Understanding
Diffuse Large B-cell Lymphomas



Resource Center
Lymphoma Research Foundation

Overview

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL). It accounts for approximately 1 in 3 new cases of B-cell NHL in the United States. DLBCL is slightly more common in men, and in people who are over 60 years old. While the incidence (number of new cases) increases with age (half of the patients are over 60 years old), DLBCL can also occur in younger adults and, rarely, in children.

DLBCL is an aggressive (fast-growing) lymphoma that can appear in lymph nodes (bean-shaped structures that help the body fight infection, Figure 1) and often the spleen, liver, or bone marrow (the spongy tissue inside the bones), though it can appear anywhere in the body.

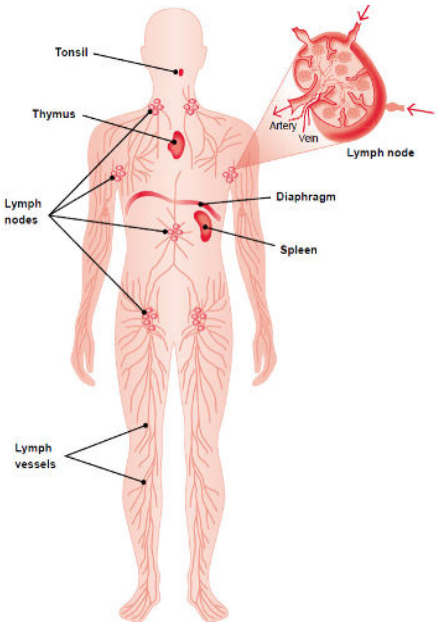


Figure 1. The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.



Symptoms, Staging, and Diagnostic Procedure

Symptoms

The first sign of DLBCL is usually a painless, rapid swelling in the neck, underarms, or groin caused by enlarged lymph nodes. For some patients, this swelling may be painful.

Other symptoms may include:

- Night sweats
- Fever
- Unexplained weight loss
- Fatigue (extreme tiredness)
- Loss of appetite
- Shortness of breath
- Pain



Staging and Diagnostic Procedure

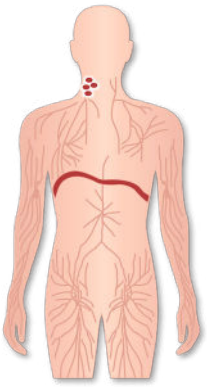
To confirm a diagnosis of DLBCL, doctors need to collect a sample of the affected lymph node and examine it under a microscope. This procedure is called a biopsy, and it can be done under local or general anesthesia. Once the diagnosis of DLBCL is confirmed, the next step is to understand the location of the disease in the body (disease staging). Because DLBCL is a blood cancer, it is important to look for any signs of lymphoma across the entire body. This is usually done with a positron emission tomography (PET) scan, which uses a special dye that is injected into the patient and shows where the cancer is.

Staging may also include:

Bone marrow biopsy (a procedure that collects a small sample of the spongy tissue inside the bone), to search for signs of cancer in the bones. Most of the time this is not required for staging.

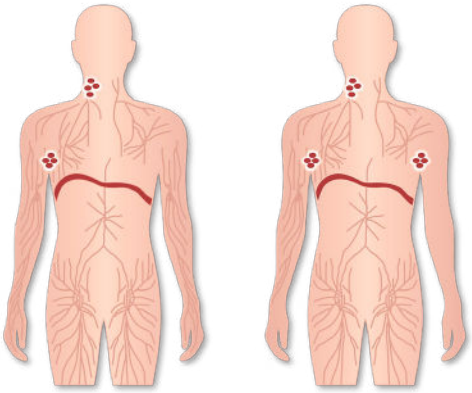
Spinal tap or lumbar puncture (a needle is inserted into the lower back to collect a sample of the fluid that surrounds the brain and spinal cord), to look for signs of cancer in the central nervous system (CNS, the brain and spinal cord).

The physician will use the results of these tests to assess the stage of the lymphoma. NHL is categorized as Stages I (limited disease) to IV (advanced disease), as shown in the figure below.



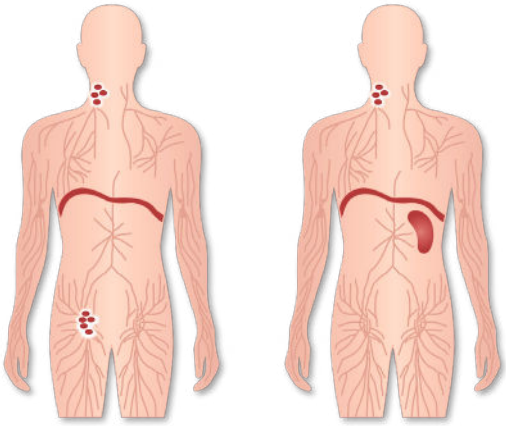
Stage I:

- Involvement of a single lymph node or group of adjacent nodes



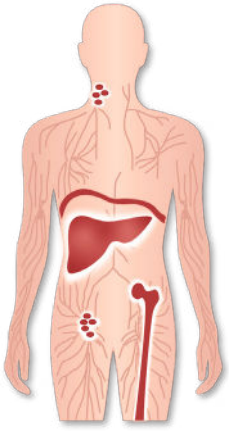
Stage II:

- Involvement of two or more groups of lymph nodes on the same side of the diaphragm (muscle that separates the chest from the abdomen)



Stage III:

- Involvement of lymph nodes on both sides of the diaphragm, or
- Involvement of lymph nodes above the diaphragm plus spleen involvement



Stage IV:

- Widespread disease in lymph nodes, bone marrow, and organ involvement, such as liver or lungs

Figure 2. Staging of NHL according to the Lugano system. This system categorizes NHL from Stage I-II (limited disease) to III-IV (advanced disease), based on whether the cancer is restricted to a single group of lymph nodes, involves several groups of lymph nodes, or has reached the bone marrow and/or other organs (like the liver or lungs).

