National Comprehensive Cancer Network®

2026

NCCN Guidelines for Patients®

Cancer care recommendations from leading experts at the National Comprehensive Cancer Network® (NCCN®)

Diffuse Large B-Cell Lymphomas



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NCCN Guidelines for Patients®

The essential guide for people facing cancer.

Based on care recommendations from leading cancer experts.

Explains high-quality cancer care provided at state-of-the-art cancer centers.

Reviewed and revised every year.

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

Because cancer care is always evolving, NCCN develops and frequently updates evidence-based cancer care recommendations used by health care providers worldwide. These recommendations are known as the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®).

The NCCN Guidelines for Patients plainly explain these expert recommendations, so you can talk with your care team about the best care for you.

These NCCN Guidelines for Patients are based on the NCCN Guidelines® for B-Cell Lymphomas, Version 4.2026 — May 20, 2026.

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About DLBCL

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6 How is DLBCL treated?

7 How can I get the best care?

Diffuse large B-cell lymphoma (DLBCL) develops from B lymphocytes, a type of white blood cell. It's a fast-growing lymphoma, affecting tissues and organs, such as bone marrow, spleen, thymus, lymph nodes, lymphatic vessels, and other parts of the body. DLBCL is treatable and curable in many cases. Read this guide to learn more about the types of DLBCL and how they're treated.

What is DLBCL?

Diffuse large B-cell lymphoma (DLBCL) is a blood cancer of lymphocytes. Lymphocytes are a type of white blood cell that helps fight and prevent infection. They are found in blood, lymph vessels, lymph nodes, and every organ in the body. Lymphocytes normally grow in response to infection or inflammation. When they grow on their own without proper regulation, they can develop into lymphoma like DLBCL.

DLBCL is a type of B-cell lymphoma. There are many types of B-cell lymphomas. In DLBCL, B-cell lymphocytes grow out of control and form tumors. These tumors are commonly found in lymph nodes, spleen, liver, bone marrow, or other tissues and organs. DLBCL can also cause swollen lymph nodes. Symptoms can include fever, drenching night sweats, fatigue, and weight loss. These symptoms are referred to as B symptoms. Not everyone has the same symptoms, and tumors can be found anywhere in the body. Many people don't have any symptoms when they're first diagnosed.

Types of lymphocytes

There are 3 main types of lymphocytes:

- **B lymphocytes, or B cells**, make antibodies and eventually mature into plasma cells. An antibody is a protein that specifically targets infections or cancer cells and recruits other parts of the immune system.
- **T lymphocytes, or T cells**, help fight infections and cancer, and control immune responses.
- **Natural killer (NK) cells** can kill tumor cells or virus-infected cells.

Some cancers start in immature, or still developing, cells. DLBCL arises in mature (fully developed) B cells.

What is the lymphatic system?

DLBCL affects the lymphatic system. The lymphatic, or lymph, system is a major part of the body's immune system. It's a germ-fighting network of tissues and organs that include bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels.

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

As lymph travels throughout your body, it passes through hundreds of small, bean-shaped structures called lymph nodes. Lymph nodes make immune cells that help the body

fight infection. They also filter the lymph fluid and remove foreign material, such as bacteria and cancer cells.

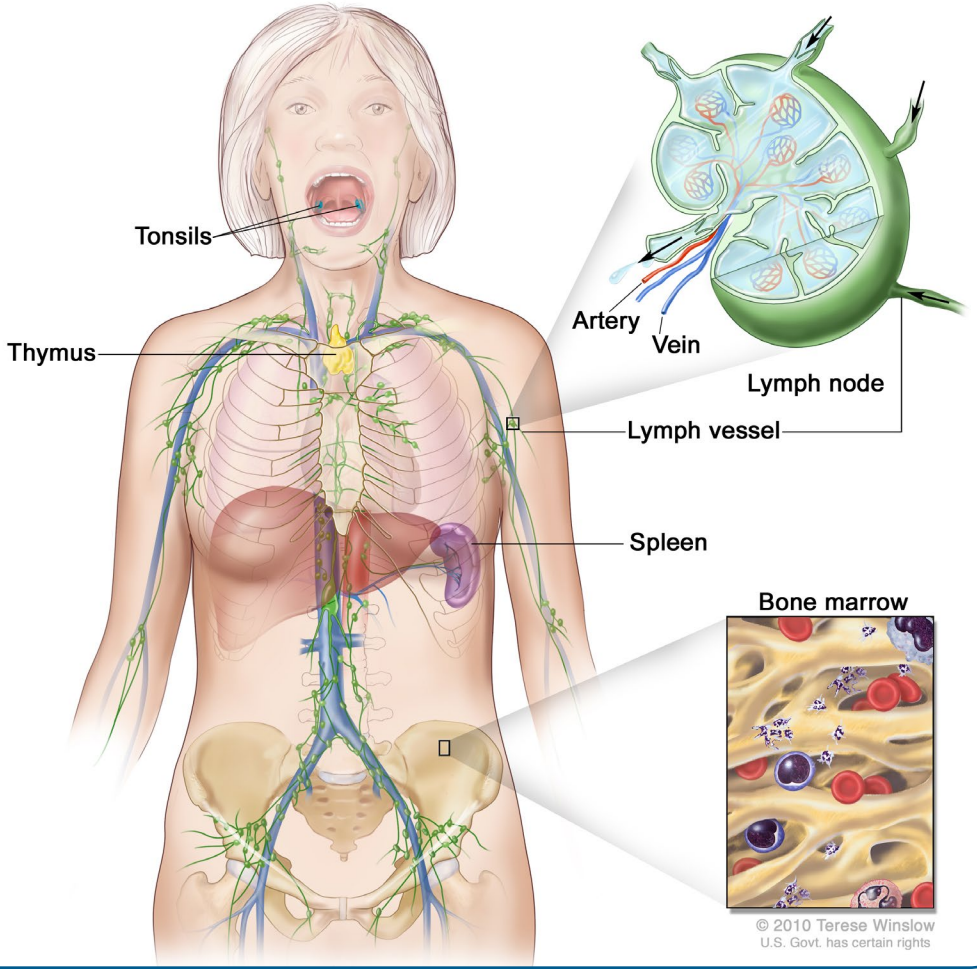
Lymph nodes can swell due to infection, inflammation, or cancer. Many types of lymphoma, including DLBCL, cause painless enlargement of lymph nodes because of cancer cell growth.

How is DLBCL treated?

DLBCL is treated with drug (systemic) therapy that travels in the bloodstream to kill lymphoma cells throughout the body. The goal of treatment is to cure the disease when possible. For many people with DLBCL, the first treatment is usually a combination of chemotherapy and immunotherapy, called chemoimmunotherapy. Radiation therapy may follow completion of systemic therapy, or radiation alone could be considered for palliative therapy. Surgery isn't a routine part of treatment for DLBCL.

DLBCL is the most common type of B-cell lymphoma

B-cell lymphomas start in the lymphatic system. The lymphatic, or lymph, system is part of the immune system. It includes lymph vessels, lymph nodes, tonsils, thymus, spleen, and bone marrow. Bone marrow is the main producer of blood cells. These include white blood cells, red blood cells, and platelets.



This guide contains treatment recommendations for DLBCL and other large B-cell lymphomas, such as

- ALK-positive large B-cell lymphomas
- Primary mediastinal large B-cell lymphomas
- High-grade B-cell lymphomas
- Mediastinal gray zone lymphomas
- Primary cutaneous DLBCL, leg type

If you've been diagnosed with DLBCL, consider seeking the opinion of a DLBCL specialist.

How can I get the best care?

