of NHL are bsAbs. Odronextamab (REGN1979) showed promising results in patients with aggressive relapsed or refractory B-cell NHL. Other bsAbs being investigated for NHL are AFM13 for the treatment of relapsed or refractory ALCL, MF, and relapsed or refractory PTCL, and blinatumomab for B-cell NHL. These drugs have thus emerged as a new class of immunotherapy with potential to treat aggressive lymphoma as second- or third-line agents.

### *Antibody-Drug Conjugates*

Antibody-drug conjugates in development for NHLs include zilovetamab vedotin (targeting receptor tyrosine kinase-like orphan receptor 1 [ROR1]) for the treatment of DLBCL, MCL, and FL.

### *Radioimmunotherapy*

Betalutin (177Lu lilotomab satetraxetan) is a radioimmunotherapy that targets CD37 and is currently under investigation for the treatment of NHL (DLBCL and FL).

## Checkpoint Inhibitors

A newer class of immunotherapies called checkpoint inhibitors has been developed more recently. Nivolumab (Opdivo), which is FDA-approved for the treatment of HL, has shown encouraging results in clinical trials for patients with B-cell NHL. Other checkpoint inhibitors are also under investigation for the treatment of NHL, such as:

- Durvalumab (Imfinzi) for DLBCL, FL, MCL, and CTCL.
- Ipilimumab (Yervoy) for B-cell and T-cell NHL.
- Atezolizumab (Tecentriq) for DLBCL, FL, and other NHLs.
- Ontopacept for B-cell and T-cell NHL.

## Targeted Therapies

Many targeted therapies for NHL are being studied in laboratories and in clinical trials. Examples include:

- HDAC inhibitors such as chidamide for PTCL, entinostat for B-cell NHL, abexinostat for FL, and vorinostat (Zolinza) for recurrent B-cell and T-cell NHL.
- Inhibitors of B-cell lymphoma-2 (BCL2) such as BGB-11417 for relapsed and refractory MCL.
- Kinase inhibitors, including:
  - BTK inhibitors such as orelabrutinib (Inokai) for DLBCL, BL, FL, and MCL, and nemtabrutinib for WM, MCL, DLBCL, FL, and MZL.
  - PI3K inhibitors such as pascalisib and liperlisib for relapsed and refractory PTCL, amdizalisib for FL and MZL, and BGB-10188 for DLBCL.
  - ALK inhibitor such as brigitanib (Alunbrig) for ALCL, and ensartinib for NHL.
- Proteasome inhibitors such ixazomib (Ninlaro) for relapsed and refractory FL, PTCL, BL, DLBCL and MCL.
- Cereblon targeting drugs such as CELMoDs (like golcadomide) for FL.

## CAR T-Cell Therapy

CAR T-cell therapies that target the CD19, CD20, CD22, and CD30 antigens are currently being investigated for several types of lymphoma. Examples include:

- IMPT-314 for relapsed and refractory NHL.
- ALLO-501A for relapsed and refractory large B-cell lymphoma.
- Azercabtagene zaprelleucel for NHL.
- ATLCAR.CD30 for PTCL.
- MB-106 for refractory B-cell lymphoma, FL, recurrent MCL, and recurrent WM.

## Vaccines

Vaccines are commonly used to help protect against viruses and other infections. In lymphoma, researchers are focused on developing vaccines for treatment rather than for disease prevention. The hope is that these vaccines might boost the immune system to recognize and kill lymphoma cells early during the course of the disease. Examples include:

- EO2463 for indolent NHL.
- Oncoquest-L for FL.
- DPX-Survivac for DLBCL.

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**Lymphoma Research Foundation  
(LRF) Helpline and Clinical Trials  
Information Service**

## **CONTACT THE LRF HELPLINE**

Trained staff are available to answer questions and provide support to patients, caregivers and healthcare professionals in any language.

Our support services include:

- Information on lymphoma, treatment options, side effect management and current research findings
- Financial assistance for eligible patients and referrals for additional financial, legal and insurance help
- Clinical trial searches based on patient's diagnosis and treatment history
- Support through LRF's Lymphoma Support Network, a national one-to one volunteer patient peer program

Monday through Friday  
9:30 am – 7:30 pm Eastern Standard Time (EST)  
Toll-Free (800) 500-9976  
or email [helpline@lymphoma.org](mailto:helpline@lymphoma.org)