Staging is needed to choose an appropriate treatment. The majority of patients wit DLBCL have advanced-stage disease but treatment can help achieve long-term remission (disappearance of signs of cancer for a long period) or cure (permanent disappearance of the cancer without ever returning). Therefore, staging does NOT have the same impact on prognosis that it does in solid tumor cancers.

Subtypes

There are several subtypes of DLBCL. Doctors determine the DLBCL subtype based on testing of the tumor tissue, as well as the clinical presentation (e.g., signs, symptoms, and location). To classify the specific DLBCL subtype, doctors may require additional tests that study:

- Cancer cell morphology: looking at the cancer cells under the microscope to examine their shape, structure, and form.
- Cancer markers: using special methods (like immunohistochemistry and flow cytometry) to look for specific proteins at the surface of cancer cells.
- Cancer genetics: using genetic tests (like fluorescence in situ hybridization or FISH) to detect mutations (permanent changes in the DNA [deoxyribonucleic acid, the molecule that carries genetic information inside the cell]) on a specific gene (a small portion of DNA that has the information needed to determine a person's physical and biological traits) of the cancer cells.

The subtype of DLBCL may affect a patient's prognosis (how well a patient will do with standard treatment [the proper treatment that is widely used by healthcare professionals and accepted by medical experts]) and treatment options.

Diffuse Large B-cell Lymphoma, Not Otherwise Specified (DLBCL-NOS)

Most cases of DLBCL do not fall into a specific subtype and are referred to as DLBCL-NOS. The different types of DLBCL-NOS are named according to their cell of origin (the normal cell that originated the cancer) and include:

- Germinal center B-cell-like (GCB): The most common subtype. However, recently approved treatments appear to improve the prognosis of this subtype.. It is an aggressive lymphoma, but patients may have a greater response to standard chemotherapy than those with the ABC subtype and, consequently, improved clinical outcomes.
- Activated B-cell-like (ABC): Less responsive to therapies than the GCB subtype and associated with poorer clinical outcomes compared to GCB subtype.

Other subtypes of DLBCL are less frequent and include:

- Primary mediastinal B-cell lymphoma (affects a specific region of the chest and occurs mainly in younger patients).
- Primary CNS lymphoma (affects the brain and/or spinal cord). For more information about CNS lymphoma, patients should view the CNS Lymphoma guide on the Foundation's website (visit lymphoma.org/publications).
- DLBCL can also result from the transformation of slow-growing lymphoma, such as follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, or nodular lymphocyte predominant Hodgkin lymphoma. These transformed lymphomas usually require more intensive types of treatment. For more information about transformed lymphoma, please view the Other Aggressive B-cell Lymphomas guide on the Foundation's website (visit lymphoma.org/publications).

Transformed Lymphoma

Transformed lymphoma is a less frequent subtype of DLBCL and occurs when genetic mutations (permanent changes) in the DNA (deoxyribonucleic acid, the molecule that carries genetic information within the cell) in some indolent lymphoma cells cause them to grow faster and behave more aggressively (see Table 1). Not all of the indolent lymphoma cells undergo transformation at once. When examined under the microscope, biopsies (samples of lymph nodes) from patients with transformed lymphomas will usually have a combination of indolent and aggressive ("transformed") lymphoma cells. If the number of fast-growing cells increases, the lymphoma can begin to behave more like an aggressive type. Compared to indolent lymphomas, this transformed lymphoma usually requires more intensive types of treatment.