Advocate for yourself. You have an important role to play in your care. Many people feel more satisfied when they actively take part in planning their cancer care.

The NCCN Guidelines for Patients will help you play a larger role in your care. Discuss the recommendations in this guide with your care team. Ask questions about your options and share your goals and concerns.

Don't know what to ask? You're not alone. That's why we include suggested questions to ask at the end of chapters.

Keep reading to find the best care for you.

How this guide can help you

Making decisions about cancer care is stressful. There's a lot to learn, and you don't know what the future holds.

Use this guide to get the information and support you need.

Patients, doctors, and other health care professionals trust the NCCN Guidelines for Patients. This guide uses clear, everyday language to explain current cancer care recommendations made by respected experts in the field. Their recommendations are based on the latest research and practices at leading cancer centers.

Your health is unique to you, so your cancer care should be, too. As you read this guide, you'll learn which treatments are likely to provide the best results for you. And you'll be better prepared to talk with your care team

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Testing for DLBCL

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Accurate testing is essential to diagnose and treat diffuse large B-cell lymphoma (DLBCL). Possible tests and procedures are discussed in this chapter. It's okay to skip over information that doesn't interest you.

Types of large B-cell lymphomas

Large B-cell lymphomas have large, abnormal B-cells. There are many types of large B-cell lymphomas. Diffuse large B-cell lymphoma (DLBCL) is just 1 type. Accurate testing is needed to determine the type of large B-cell lymphoma. For types of large B-cell lymphomas, see **Guide 1**.

Guide 1
Types of large B-cell lymphoma

DLBCL, not otherwise specified (NOS)	Fibrin-associated large B-cell lymphoma
T-cell/histiocyte-rich large B-cell lymphoma	Fluid overload-associated large B-cell lymphoma
DLBCL/high-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements	Plasmablastic lymphoma
ALK-positive large B-cell lymphoma	Primary large B-cell lymphoma of immune-privileged sites
Large B-cell lymphoma with *IRF4* rearrangement	Primary cutaneous DLBCL, leg type
High-grade B-cell lymphoma with 11q aberrations	Intravascular large B-cell lymphoma
Lymphomatoid granulomatosis	Primary mediastinal large B-cell lymphoma
Epstein-Barr virus-positive DLBCL	Mediastinal gray zone lymphoma
DLBCL associated with chronic inflammation	High-grade B-cell lymphoma, NOS

General health tests

Some general health tests are described next. Possible tests to plan treatment can be found in **Guide 2**.

Guide 2
Tests to diagnose DLBCL and plan treatment

Biopsy and pathology review
Immunophenotyping with immunohistochemistry and flow cytometry, and biomarker tests such as fluorescence in situ hybridization (FISH)
Physical exam with special attention to lymph node-bearing areas (including Waldeyer's ring) and to size of liver and spleen
Performance status
B symptoms (fever, drenching night sweats, and loss of more than 10 percent of body weight over 6 months)
Complete blood count with differential, lactate dehydrogenase, comprehensive metabolic panel, uric acid, and hepatitis B testing
PET/CT scan (preferred) or CT with contrast of chest, abdomen, and pelvis
Calculation of International Prognostic Index (IPI), which predicts overall and progression-free survival in DLBCL based on risk factors
Pregnancy test for people of childbearing age
Possible: • Heart tests • Head or neck CT or MRI with contrast • HIV testing • Hepatitis C testing • Beta-2-microglobulin • Lumbar puncture for people at risk for central nervous system (CNS) involvement • Bone marrow biopsy with or without aspirate • Discussion of fertility preservation

Medical history

A medical history is a record of all health issues and treatments you've had in your life. It asks about past surgeries and current health conditions. If you have history of rheumatologic disorders or solid organ transplantation and treatments, it's very important to share this information with your care team. Bring a list of old and new medicines and any over-the-counter medicines, herbals, or supplements you take. Some supplements interact with and affect medicines your care team may prescribe. Since there's often a lack of published information about how certain supplements interact with standard medicines, your care team may recommend that many of them be discontinued during treatment.

Family history

Some cancers and other diseases can run in families. Your care team will ask about the health history of family members who are blood relatives. This information is called family history. Ask members on both sides of your family about their health issues, like heart disease, cancer, and diabetes, and at what age they were diagnosed. It's important to know their specific type of cancer, where the cancer started, if it's in multiple locations, and if they had genetic testing.

Physical exam

During a physical exam, your health care provider may:

- Feel and apply pressure to parts of your body to see if organs are a normal size, are soft or hard, or cause pain when touched.
- Feel for enlarged lymph nodes in your neck, armpit, and groin.

Performance status

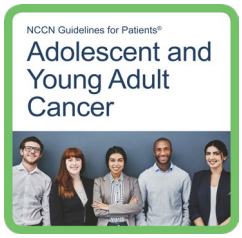
Performance status is a rating of your general level of fitness and ability to perform daily tasks. It includes whether you can walk, work, and take care of yourself. It's 1 factor taken into consideration when choosing a treatment plan.

Fertility (all genders)

Treatment with systemic therapy can affect your fertility, or the ability to have children. If you think you want children in the future, ask your care team how lymphoma treatment might affect your fertility.

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

More information on fertility preservation can be found in *NCCN Guidelines for Patients: Adolescent and Young Adult Cancer* NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.



Preventing pregnancy during treatment

Preventing pregnancy during treatment is important. Lymphoma treatment can affect ovaries, damage sperm, and hurt a developing baby. Therefore, becoming pregnant or having one's partner become pregnant during treatment should be avoided. If you're pregnant or breastfeeding at the time of your lymphoma diagnosis, treatments may need to be adjusted.

Blood tests

Blood tests check for signs of disease and how well organs are working. They require a sample of your blood, which is removed through a needle placed into your vein.

Some possible blood tests are described next. They are listed alphabetically and not in order of importance.

Complete blood count and differential

A complete blood count measures the levels of red blood cells, white blood cells, and platelets in your blood. A differential counts the number of each type of white blood cell (neutrophils, lymphocytes, monocytes, eosinophils, and basophils). It also checks if the counts are in balance with each other.

Comprehensive metabolic panel

A comprehensive metabolic panel measures different substances in your blood. It provides important information about how well liver and kidneys are working, among other things.

International Prognostic Index

The International Prognostic Index (IPI) is a scoring system to predict prognosis in people with lymphoma. A prognosis is the likely course your disease will take. IPI is based on age, performance status, Ann Arbor cancer stage, lactate dehydrogenase results, and if cancer is found in more than 1 area besides the lymph nodes.

Hepatitis B and hepatitis C testing

Hepatitis B and hepatitis C virus infections can affect the liver. A hepatitis blood test shows if you had hepatitis in the past or if you have it now. Some lymphoma treatments can wake up (or reactivate) the virus. If this happens, it can harm the liver.

HIV testing

Human immunodeficiency virus (HIV) weakens the immune system, increasing the risk of cancers. It may cause acquired immunodeficiency syndrome (AIDS). An HIV antibody test checks for HIV antibodies in a sample of blood. It's important to let your doctor know if you've ever been infected with HIV. HIV screening is recommended for people with a new lymphoma diagnosis.

Lactate dehydrogenase

Lactate dehydrogenase (LDH), or lactic acid dehydrogenase, is a protein found in most cells, including red blood cells and lung cells. Dying cells release LDH into blood. Fast-growing cells, such as lymphoma cells, also release LDH.

Pregnancy test

If planned treatment might affect pregnancy, then people who can become pregnant are given a pregnancy test before treatment begins.