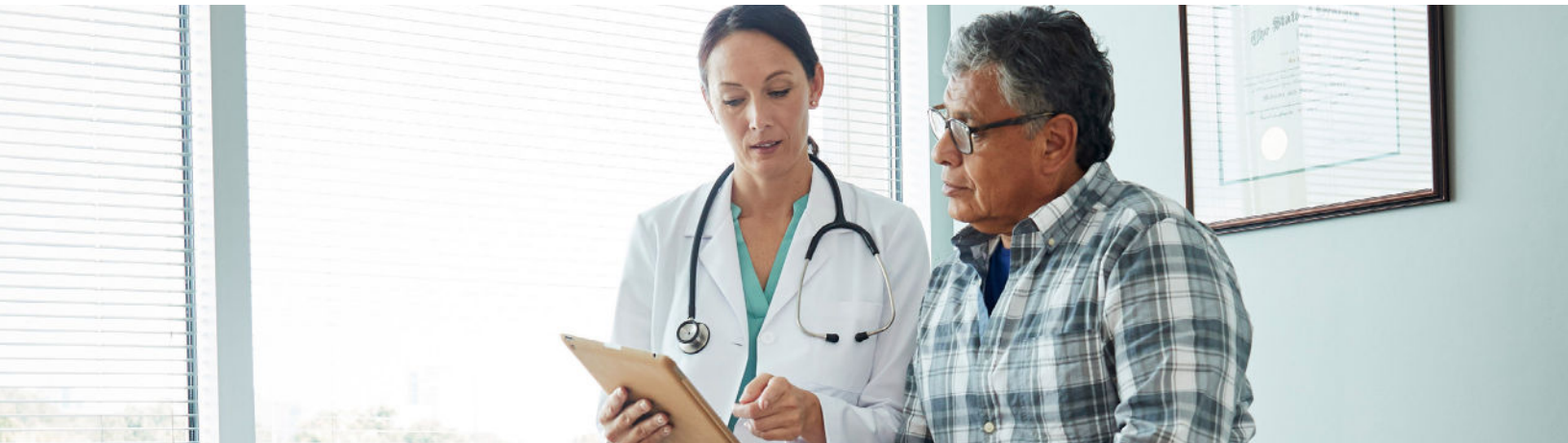


Table 1. Examples of Transformation

Indolent Lymphoma	Transformed Lymphoma
CLL/SLL	• DLBCL (Richter syndrome) • HL (uncommon)
FL (grades 1-2) Grade 1-3A FL are low-grade (slow growing) lymphomas. Grade 3B is treated as high-grade (fast-growing) lymphoma.	• DLBCL • HGBL with mutations in the MYC and BCL2 and/or BCL6 genes (a piece of DNA that contains information needed to produce the MYC and BCL2 proteins, respectively).
WM	• DLBCL
MZL	• DLBCL
Nodular lymphocyte-predominant HL (also called nodular lymphocyte predominant B-cell lymphoma)	• DLBCL

BCL2, B-cell lymphoma 2; BCL6, B-cell lymphoma 6; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; DNA, deoxyribonucleic acid; FL, follicular lymphoma; HGBL, high-grade B-cell lymphoma; HL, Hodgkin lymphoma; MYC, myelocytomatosis oncogene; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.

For transformed lymphomas, multiple risk factors associated with transformation have been identified, even though the presence of a risk factor does not mean that the lymphoma will transform. The overall risk of developing a transformed lymphoma is low among patients with an indolent disease, with an average risk of 3-4% per year that may stabilize (no longer increase) beyond 6 to 12 years after diagnosis. This means that the majority of these patients will never develop a transformed lymphoma. Patients who develop transformed lymphoma may have symptoms such as cough, chest pain, weight loss, and night sweats.

It is important to note that DLBCL is a complex disease and some cases that were previously considered to be DLBCL are now diagnosed as high-grade B-cell lymphoma (HGBL). HGBL is a category of B-cell NHL introduced in 2016 by the World Health Organization (WHO). HGBL in general is more likely to relapse (disease returns after treatment) than DLBCL and may have a higher risk of relapse in the patient's CNS.

HGBL can be grouped in two subtypes:

- Diffuse large B-cell lymphoma/high grade B-cell lymphoma with MYC and BCL2 rearrangements (DLBCL/HGBL-MYC/BCL2). This subtype is characterized by permanent changes (mutations) called translocations (Figure 3) in the parts of the DNA that contain the information for the MYC and BCL2 proteins. This category includes most NHL previously known as double/triple hit lymphoma.
- HGBL, not otherwise specified (NOS). This subtype of aggressive B-cell lymphoma has mixed features or characteristics of DLBCL, Burkitt lymphoma (BL), blastoid-appearing large B-cell lymphomas, and lymphomas that do not have MYC and BCL2 translocation.

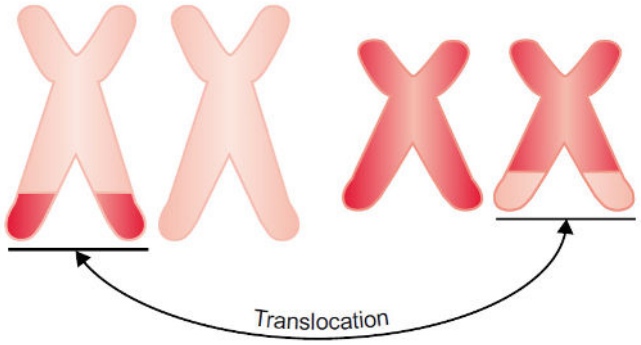


Figure 3. Example of a translocation, where a chromosome (a structure made of DNA and proteins found inside the cell) breaks and part of it reattaches to another chromosome.

Cancer cells in HGBL can look similar to B-lymphoblastic leukemia/lymphoma (B-LBL), BL, and DLBCL. Because of this, an expert review conducted by a hematopathologist (doctor who specializes in diagnosing blood diseases by examining cells and tissues under the microscope) is important. The signs and symptoms of HGBL may also be similar to those of DLBCL and BL.

Treatment Options

First Treatment after Diagnosis

DLBCL treatment typically begins shortly after diagnosis. The goal is to achieve durable remission or cure. Treatment types for DLBCL include:

Chemoimmunotherapy

Chemoimmunotherapy is a combination of chemotherapy (drugs that stop the growth of or kill cancer cells) with immunotherapy (drugs that use the body's immune system to fight cancer).