Uric acid

Uric acid is released by cells when DNA breaks down. It's a normal waste product that dissolves in your blood and is filtered by the kidneys where it leaves the body as urine. Too much uric acid in the body is called hyperuricemia. With DLBCL, it can be caused by a fast turnover (cell death) of lymphoma cells. High uric acid might be a side effect of treatment. Very high levels of uric acid in the blood can cause kidney stones, kidney damage, and gout (inflammation of joints).

Biopsy

A biopsy removes a tissue sample from your body for testing. It's an important part of an accurate diagnosis of lymphoma. Your sample should be reviewed by a pathologist who's an expert in lymphoma. The pathologist (or hematopathologist) will note the overall appearance and size, shape, and type of cells and will write a report. This review is often referred to as a histology, histopathology, or hematopathology review. Tests are done on the biopsied cells to accurately diagnose DLBCL.

"I was so fortunate to find an expert oncologist and health care team that I could openly and honestly talk to during and after my treatment. This resulted in shared decision-making over my care. I credit this to my being here 35 years later."



Types of biopsies include the following:

- **Fine-needle aspiration** uses a very thin needle to remove a sample of tissue.
- **Core needle biopsy** uses a hollow needle to remove a larger sample of tissue.
- **Incisional biopsy** removes a small amount of tissue through a cut in the skin or body.
- **Excisional biopsy** removes the entire tumor through a cut in the skin or body.
- **Lymph node biopsy** removes tissue from a lymph node. This is further explained below.

When possible, larger tissue samples obtained through excisional, incisional, or lymph node biopsies are often preferred for diagnosing DLBCL.

Lymph node biopsy

You might need a lymph node biopsy to diagnose DLBCL. Lymph nodes can be too small to see or feel. Sometimes, lymph nodes can be swollen, enlarged, or hard or don't move when pushed (fixed or immobile). A lymph node biopsy can be done as a needle biopsy or procedure to remove (excise) a lymph node.

Bone marrow tests

Bone marrow tests might be done depending on your situation.

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

- Aspiration
- Biopsy

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

Bone marrow aspiration and biopsy are often bedside procedures. They aren't surgeries and don't usually require an operating room. Your care team will try to make you as comfortable as possible during the procedures.

The samples are usually taken from the back of the pelvis. You'll likely lie on your belly or side. For the aspiration, a hollow needle is pushed through your skin and into the bone marrow. Liquid bone marrow is then drawn into a syringe. For the biopsy, a wider needle is used to remove a small piece of bone marrow. You may feel pain at your hip for a few days. Your skin may bruise.

Immunophenotyping

Immunophenotyping is a process that uses antibodies to detect the presence or absence of white blood cell antigens called biomarkers. These antigens are proteins that can be found on the surface or inside white blood cells. They help the pathologist tell what type of cells make up a tumor. Certain biomarkers help identify DLBCL or are targeted in DLBCL treatment.

Specific groupings of antigens are normal. However, some specific patterns of antigens,

called the immunophenotype, are found on abnormal cells, including DLBCL.

Immunophenotyping can be done using specialized techniques called flow cytometry or immunohistochemistry. These techniques are used to distinguish DLBCL from other types of lymphoma. The immunophenotype can change as lymphoma progresses.

Immunophenotyping is used to help support a diagnosis. However, an accurate diagnosis requires a trained pathologist (or hematopathologist) to review the tissue for abnormal cells seen under a microscope. More testing may be needed to establish a subtype.

DLBCL is divided into 2 broad categories:

- Germinal center B cell (GCB)
- Non-GCB

Immunophenotyping is used to establish diagnosis and GCB versus non-GCB origin. Origin influences initial treatment options.

Flow cytometry

Flow cytometry is a laboratory method used to detect, identify, and count specific cells. It involves adding a light-sensitive dye to cells. The dyed cells are passed through a beam of light in a machine. The machine measures the number of cells, as well as things like their size and shape.

Flow cytometry may be used on cells from circulating (peripheral) blood, bone marrow, or biopsy. The most common use of flow cytometry is to identify markers on cells, particularly in the immune system (called immunophenotyping).

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

Immunohistochemistry

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

Biomarker tests and DLBCL genetic changes

Biomarker and genetic tests are used to learn more about your type of DLBCL, to guide treatment, and to determine the likely path your DLBCL will take (prognosis). This genetic testing is different from family history genetic testing or genetic cancer risk testing. It looks for changes only in the DLBCL cells that have developed over time and not changes in the rest of your body's cells.

Inside our cells are DNA molecules. These molecules are tightly packaged into what's called a chromosome. Chromosomes contain most of the genetic information in a cell. Normal human cells contain 23 pairs of chromosomes, for a total of 46 chromosomes. Each chromosome contains thousands of genes. Most genes contain information for making a specific protein. A mutation is when something goes wrong in the genetic code.

Proteins are written without italics, like this: BCL6. Genes are written with italics, like this: *BCL6.* When a gene or protein is found (expressed), it's shown with a plus sign (+), as in CD10+. When a gene or protein isn't found, it's written with a minus sign (-), as in CD10-.

DLBCL cells sometimes have changes in genes and chromosomes that can be seen under a microscope or found with other tests.

- Testing your DLBCL cells can gather specific information about your lymphoma to help guide treatment.
- Some results take days to weeks, but treatment may start before all results are in.

For more information on tests to diagnose DLBCL, see **Guide 3**.

Beta-2-microglobulin tumor marker test

Beta-2-microglobulin (B2M) is a protein that can be found in the blood, urine, or fluid that surrounds your spine and brain. B2M is a type of tumor marker. Tumor markers are substances made by cancer cells or by normal cells in response to lymphoma in the body.

Epstein-Barr virus testing

Epstein-Barr virus-encoded RNA in situ hybridization (EBER-ISH) is used to detect the Epstein-Barr virus (EBV) in tissue samples. EBV sometimes can be found in people with DLBCL. This test can help determine the subtype of DLBCL.

Guide 3
DLBCL biomarker and genetic tests

Needed	• Biopsy and hematopathology review • IHC panel: CD3, CD20, CD10, CD21, BCL2, BCL6, IRF4/MUM1, and MYC with or without cell surface marker analysis by flow cytometry: kappa/ lambda, CD3, CD5, CD19, CD10, CD20, and CD45 • FISH for *MYC* • FISH for *BCL2* and *BCL6* rearrangements if *MYC* positive
In some cases	• Additional IHC studies to determine LBCL subtype: cyclin D1, kappa/ lambda, CD5, CD30, CD45, CD138, anaplastic lymphoma kinase (ALK), human herpesvirus-8 (HHV8), SOX11, and Ki-67 • Epstein-Barr encoding region in situ hybridization (EBER-ISH) • FISH for *IRF4/MUM1* rearrangements • Multigene panel testing with lymphoma panel

DLBCL molecular testing

Molecular testing using methods such as fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), and multigene panel testing (MGPT) look for changes or abnormalities unique to DLBCL cells. A sample of your blood, bone marrow, or lymph nodes might be used to see if the DLBCL cells have any specific gene abnormalities or mutations.

Some gene abnormalities may determine the type of treatment given. Subtle, new, drug-resistant changes may occur over time. It can happen during treatment and lead to resistance to certain therapies.

Translocations

Translocation is a switching of parts between 2 chromosomes. A translocation between chromosome 14 and 18 is written as t(14;18). It might also be referred to as *BCL2* gene rearrangement. Specific translocations can help distinguish between types of lymphomas.

- *MYC*, *BCL2*, and *BCL6* gene rearrangements are commonly found in DLBCL.

MYC gene rearrangement

The *MYC* (proto-oncogene) gene is found on chromosome 8. An *MYC* gene rearrangement (MYC-R) is often found with a *BCL2* or *BCL6* gene rearrangement.

BCL2 gene rearrangement

The *BCL2* (B-cell lymphoma 2) gene is found on chromosome 18. The transfer of the *BCL2* gene to a different chromosome causes the BCL2 protein to be made in larger amounts, which may keep lymphoma cells from dying.



DLBCL genetic changes

DLBCL cells can have changes in genes and chromosomes. Molecular testing looks for these changes or abnormalities that are unique to DLBCL cells.

Examples include the following:

- **Amplification** – When a part or whole chromosome or gene is increased (for example, duplicated)
- **Deletion** – When part of a chromosome or gene is missing
- **Insertion** – When a new part of a chromosome or gene is included
- **Inversion** – When parts within 1 chromosome are switched
- **Point mutation** – When part of a gene is changed
- **Chromosome translocation and gene rearrangement** – When parts between 2 chromosomes are switched. When described at the chromosome level, it's called a translocation. When described at the gene level, it's called rearrangement.

BCL6 gene rearrangement

The *BCL6* (B-cell lymphoma 6) gene is found on chromosome 3. *BCL6* rearrangement is the most frequent chromosomal abnormality found in DLBCL.

Deletions

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

FISH

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

FISH can find translocations that are too small to be seen with other methods. However, it can only be used for known specific changes. It cannot detect all possible changes found in the chromosomes or genes.

- For example, FISH is used to detect *MYC*, *BCL2*, and *BCL6* gene rearrangements.

Imaging tests

Imaging tests take pictures of areas inside the body to look for cancer, enlarged lymph nodes, or other abnormalities that might suggest lymphoma. A radiologist, an expert in interpreting imaging tests, will write a report and send it to your care team.

Imaging tests are used to look for areas of lymphoma involvement and are part of DLBCL staging. Possible imaging tests are described next. They're listed in alphabetical order and not in order of importance. You won't have all of these tests.

Contrast material

Contrast material is a substance used to improve the quality of CT and MRI imaging scans. It's used to make the pictures clearer. Not all imaging tests require contrast, but many do.

Contrast might be taken by mouth (oral) or given through a vein (intravenously, or IV).The types of contrast vary and are different for CT and MRI.

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

CT scan

A CT, or CAT, scan uses x-rays and computer technology to take pictures of the inside of the body. It takes many x-rays of the same body part from different angles. All the images are combined to make 1 detailed picture. A CT scan of your head, neck, chest abdomen, and pelvis may be one of the tests to look for lymphoma. In most cases, contrast is used.

MRI scan

An MRI scan uses radio waves and powerful magnets to take pictures of the inside of the body. MRI doesn't use high-energy (ionizing) radiation. Because of the very strong magnets

used in the MRI machine, tell the technologist if you have any metal or a pacemaker in your body. Contrast is often used.

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

An MRI may be used to evaluate the brain and spinal cord.

PET scan

A PET scan uses a radioactive substance called a tracer. A tracer is injected into a vein to see where lymphoma cells are in the body and how much sugar they take up, since malignant cells metabolize sugar faster than normal cells. This gives an idea about how fast these cells are growing. Lymphoma shows up as bright spots on PET scans. However, not all tumors appear on a PET scan, and not all bright spots are lymphoma. It's normal for the brain, heart, kidneys, and bladder to be bright on PET. Inflammation or infection can also show up as a bright spot. When a PET scan is combined with CT, it's called a PET/CT scan.

Scrotal ultrasound

DLBCL can occasionally be found in the testicles. A scrotal ultrasound uses sound waves to make images of the scrotum. The scrotum is the pouch of skin at the base of the penis that contains the testicles.

Lumbar puncture

Lymphoma can travel to the fluid that surrounds the spine and brain. This may cause symptoms, such as headaches, neck pain, and sensitivity to light. To know if lymphoma cells are in your central nervous system (CNS), a sample of spinal fluid must be taken and tested. A lumbar puncture is a procedure that removes spinal fluid. It's also called a spinal tap. A lumbar puncture may also be used to inject cancer drugs into spinal fluid. This is called intrathecal (IT) chemotherapy. When systemic therapy and IT therapy are given together to prevent CNS disease, it's called CNS prophylaxis.

Heart tests

Heart, or cardiac, tests are used to see how well the heart works. These tests might be used to monitor treatment side effects or to measure your heart function before you start treatment. You might be referred to a heart specialist called a cardiologist.

Key points

- Blood tests are used during diffuse large B-cell lymphoma (DLBCL) treatment and recovery to check blood counts, treatment results, and the health of your organs.
- A biopsy removes tissue or fluid for testing. It's an important part of an accurate DLBCL diagnosis.
- A sample from your biopsy may undergo lab tests to learn more about your DLBCL and choose the best treatment for you.
- Immunophenotyping is used to diagnose and pinpoint the specific subtype of DLBCL.
- Biomarker and genetic tests are used to learn more about your subtype of DLBCL, to target treatment, and to determine the likely course the lymphoma will take.
- *MYC*, *BCL2*, and *BCL6* are gene rearrangements that might be found in DLBCL.
- Imaging tests are used to look for areas of lymphoma involvement and are part of DLBCL staging.

Questions to ask

- What can you tell me about my type and stage of DLBCL? What is the prognosis?
- What websites about my condition do you recommend? Is there any information I can take home to read?
- Is there a cancer center or hospital nearby that specializes in treating lymphoma?
- What type of biopsy will I have?
- What types of biomarker and genetic tests will be done on the biopsy sample? How long will it take to get the results??

What's next?

The next chapter provides information on the types of treatment and what to expect from treatment.

3
Types of treatment

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22 Treatment phases

23 Systemic therapy

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There's more than one treatment for large diffuse B-cell lymphomas (DLBCLs). This chapter presents an overview of the possible types of treatment and what to expect. Not everyone will receive the same treatment. Treatment options are based on many factors. Together, you and your care team will choose a treatment plan that's best for you.

Your care team

Treating lymphoma takes a team approach. Treatment decisions should involve a team of health care and psychosocial care professionals from different backgrounds who have knowledge and experience in your type of lymphoma. This team is united in planning and implementing your treatment.

Treatment phases

The goal of treatment is remission, which means there is no evidence of lymphoma. You might hear the following terms used by your care team.

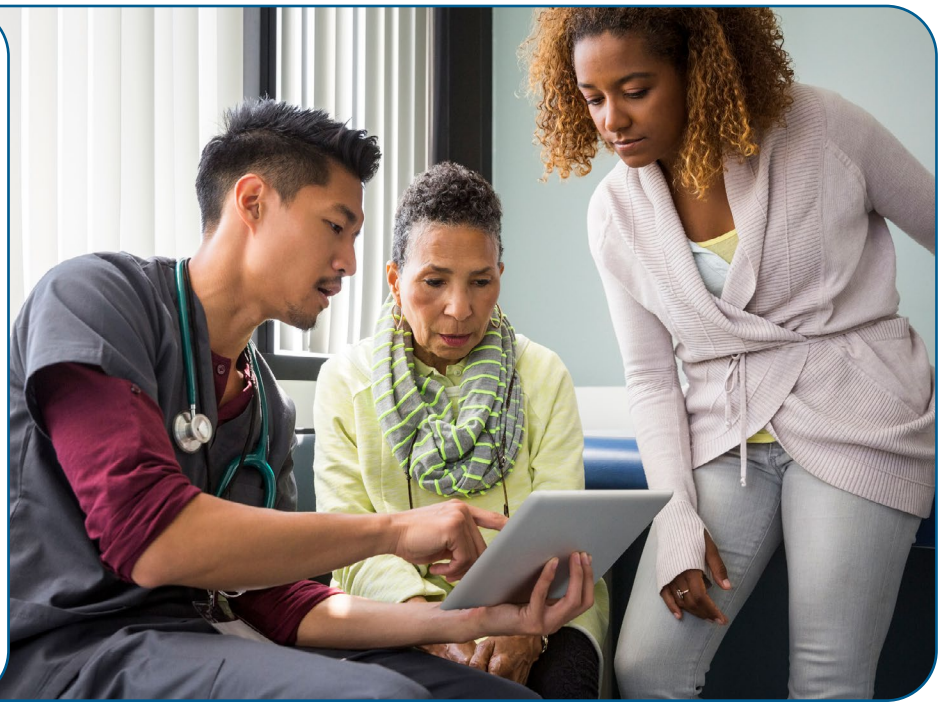
First-line therapy

First-line therapy is the first phase of treatment. The goal is a complete response, or complete remission. After completing first-line therapy, you'll have tests to look for a response (remission).