- The most common chemoimmunotherapy combination is chemotherapy and a monoclonal antibody (a protein produced in the laboratory that recognizes cancer cells and helps the body fight cancer) that targets CD20 (a protein found at the surface of lymphoma cells), such as rituximab (Rituxan) given intravenously (injected into a vein).

- RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and Pola-R-CHP (polatuzumab [Polivy], rituximab, cyclophosphamide, doxorubicin, prednisone) are the two most widely used chemoimmunotherapy combination regimens for DLBCL. These regimens are very similar and are usually given in 21-day cycles (a period of treatment followed by a period of rest that is repeated on a regular schedule). The only difference between the two regimens is whether vincristine, a chemotherapy drug, or polatuzumab are given. Polatuzumab is an antibody drug conjugate which binds to a protein on the surface of lymphoma cells called CD79b and is attached to a chemotherapy drug. In specific cases, patients may receive a regimen including etoposide (VePesid, Toposar, Etopophos), in a drug combination called R-EPOCH (also referred to as dose-adjusted R-EPOCH).

- R-mini-CHOP (rituximab and reduced-dose CHOP) may be considered for patients who are older or frail.

- Biosimilar therapies (a biologic therapy [molecule that are created inside living cells] that is modeled after an existing biologic therapy or reference product already approved by the FDA) may be an option for patients who are taking rituximab (Rituxan). These include rituximab-abbs and rituximab-pvvr. For more information about biosimilars, please see the Biosimilar Therapies publication on the Foundation's website (lymphoma.org/publications).

Radiation Therapy

- Radiation therapy that uses high-energy radiation to kill cancer cells may be considered in certain situations.

Patients seeking more information about immunotherapy should view the Immunotherapy and Other Targeted Therapies guide on The Foundation's website (**lymphoma.org/publications**).

Treatment for transformed lymphoma usually includes aggressive chemotherapy regimens, which vary depending on the clinical condition (signs and symptoms of disease and overall health) of the patient.

The type of treatments for transformed lymphoma may include any of the following (Table 2):

- Chemotherapy
- Immunotherapy with monoclonal antibodies
- Stem cell transplant (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells and then receives healthy stem cells to restore the bone marrow's ability to make new blood cells).
- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread).
- Chimeric antigen receptor (CAR) T-cell therapies (a special type of immunotherapy that uses the patient's immune cells to fight cancer). Patients seeking more information about stem cell transplantation and/or CAR T-cell therapy should view the Understanding Cellular Therapy guide on the Foundation's website (visit lymphoma.org/publications).
- Chemoimmunotherapy:
  A common approach is the combination of chemotherapy with a monoclonal antibody that targets CD20 (a protein at the surface of cancer cells), such as rituximab (Rituxan). Subcutaneous rituximab (Rituxan Hycela) or rituximab biosimilars (like rituximab-abbs and rituximab-pvvr) are often used.

Table 2. Available Treatment Options for Transformed Lymphoma

Agents (Drug)	Class of Drug (type of treatment and approved indication
Tafasitamab-cxix (Monjuvi)	• Immunotherapy; anti-CD19 monoclonal antibody. • Approved for patients with DLBCL arising from low-grade lymphoma. • Tafasitamab can be combined with lenalidomide for an improved effect on the body.
Loncastuximab tesirine (Zynlonta)	• Immunotherapy; anti-CD19 ADC. • DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma.
Epcoritamab (Epkinly)	• Immunotherapy; Bispecific anti-CD20 antibodies. • DLBCL arising from indolent lymphoma and high-grade B-cell lymphoma.
Glofitamab (Columvi)	• Immunotherapy; Bispecific anti-CD20 antibodies. • DLBCL arising from FL
Axicabtagene ciloleucel (Yescarta) Tisagenlecleucel (Kymriah)	• CAR T-cell therapy • Approved for patients with DLBCL arising from FL.

Agents (Drug)	Class of Drug (type of treatment and approved indication)
Lisocabtagene maraleucel (Breyanzi)	• CAR T-cell therapy • Approved for patients with DLBCL arising from indolent lymphoma.
Selinexor (Xpovio)	• Targeted therapy; XPO1 inhibitor. • Approved for patients with DLBCL arising from FL.

ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; XPO1, blocking exportin 1.

HGBL is generally treated with chemoimmunotherapy, similarly to DLBCL. The most common chemoimmunotherapy regimens for HGBL include:

- DA-R-EPOCH (dose-adjusted etoposide/VP16 [VePesid, Toposar, Etopophos], prednisone [Deltasone], vincristine [Oncovin], cyclophosphamide [Cytoxan, Neosar], and doxorubicin/hydroxydaunorubicin [Rubex, Adriamycin PFS] plus the monoclonal antibody rituximab [Rituxan]).
- R-Hyper-CVAD/MA (rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [Decadron], alternating with high-dose methotrexate [Mexate] and cytarabine/high-dose Ara-C [Cytosar-U, Tarabine PFS]).
- R-CODOX-M/R-IVAC (rituximab plus cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with rituximab plus ifosfamide [Ifex], etoposide, and cytarabine).
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).
- Pola-R-CHP (polatuzumab, rituximab, cyclophosphamide, doxorubicin, prednisone)

Surgery is not a typical treatment for DLBCL or HGBL because these are blood cancers, and surgery will not be able to get rid of all the cancer cells.