Remission

There are different types of remission. When there are no signs of lymphoma, it's called a complete response or complete remission.

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



Remission can be short-term (temporary) or long-lasting (permanent). In a partial response, lymphoma is still present, but it's reduced in size or amount.

Relapse

When DLBCL returns after a period of remission, it's called a relapse. The goal of treatment is to achieve remission again. A relapse is very serious. It's important to ask about your prognosis.

Refractory

When DLBCL remains and doesn't respond to treatment, it's called refractory, or resistant, disease. DLBCL may be resistant at the start of treatment or become resistant during treatment. Refractory disease is very serious. It's important to ask about your prognosis.

Surveillance and monitoring

You'll be monitored during and after treatment. Surveillance watches for any changes in your condition. You'll have tests during surveillance to check for relapse. You might hear it called active surveillance.

About NCCN recomendations for therapy

DLBCL is treated with systemic therapy, radiation therapy, or combination of both.

All treatments listed in this guide are deemed recommended and appropriate, by our NCCN panel members for DLBCL. This panel often assign levels of preferrence to the treatment recommendations as described below.

- **Preferred therapies** have the most evidence they may work better and be safer than other therapies.
- **Other recommended therapies** can provide effective results but may have less evidence, more side effects, or may not work quite as well as preferred therapies.
- **Therapies used in certain cases** work best for individuals with specific cancer features or health circumstances.

Systemic therapy

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

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

Chemotherapy

Chemotherapy kills fast-dividing cells throughout the body, including lymphoma cells and some normal cells. More than 1 chemotherapy may be used to treat DLBCL. When only 1 drug is used, it's called a single-agent regimen. When 2 or more drugs are used, it's called a combination or multi-agent regimen.

Some chemotherapy drugs are liquids given through a vein or injected under the skin with a needle. Other chemotherapy drugs are given as a pill. The dose differs between people because it's based on body weight and height.

Intrathecal chemotherapy is injected into the fluid surrounding the brain and spinal cord.

Most chemotherapy is given in cycles of days of treatment followed by days of rest. This allows the body to recover before the next cycle. Cycles vary in length depending on which drugs are used. The number of treatment days per cycle and the total number of cycles also vary. You might spend time in the hospital during treatment.

Chemoimmunotherapy

Chemoimmunotherapy, also called immunochemotherapy, includes chemotherapy and immunotherapy drugs to treat lymphoma. There are several chemoimmunotherapy regimens used to treat DLBCL.

Examples include:

- **RCHOP** – Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
- **Pola-R-CHP** – Polatuzumab vedotin-piiq (Polivy), rituximab, cyclophosphamide, doxorubicin, and prednisone

Immunotherapy

Immunotherapy increases the activity of your immune system. By doing so, it improves your body's ability to find and destroy lymphoma cells. Immunotherapy can be given alone or with other types of treatment.

Antibody therapy

Monoclonal antibody and bispecific antibody therapies use antibodies to help the body's immune system fight lymphoma, infection, or other diseases. Antibodies are proteins made by the immune system that bind to specific markers (proteins) on cells or tissues.

Monoclonal antibody therapy

A monoclonal antibody (mAb) is made from a unique white blood cell, such as a B cell or plasma cell. mAbs used in DLBCL treatment may kill lymphoma cells directly or help the immune system kill lymphoma cells.

CD19-targeting monoclonal antibody therapy

Tafasitamab-cxix (Monjuvi) is used to treat DLBCL by targeting the CD19 protein.

CD20-targeting monoclonal antibody therapy

CD20-targeting mAbs (also called anti-CD20 mAbs), such as rituximab (Rituxan or biosimilars) and obinutuzumab (Gazyva), target the CD20 protein found on the surface of B cells and DLBCL. The drug attaches to the CD20 protein, alerting the immune system to DLBCL. This triggers normal immune cells to kill the lymphoma cells.

PD-1-targeting monoclonal antibody therapy

Pembrolizumab (Keytruda) and nivolumab (Opdivo) with or without brentuximab vedotin (an antibody-drug conjugate) might be used to treat relapsed or refractory primary mediastinal large B-cell lymphoma. These drugs block the ability of cancer cells to hide from your body's immune system.

Bispecific antibody therapy

Bispecific antibodies bind to 2 different proteins (CD20 and CD3 antigen) at the same time—one on the immune T cells and the other on the lymphoma cells. Bispecific antibody therapy treats lymphoma by engaging and activating T cells and redirecting them to the lymphoma site. Examples of bispecific therapies include epcoritamab-bysp (Epkinly), glofitamab-gxbm (Columvi), and mosunetuzumab-axgb (Lunsumio).



Warnings about supplements and drug interactions

Some supplements and foods can affect the ability of a drug used to treat lymphoma to do its job. This is called a drug interaction. Since there's often a lack of published information about how certain supplements interact with standard medicines, your care team may recommend that many of them be discontinued during treatment.

Also, certain medicines can affect the ability of a drug to do its job. Antacids, heart or blood pressure medicine, and antidepressants are just some of the medicines that might interact with systemic therapy or supportive care medicines given during systemic drug therapy.

Therefore, it's very important to tell your care team about all medicines, vitamins, over-the-counter drugs, herbals, or supplements you're taking.

Bring a list with you to every visit.

CD19-targeting CAR T-cell therapy

CAR T-cell therapy is a personalized form of immunotherapy called cellular therapy. T cells from your body are removed in a process called pheresis, or apheresis. Then a CAR (chimeric antigen receptor) is added to your T cells. This programs the T cells to find and attack lymphoma cells. The programmed T cells are infused back into your body after a brief course of chemotherapy (called lymphodepleting chemotherapy). Chemotherapy is needed to get the body ready to accept the CAR T cells. This treatment isn't for everyone.

CAR T-cell therapy is one way to target the CD19 protein found on almost all B-cell lymphomas, including DLBCL. CD19-targeted CAR T-cell therapy options for DLBCL include axicabtagene ciloleucel (Yescarta), lisocabtagene maraleucel (Breyanzi), and tisagenlecleucel (Kymriah).

Targeted therapy

Targeted therapy focuses on specific or unique features of lymphoma cells. Targeted therapies seek out how lymphoma cells grow, divide, and move in the body. They stop or inhibit the action of molecules that help lymphoma cells grow and/or survive. For example, alectinib (Alecensa) and lorlatinib (Lorbrena) target the activity of the ALK protein found in people with an *ALK* gene mutation.

Other systemic therapies

Antibody-drug conjugate

An antibody-drug conjugate (ADC) delivers cell-specific chemotherapy. It attaches to a protein found on the outside of the cancer cell and then enters the cell. Once inside the cell, chemotherapy is released. Loncastuximab tesirine-lpyl (Zynlonta) is an ADC that targets the CD19 protein. Polatuzumab vedotin-piiq (Polivy) targets the CD79b protein. Brentuximab vedotin (Adcetris) targets the CD30 protein.