To reduce this risk of relapse in the patient's CNS, some patients with DLBCL or HGBL may receive additional chemotherapy drugs to treat the CNS in addition to one of the chemotherapy regimens described above. CNS treatments may include methotrexate and/or cytarabine that is administered either intravenously, through a lumbar puncture or both. During the lumbar puncture chemotherapy is injected directly into the cerebrospinal fluid surrounding the CNS.

After completing the initial treatment, follow-up for DLBCL typically involves medical check-ups every two or three months. The follow-up may include physical exams, blood tests, and PET and PET/computed tomography (CT) scans.

Relapsed and Refractory DLBCL

Some patients with DLBCL respond to initial treatment and go into remission. In other cases, the disease may relapse or become refractory (does not respond to treatment). For these patients, different therapies may result in improved treatment outcomes.

It is important to understand that patients should speak with their healthcare providers about their options for additional therapy in the future in case of relapse or if the lymphoma becomes refractory. These patients are eligible for second-line treatment (treatment received after initial treatment), which can reduce symptoms, control cancer growth, provide a second chance at cure, and extend life.

Early evaluation with a team of specialists is recommended for patients with relapsed/refractory DLBCL. Treatment options will depend on a number of factors, including when the relapse happened and whether the patient is eligible for (SCT) or (CAR) T-cell therapy.

Therapeutic options for relapsed/refractory transformed lymphoma may include:

-CAR T-cell therapy:

-Axicabtagene ciloleucel (Yescarta)

-Lisocabtagene maraleucal (Breyanzi)

-Autologous or allogeneic SCT

-Chemoimmunotherapy

-Involved-site radiation therapy

Primary Refractory Disease or Relapse Within 12 Months

For patients with DLBCL or HGBL who become primary refractory or relapse within 12 months, the standard second-line therapies are a type of immunotherapy called CAR T-cell therapy:

- CAR T-cell therapies (a special type of immunotherapy that uses the patient's immune cells to fight cancer):
  - Axicabtagene ciloleucel (Yescarta)
  - Lisocabtagene maraleucel (Breyanzi)

Patients should talk to their doctors about having a consultation with a physician at an authorized CAR T center early after a relapse or if the lymphoma does not respond to the initial treatment. For more information on the CAR T-cell therapy process, please view the Understanding Cellular Therapy guide at **lymphoma.org/publications.**

If CAR T-cell therapy is not recommended, additional treatment options include:



Immunotherapy:

- Bispecific antibodies (antibodies that recognize two different antigens, which can be on the same cell or two different cells). Bispecific antibodies used to treat lymphoma are called T-cell engagers and work by linking cancer cells to healthy immune cells, such as glofitamab (Columvi) and epcoritamab (Epkinly). To learn more about bispecific antibodies, view the Bispecific Antibodies fact sheet on the Foundation's website (visit **lymphoma.org/publications**).

- Monoclonal antibodies such as tafasitamab-cxix (Monjuvi)

- Antibody-drug conjugates (ADC, a monoclonal antibody attached to a chemotherapy drug) such as polatuzumab vedotin (Polivy), loncastuximab teserine (Zynlonta), and brentuximab vedotin (Adcetris). The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication.

- Immunomodulatory agents (drugs that regulate the immune system directly by activating or slowing down the activity of specific proteins), such as lenalidomide (Revlimid).

Relapse After 12 Months

For patients where the lymphoma relapses after 12 months, the standard second-line treatment is additional chemotherapy followed by an autologous SCT (the patient's own stem cells are used for transfusion). The patient is treated with high-dose chemotherapy or radiation to remove the blood forming cells or stem cells and then receives their own healthy stem cells back to replace the ones that were destroyed. The aim is to get rid of any remaining cancer cells with high-dose chemotherapy.

If more chemotherapy and an autologous SCT are not recommended because of age or other health conditions, patients will often be recommended CAR T-cell therapy, typically with lisocabtagene maraleucel (Breyanzi) for a late relapse.

Patients should talk to their doctors about having a consultation with a physician at an authorized CAR T center or SCT center early after a relapse or if the lymphoma does not respond to the initial treatment. For more information on the CAR T-cell therapy process, please view the Understanding Cellular Therapy guide at **lymphoma.org/publications.**

If SCT and CAR-T cell therapy are not recommended, other therapeutic options for relapsed/refractory DLBCL are listed below (Table 3) and may include:

Immunotherapy, including:

- Bispecific antibodies such as glofitamab (Columvi) and epcoritamab (Epkinly).
- Monoclonal antibodies such as tafasitamab-cxix (Monjuvi)
- Antibody-drug conjugates such as polatuzumab vedotin (Polivy).
- Immunomodulatory agents, such as lenalidomide (Revlimid).

For more information about SCT, please view the Understanding Cellular Therapy Guide, also on the Foundation's website (**lymphoma.org/publications)**.