Enzyme inhibitor

A topoisomerase inhibitor blocks enzymes involved in cell division. One example is etoposide (Etopophos). A topoisomerase enzyme inhibitor may be used with other types of chemotherapy.

Immune modulator

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

It's very important to continue to take your medicine as prescribed—don't miss or skip any doses.

Radiation therapy

Radiation therapy (RT) uses high-energy beams to kill lymphoma cells and shrink tumors. Most DLBCLs are sensitive to radiation. Because of this, RT may be used as a curative treatment after completion of chemotherapy for early-stage disease, or for palliative treatment at any stage. The dose of radiation typically prescribed for DLBCL is relatively low.

The first step of RT is simulation (or mapping), a dedicated CT scan done in the radiation oncology department. Your radiation oncologist uses that scan and computer software to create a 3D radiation treatment plan. During treatment, radiation in the form of beams shaped to the tumor area is delivered from outside the body by a device.

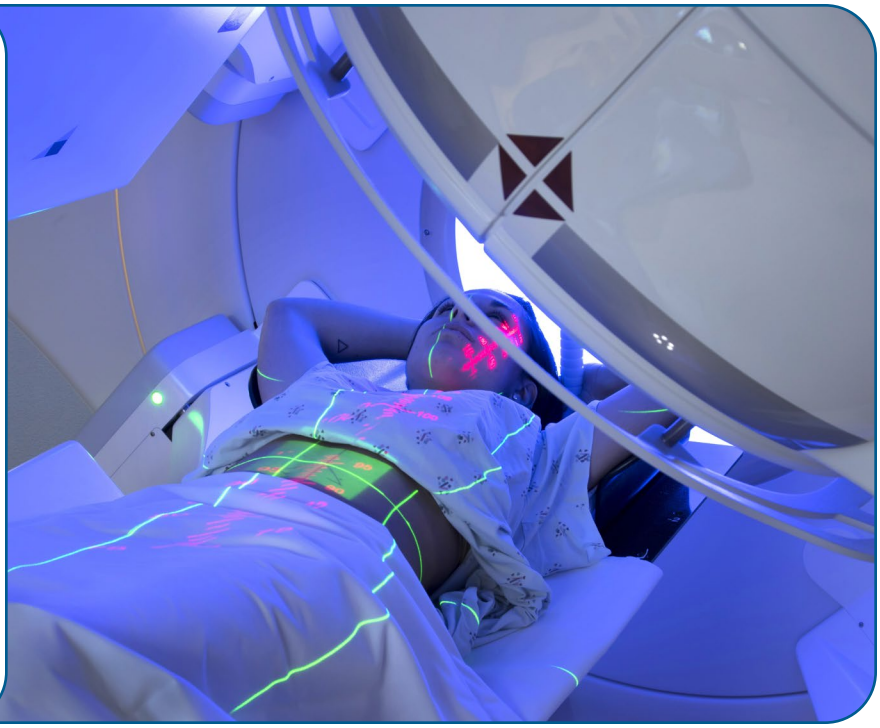
Depending on your situation, you may receive as little as 1 treatment or as many as 20 or more. Treatment is given in small daily doses, typically Monday through Friday. Some people receive 2 treatments a day.

- **Involved-site radiation therapy**, a technique that treats the area surrounding the tumor, is currently the typical approach used in DLBCL treatment.

You'll see your radiation oncologist at least once a week during RT. During these visits, the doctor will examine you and ask how you're feeling.

Most DLBCLs are sensitive to radiation therapy

Radiation therapy is used to treat DLBCL as a curative treatment after completing chemotherapy for early-stage disease, or for palliative treatment at any stage.



Hematopoietic cell transplant

A hematopoietic cell transplant (HCT) is a cellular therapy that replaces a person's bone marrow and immune system with their own healthy cells or donor cells. More specifically, an HCT replaces hematopoietic stem cells that have been destroyed by high doses of chemotherapy and/or radiation therapy as part of the transplant process. A hematopoietic stem cell is an immature cell that can develop into any type of blood cell. HCTs are performed in specialized centers.

There are 2 types of HCTs:

- **Autologous** – Stem cells come from you. It's also called high-dose therapy with autologous stem cell rescue (HDT/ASCR). Before high-dose chemotherapy, your healthy stem cells are removed (rescued) from your blood or bone marrow.
- **Allogeneic** – Stem cells come from a matched donor. These stem cells may be able to detect and eliminate lymphoma cells better than your own immune system.

Before an autologous HCT, your healthy stem cells are removed (rescued) from your blood or bone marrow. Then a treatment called conditioning is used to destroy damaged bone marrow cells. Chemotherapy, and sometimes radiation therapy, is used as part of conditioning treatment. After conditioning, you'll receive a transfusion of your healthy stem cells back into your body.

Before an allogeneic HCT, a treatment called conditioning is needed to destroy your bone marrow cells. Conditioning creates room for transplanted donor stem cells. It also weakens your immune system, so your body won't kill the transplanted cells. After conditioning, you'll receive a transfusion of healthy stem cells from a donor who's matched to you.

After conditioning

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

The goal of the transplant is for the new immune system to recognize the lymphoma as foreign and destroy it and to provide you with a new, healthy immune system.

Surgery

Surgery is an operation or procedure to remove cancer from the body. Surgery isn't a routine part of treatment for DLBCL. If surgery is needed, seek the opinion of an experienced surgeon. Hospitals that perform many surgeries often have better results. You can ask for a referral to a hospital or cancer center with experience in treating your type of cancer.

Clinical trials

You may also be able to receive treatment through a clinical trial. A clinical trial is a type of medical research study. After being developed and tested in a lab, potential new ways of treating cancer need to be studied in people.

If found to be safe and effective in a clinical trial, a drug, device, or treatment approach may be approved by the U.S. FDA.

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

Phases

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

- **Phase 1** trials study the safety and side effects of an investigational drug or treatment approach.
- **Phase 2** trials study how well the drug or approach works against a specific type of cancer.
- **Phase 3** trials test the drug or approach against a standard treatment. If the results are good, it may be approved by the FDA.
- **Phase 4** trials study the safety and benefit of an FDA-approved treatment.



Finding a clinical trial

In the United States

NCCN Cancer Centers
NCCN.org/cancercenters

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

Worldwide

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

Need help finding a clinical trial?

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

Who can enroll?

It depends on the clinical trial's rules, called eligibility criteria. The rules may be about age, cancer type and stage, treatment history, or general health. They ensure that participants are alike in specific ways and that the trial is as safe as possible for the participants.

Informed consent

Clinical trials are managed by a research team. This group of experts will review the study with you in detail, including its purpose and the risks and benefits of joining. All of this information is also provided in an informed consent form. Read the form carefully and ask questions before signing it. Take time to discuss it with people you trust. Keep in mind that you can leave and seek treatment outside of the clinical trial at any time.

Will I get a placebo?

Placebos (inactive versions of real medicines) are almost never used alone in lymphoma clinical trials. It's common to receive either a placebo added to a standard treatment, or a new drug with a standard treatment.

Are clinical trials free?

There's no fee to enroll in a clinical trial. The study sponsor pays for research-related costs, including the study drug. Routine costs of clinical trials are usually covered by third party carriers. But you may need to pay for other services, like transportation or childcare, due to extra appointments. Most clinical trials cover routine CT scans or other imaging tests. Imaging studies specific to the trial aren't covered. During the trial, you'll continue to receive standard cancer care. This care is usually covered by insurance.

Key points

- Diffuse large B-cell lymphoma (DLBCL) is highly treatable. The goal of treatment is to cure the disease.
- The choice of therapy takes into consideration many factors, including age, other serious health issues, and future treatment possibilities (like hematopoietic cell transplant or CAR T-cell therapy).
- DLBCL is treated with systemic therapy with or without radiation therapy.
- Systemic therapy works throughout the body. It includes chemotherapy, targeted therapy, and immunotherapy.
- Radiation therapy uses high-energy beams to kill lymphoma cells and shrink tumors.
- A clinical trial is a type of research that studies a treatment to see how safe it is and how well it works.

Questions to ask

- What type of DLBCL do I have?
- What experience do you have treating DLBCL?
- How long will treatment take, and in what order will it be given?
- Will I spend time in the hospital?
- Are there resources to help pay for treatment or other care I may need?

What's next?

Now that you've read about the different types of treatment and what to expect, the next chapter talks about some general side effects of treatment and what might be done to manage those effects.

4
Supportive care

33 What is supportive care?

34 Side effects

38 Key points

38 Questions to ask

Supportive care helps manage the symptoms of diffuse large B-cell lymphoma (DLBCL) and the side effects of treatment. This chapter discusses supportive care for possible treatment side effects.

What is supportive care?

Supportive care is an important part of cancer care. The goal is to improve your quality of life during and after cancer treatment. Supportive care is for everyone with cancer and their families, not just for those at the end of life.

Supportive care includes a wide range of services. Supportive care prevents or manages the symptoms of cancer and the side effects of cancer treatment, like pain and cancer-related fatigue. It also addresses the mental, social, emotional, and spiritual concerns faced by people with cancer.

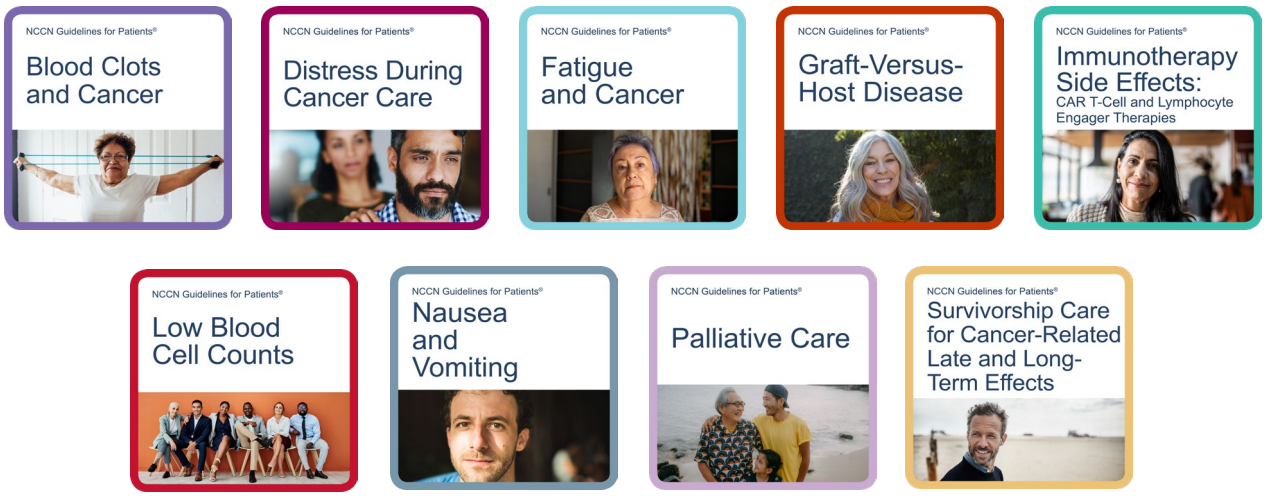
Supportive care provides help with additional needs, such as:

- Making treatment decisions
- Coordinating your care
- Paying for care
- Planning for advance care and end of life

Some health care professionals refer to palliative care as supportive care. They think these types of care are alike or overlap. Others think there are important differences, but both help people with cancer to live as well as they can. Your cancer center may have palliative care specialists, who can give you additional support and help coordinate your supportive care needs.

Supportive care resources

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



Read more about the types of support you may receive in *NCCN Guidelines for Patients: Palliative Care*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.

Tell your care team about any new or worsening symptoms so they can be managed.

Side effects

All lymphoma treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person. Some side effects are very serious. Tell your care team about any new or worsening symptoms.

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

Blood clots

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

Cytokine release syndrome

Cytokine release syndrome only happens during treatment with CAR T-cell therapy or bispecific antibody therapy. It's caused by a large, rapid release of cytokines from immune cells. Cytokines are proteins made and released by the body in response to infection, inflammation, or some treatments. Signs and symptoms include fever, muscle aches, nausea, headache, rash, fast heartbeat, low blood pressure, and trouble breathing.

Diarrhea or constipation

Diarrhea, frequent and watery bowel movements, is a common side effect. Your care team will tell you how to manage diarrhea. When it occurs, it's important to drink lots of fluids.

Constipation means having less frequent and more difficult bowel movements. Constipation is also common, especially if you're taking certain pain medicines and some anti-nausea medicines. Drinking fluids, staying active, and taking medicines for constipation are often recommended.

Emotional distress

Depression, anxiety, and sleeping issues are common during a lymphoma diagnosis. Talk to your care team and those with whom you feel most comfortable about how you're feeling. There are services, people, and medicine that may help relieve your distress.

Fatigue

Fatigue is a state of physical or mental tiredness that can feel like a lack of energy, motivation, or stamina. Fatigue is complex. and may be caused by lymphoma. It may be a side effect of treatment, or it may be caused by other things. Let your care team know how you're feeling and if fatigue is getting in the way of doing the things you enjoy. Eating a

balanced diet, exercise, yoga, acupuncture, and massage therapy can help. You might be referred to a nutritionist or dietitian to help with fatigue. It's important to try to stay active.

GVHD

Graft-versus-host disease (GVHD) is a possible side effect of a hematopoietic cell transplant (HCT). In GVHD, the donor cells attack your normal, healthy tissue, such as your organs and skin. There are treatments for GVHD.

Hair loss

Chemotherapy may cause hair loss (alopecia) all over your body—not just on your scalp. Some chemotherapy drugs are more likely than others to cause hair loss. Dosage might also affect the amount of hair loss. Most of the time, hair loss from chemotherapy is temporary. Hair often regrows 3 to 6 months after treatment ends. Your hair may be a different shade or texture at first. Scalp cooling (or scalp hypothermia) might help lessen hair loss in people receiving certain types of chemotherapy. However, scalp cooling isn't recommended for DLBCL.

Hand-foot syndrome

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

Hypersensitivity, allergy, and anaphylaxis

Hypersensitivity is an exaggerated response by the immune system to a drug or other substance. This response can include hives, skin welts, and trouble breathing. An allergy is an immune reaction to a substance that normally is harmless or would not cause an immune response in most people. An allergic response may cause symptoms, such as itching or inflammation (swelling). Anaphylaxis or anaphylactic shock is a severe and possibly life-threatening allergic reaction.

Infections

Infections are more common and more severe in people with a weakened immune system. Drug treatment for lymphoma can reduce the body's natural defense against infections. If not treated early, infections can be fatal.

Neutropenia, a low number of white blood cells, can lead to frequent or severe infections. When someone with neutropenia also develops a fever, it's called febrile neutropenia (FN). With FN, your risk of infection may be higher than normal. This is because a low number of white blood cells reduces your ability to fight infections. FN is a side effect of some types of systemic therapy. **Notify your care team immediately of any fevers while you may be neutropenic.**

Loss of appetite

The side effects of lymphoma treatment and the stress of having DLBCL might cause you to feel not hungry or sick to your stomach (nauseated). You might have a sore mouth or difficulty swallowing.