Third Line and Later Therapies

For patients whose lymphoma has not responded to two different lines of therapy, several third-line therapies are available (Table 3):

- Immunotherapy:
  - Bispecific antibodies such as glofitamab (Columvi) and epcoritamab (Epkinly).
  - Monoclonal antibodies such as tafasitamab-cxix (Monjuvi)
  - Antibody-drug conjugates such as polatuzumab vedotin (Polivy), loncastuximab restoring (Zynlonta), and brentuximab vedotin (Adcetris).
  - Immunomodulatory agents such as lenalidomide (Revlimid).

- CAR T-cell therapies, including:
  - Axicabtagene ciloleucel (Yescarta)
  - Tisagenlecleucel (Kymriah)
  - Lisocabtagene maraleucel (Breyanzi)

- Targeted therapies such as ibrutinib (Imbruvica) and selinexor (Xpovio).

- Chemotherapy

Table 3. Second- and Third-Line Treatments for Relapsed or Refractory DLBCL

Patients with Refractory Disease or an Early Relapse and Who Are Candidates for CAR-T Cell Therapy	
	Axicabtagene ciloleuclel (Yescarta)
	Lisocabtagene maraleucel (Breyanzi)
Patients with a Late Relapse Who Are Candidates for a Stem Cell Transplant	
Chemotherapy is the preferred second-line treatment (other chemotherapies are also options sometimes)	DHAP +/- rituximab (Rituxan)
	DHAX or DHAC +/- rituximab (Rituxan)
	GDP +/- rituximab (Rituxan)
	ICE +/- rituximab (Rituxan)
Additional Treatments in the Second Line and Beyond	
Other second-line regimens	Lisocabtagene maraleucel (Breyanzi) (for a late relapse but not a candidate for SCT)
	Glofitamab (Columvi) +gemcitabine + oxaliplatin
	Epcoriramab (Epkinly) + gemcitabine + oxaliplatin
	Mosunetuzumab (Lunsumio) + polatuzumab (Polivy)

	Tafasitamab-cxix (Monjuvi) and lenalidomine (Revlimid)
	Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)
After ≥ 2 lines of systemic therapy	Axicabtagene ciloleucel (Yescarta)
	Tisagenlecleucel (Kymriah)
	Lisocabtagene maraleucel (Breyanzi)
	Epcoritamab (Epkinly) +/- gemcitabine + oxaliplatin
	Glofitamab (Columvi) +/- gemcitabine + oxaliplatin
	Tafasitamab-cxix (Monjuvi) and lenalidomine (Revlimid)
	Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)
	Loncastuximab tesirine (Zynlonta)
	Brentuximab vedotin (Adcetris) + lenalidomide (Revlimid) + rituximab (Rituxan)
	Selinexor (Xpovio)
Other second-line regimens	Ibrutinib (Imbruvica)
	Lenalidomide (Revlimid) +/- rituximab (Rituxan)

CA, chimeric antigen receptor; DHAC, dexamethasone, high-dose Ara-C, and carboplatin; DHAP, dexamethasone, cisplatin and cytarabine; DHAX, dexamethasone, cytarabine and oxaliplatin; DLBCL, diffuse large B-cell lymphoma; GDP, gemcitabine, dexamethasone and cisplatin or carboplatin; ICE, ifosfamide, carboplatin and etoposide; SCT, stem cell transplant.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) are currently being studied in clinical trials for patients with DLBCL and HGBCL (Table 4). Results from these clinical trials may improve or change the current standard of care. For more information on clinical trials, view the Understanding Clinical Trials publication on the Foundation's website at lymphoma.org/publications. Please consult with your doctor or a specialist in DLBCL and HGBCL to discuss any questions you may have about clinical trials.

Table 4. Selected Agents Under Investigation for DLBCL, Transformed Lymphoma, and HGBCL in Phase 2 and Phase 3 Trials

Agent(s) (Drug)	Class (type of treatment)	Under investigation for
Abexinostat	Targeted therapy; HDAC inhibitor	R/R DLBCL
Acalabrutinib (Calquence)	Targeted therapy, BTK inhibitor	Untreated DLBCL, R/R DLBCL, untreated TL, untreated HGBCL and R/R HGBCL
BGB-16673	Targeted therapy; BTK degrader	Untreated DLBCL, R/R TL
Cemacabtagene ansegedleucel	CAR T-cell therapy; anti-CD19	Untreated DLBCL and untreated HGBCL
Copanlisib (Aliqopa)	Targeted therapy; PI3K inhibitor	Untreated DLBCL and R/R DLBCL
CRC01	Immunotherapy; CAR T-cell therapy, anti-CD19	R/R DLBCL and R/R HGBCL
E7777	Immunotherapy; fusion protein	R/R DLBCL and R/R HGBCL
GLPG5101 (19CP02)	Autologous CAR T-cell; anti-CD19	R/R DLBCL

Agent (drug)	Class (type of treatment)	Under investigation for
Golcadomide (CC-99282)	Immunomodulatory therapy; Cereblon E3 ligase modulator	R/R TL
Itacitinib	Targeted therapy; JAK1 inhibitor	Untreated DLBCL
Maplirpacept (TTI-622)	Immunotherapy; fusion protein	R/R DLBCL and R/R HGBCL
MRT-2359	Targeted therapy; Molecular glue protein degrader	Untreated DLBCL
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1	R/R DLBCL, R/R TL, untreated HGBCL, and R/R HGBCL
Obinutuzumab (Gazyva)	Monoclonal antibody; anti-CD20	Untreated TL, R/R TL
Odronextamab	Bispecific monoclonal antibody; anti-CD20	R/R DLBCL
Ontorpacept (TTI-621)	Immunotherapy; fusion protein	R/R DLBCL and R/R HGBCL
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1	Untreated DLBCL, R/R DLBCL, untreated TL, untreated HGBCL, and R/R HGBCL
Relmacabtagene autoleucel	Immunotherapy; CAR T-cell therapy, anti-BCMA	R/R DLBCL and R/R HGBCL
Retifanlimab	Immunotherapy; immune checkpoint inhibitor, anti-PD-1	Untreated DLBCL and untreated HGBCL
RNK05047	Targeted therapy; chaperone-mediated protein degrader	Untreated DLBCL
Sepantronium bromide (SepB)	Targeted therapy; surviving inhibitor	R/R HGBCL

Agent (drug)	Class (type of treatment)	Under investigation for
Tazemetostat (Tazverik)	Targeted therapy: EZH2 inhibitor	Untreated DLBCL, R/R DLBCL and R/R HGBCL
Varlilumab (CDX-1127)	Immunotherapy; monoclonal antibody, anti-CD27	R/R DLBCL and R/R HGBCL
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor	R/R DLBCL, R/R TL, and R/R HGBCL
WZTL-002	CAR-T cell therapy; anti-CD19	R/R TL
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Untreated DLBCL, R/R DLBCL and R/R HGBCL
Zilovertamab vedotin	Antibody-drug conjugate; anti-extracellular ROR1	Untreated DLBCL and R/R DLBCL

BCL-2, B-cell lymphoma 2; BCMA, B-cell maturation antigen; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; HGBCL, high grade B-cell lymphoma; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; ROR1, Receptor tyrosine kinase-like orphan receptor 1; R/R, relapsed/refractory. TL, transformed lymphoma.

It is important to remember that scientific research is always evolving. Treatment options may change as new treatments are discovered, and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients with DLBCL or HGBCL consult a specialist to clear up any questions.

Clinical Trials



Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. They 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. There are four main types or phases of clinical trials. The phase is based on the study's objective and the number of participants.

Phase I

- To identify a safe dose of a new drug
- To decide on a dosing schedule for the drug
- To see what side effects are related to the therapy

Phase II

- To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I
- To confirm and learn more about the side effects identified in Phase I



Phase III

- To compare the new treatment or new use of an existing treatment with the current standard treatments
- To obtain detailed information about how well the treatment works and the types and severity of side effects it causes

Phase IV

- To look at long-term safety and effectiveness that take place after a new treatment has been approved by the FDA and is available to the public.

Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on the Foundation's website (visit **lymphoma.org/publications**), and the Clinical Trials Search Request Form at **lymphoma.org**, talk to their physician, or contact the Foundation's Lymphoma Resource Center for an individualized clinical trial search by calling or emailing **connect@lymphoma.org.**

How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience. It may help patients regain a sense of control that they may have lost following the lymphoma diagnosis by making sure patients receive the best care. Patients and care partners should remember they are partners in their treatment plan.

- Do not be afraid to ask your doctors or nurses questions about your care. An educated patient asking questions is not 'being a challenge to your physician' (or 'being a difficult patient').
- Learn more about lymphoma by asking your doctor for information and visiting reliable websites, such as the Foundation's at **www.lymphoma.org.**
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor's office, cancer center, or hospital.
- Consider joining the Foundation's Lymphoma Support Network, a nationwide peer support program that matches patients and caregivers with people who have had similar experiences.
  For information about the program, call **(800) 500-9976** or email **connect@lymphoma.org.**
- Finally, it is important that patients not be afraid to talk with the healthcare team about nonmedical issues such as transportation, finances, insurance, working through treatment or taking time off, and childcare. There are nurses, social workers, physician's assistants that are be able to provide the support and resources to help.



Follow-Up

Survivorship

As a cancer survivor, it is important that you practice self-care regularly to reset your physical and emotional well-being. Adopting routines of self-care will help you recharge your batteries and stay healthy. Talk with your healthcare team about developing a wellness plan to help you stay physically and emotionally healthy and improve your mood. Consider the following suggestions:

- Watch your health. Stay up-to-date with your own medical appointments and take any medications as prescribed.
- Exercise. Stay active with short periods of daily exercise (30 minutes of power walking, jogging or biking). If not possible, take the stairs instead of the elevator or park farther away than usual.
- Eat well. Include fruits and vegetables in your meals and maintain a balanced diet.
- Cut down on risk factors. Quit smoking and reduce alcohol intake.
- Sleep. Try to get 7 hours of sleep per night, or take naps when needed.
- Rest. Meditation, deep breathing and stretching can help you relax and reduce stress.
- Write it down. Keeping a journal with thoughts and feelings may help to let go of worries and fears.

View the Foundation's Survivorship Series fact sheet on the Foundation's website at lymphoma.org/publication *for more info.*

Long Term Follow-Up Care Plan

All lymphoma survivors should have a long term follow up plan (also called a "survivorship care plan") after treatment ends. This plan is arranged by your healthcare team and includes a summary of the treatments you received, recommendations for follow-up care based on your medical history, and schedules for medical exams to check if the lymphoma has come back (recurrence). This allows your healthcare team to monitor your overall health and look out for long-term effects or other problems that may occur at any point after treatment. Your doctor will let you know how often you need to return for checkup appointments and which physical exams and blood tests are necessary. These checkups usually include a review of your medical history, physical exam and bloodwork, as well as specific exams or screenings recommended by your doctor (see Health Screenings to Consider on next page).

A follow-up care plan may also provide information to help you meet any emotional, social, legal, and/or financial needs. Your health care team can help you decide which doctor to see for your follow-up care plan (the same doctor who treated your lymphoma, a health care provider specialized in caring or cancer survivors, or your primary care provider [PCP]). Some clinics specialized in follow-up cancer plans offer comprehensive support to cancer survivors (called "survivorship clinics"). You can visit **oncolink.org/clinics/** search to check for survivorship clinics in your area.

Health Screenings To Consider

As a survivor, there are specific health screenings and exams that you may do at an earlier age than the general population. These will be adapted to the type of lymphoma you had and the treatment you received. For instance, due to the increased risk of secondary breast cancer from radiation therapy, women who received radiation therapy to the chest area during childhood, adolescence, or young adulthood should have clinical breast examinations yearly until age 25, then every six months thereafter. In addition, these women should receive yearly mammograms and breast magnetic resonance imaging (MRI) beginning at age 25 or eight years after completion of the radiation therapy, whichever comes last.

Other health screenings the physician may suggest include:

- Bone density scans
- Cardiovascular monitoring
- Chest or whole body imaging
- Screening for other cancers (e.g. colorectal or skin)
- Dental screenings
- Eye exams
- Lipid blood tests
- Thyroid function tests

Because everyone is different, survivors should talk with their physicians about which screenings are most appropriate and when they should be started.

Care Partners

There are many ways you can help a loved one with lymphoma, as follows:

- Be present. The most important thing that a care partner can do is to "just show up."
- Be prepared. Talk with the healthcare team so that you know what to expect throughout the treatment, how to manage symptoms and when to ask for help.
- Listen. Each person asks for help in different ways, verbally (through words) and nonverbally, and some may require more comfort while others are more action oriented.
- Avoid "cheerleading". Do not disregard your love one's negative feelings (sadness, anger or worry).
- Organize the help. A rush of sudden help upon diagnosis can make the situation harder to manage and create unproductive tension.
- Set up remote access with computer and/or phone access. This is helpful for regular communication with your loved one.
- Offer rides. This is important for people with decreased mobility or limited resources.
- Take notes. If you go into the appointments, write down notes with the doctor's plan, medications, potential side effects and other relevant information.

Patients and their care partner are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation can help patients manage this documentation.

*View the Care Partners fact sheet on the Foundation's website at **lymphoma.org/publication** for more info.*

Questions to Ask Your Healthcare Team

- What is my exact diagnosis? What subtype of lymphoma do I have? May I have a copy of the report from the pathologist?
- What is the stage of my disease? In what area of the body is it specifically located?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment later on? How are the different treatments administered?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of lymphoma? Would a clinical trial be appropriate for me? How would I benefit? Are there any drawbacks of participating in a clinical trial?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?



The Foundation's Programs and Services

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plans organize information on your health care team, treatment regimen, and follow-up care. The Foundation also provides a Lymphoma Care Plan for Aggressive Lymphomas, Chronic Lymphocytic Leukemia (CLL), and one dealing with Survivorship. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications.**

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

Lymphoma Resource Center

The Foundation's Lymphoma Resource Center staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Treatment Navigation Service. For more information about any of these resources, visit our website at lymphoma.org, or contact The Foundation's Lymphoma Resource Center at **(800) 500-9976** or **connect@lymphoma.org.**

Para información en español, por favor visite **lymphoma.org/es** (For Information in Spanish please visit **lymphoma.org/es**).

Lymphoma Support Network

The Foundation's one-to-one peer support program – Lymphoma Support Network – connects patients and care partners with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission.
For more information about this program, please contact the Foundation's Lymphoma Resource Centerat **(800) 500-9976** or visit lymphoma.org/resources/supportservices/lsn.

Treatment Navigation Service

A lymphoma diagnosis can bring a lot of questions about your subtype, your treatment options, and what comes next. The Lymphoma Resource Center's Treatment Navigation Service is here to help you find answers. Through a one-on-one consultation with the Resource Center team, you'll receive personalized educational materials, a comprehensive overview of standard and emerging treatments, and a customized clinical trials search list tailored to your diagnosis. You'll walk into your next appointment feeling prepared and empowered to ask the right questions and take the next step in your journey. This free service is available to every member of our community, patients, survivors, and care partners alike. Reach out to the Lymphoma Resource Center to take your next step with confidence.

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For individuals outside of the U.S. seeking information, the Foundation recommends the Lymphoma Coalition. The Lymphoma Coalition is a global network of worldwide nonprofit/NGO lymphoma patient organizations with information appropriate for non-U.S.-based audiences. Additional information can be found by visiting their website at https://lymphomacoalition.org/.

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Last Updated 2026