Healthy eating is important during treatment. It includes eating a balanced diet, eating the right amount of food, and drinking enough fluids. A registered dietitian who's an expert in nutrition and food can help.

Low blood cell counts

Some lymphoma treatments can cause low blood cell counts.

- **Anemia** is a condition where your body doesn't have enough healthy red blood cells, resulting in less oxygen being carried to your organs. You might tire easily if you're anemic.
- **Neutropenia** is a decrease in neutrophils, a type of white blood cell. This puts you at risk of infection.
- **Thrombocytopenia** is a condition where there aren't enough platelets. This puts you at risk of bleeding.

Lymphedema

Lymphedema is a condition in which lymph fluid builds up in tissues and causes swelling. It may occur when part of the lymph system is damaged or blocked. Lymphomas that block lymph vessels can also cause lymphedema in the arms or legs. Swelling usually develops slowly over time. If you have lymphedema, you may be referred to an expert in lymphedema management. The swelling may be reduced by exercise, massage, compression devices, and other means.

Nausea and vomiting

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

Neuropathy and neurotoxicity

Some treatments can damage the nervous system (neurotoxicity), causing neuropathy and problems with concentration, memory,

"My doctor reminded me that stress cannot help me, but it can hurt me! It helped me remember to control those things I could control and relax in front of those that I could not control."



and thinking (brain fog). Neuropathy is a nerve problem that causes pain, numbness, tingling, swelling, or muscle weakness in different parts of the body. It usually begins in the hands or feet and gets worse with additional cycles of treatment. Most of the time, neuropathy improves gradually and may eventually go away after treatment.

Organ issues

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

Pain

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

Palliative care

Palliative care is appropriate for anyone, regardless of age, cancer stage, or the need for other therapies. It focuses on physical, emotional, social, and spiritual needs that affect quality of life.

Radiation dermatitis

Radiation dermatitis is a common side effect of radiation therapy. It can cause the skin to change color or cause dry and itchy skin, pain, peeling, blistering, or swelling. Your health care provider can help you find the best treatment for radiation dermatitis.

Second cancers

Chemotherapy, immunotherapy, radiation therapy, and hematopoietic cell transplant can increase your risk of a future, different cancer. Therefore, it's very important to continue follow-up visits with your doctors.

Therapy-related toxicity

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

Tumor lysis syndrome

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

Weight gain

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

Key points

- Supportive care is health care that has the goal of relieving symptoms caused by treatment and improves quality of life.
- All lymphoma treatments can cause unwanted health issues called side effects. Side effects depend on many factors. These factors include the drug type and dose, length of treatment, and the person.
- Some side effects are very rare. Ask your care team what to expect.
- Tell your care team about any new or worsening symptoms.
- During and after treatment, your health will be monitored for side effects and the return of diffuse large B-cell lymphoma.

Questions to ask

- Who will coordinate my care?
- Who should I call when I have questions or notice changes in my condition?
- How long should I wait if I notice changes in my condition?
- What should I do on weekends and other non-office hours?
- Will my care team be able to communicate with the emergency department or urgent care team?

What's next?

The next chapter explains how DLBCL is staged and treated.

5
DLBCL stages 1, 2, 3, and 4

40 DLBCL staging overview

41 Stages 1 and 2 non-bulky (limited)

41 Stages 1 and 2 bulky (limited)

42 Stages 3 and 4 (advanced)

43 Follow-up testing

43 Key points

44 Questions to ask

Treatment for diffuse large B-cell lymphoma (DLBCL) is based on imaging and other tests results. Treatment is often a combination of chemoimmunotherapy and radiation therapy.

DLBCL staging overview

Cancer staging is used to reflect prognosis and help guide treatment decisions. Prognosis is the likely course your lymphoma will take. In diffuse large B-cell lymphoma (DLBCL), your age, the number and location of sites affected by cancer, blood test results, and other factors play a role in prognosis.

A PET and/or CT scan is done to stage DLBCL. In addition to imaging test results, treatment decisions are based on histology and results of biomarker and genetic tests.

Histology is the overall appearance and the size, shape, and type of lymphoma cells.

There are different kinds of cancer staging systems. The Lugano Modification of the Ann Arbor Staging System is used for DLBCL.

In general, stages are as follows:

- **Stage 1** – Disease found in 1 lymph node or a group of nearby lymph nodes.
- **Stage 2** – Disease found in 2 or more lymph node groups on the same side of the diaphragm.
- **Stage 3** – Disease found in lymph nodes above and below the diaphragm on the same side of the body, or disease found in nodes above the diaphragm and in the spleen.
- **Stage 4** – Disease that has spread outside the lymphatic system to other parts of the body.

"When you are going through treatment that's difficult, remember it's about the cancer. Don't let the side effects of treatment become your focus!"



Stages 1 and 2 non-bulky (limited)

Initial treatment for non-bulky stage 1 or 2 limited disease is often 3 cycles of RCHOP. This is called first-line chemoimmunotherapy. DLBCL is restaged using PET/CT after 3 cycles of RCHOP and again after the last cycle.

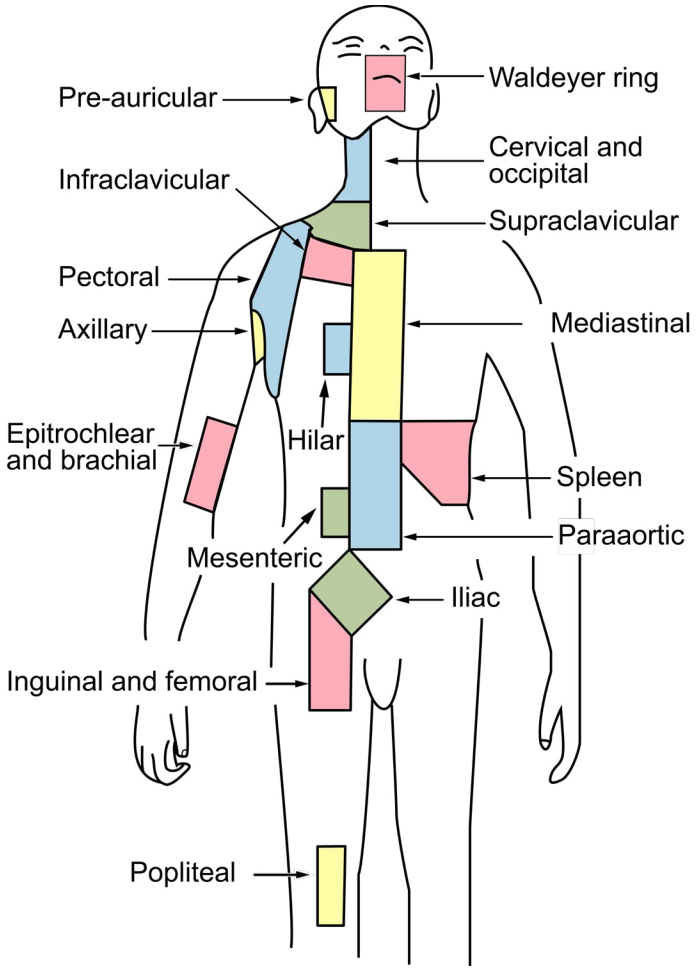
- If a complete response, you'll have 1 more cycle of RCHOP for a total of 4 cycles or involved-site radiation therapy (ISRT). Then you'll enter surveillance and be monitored for relapse.
- If a partial response, you'll have 1 to 3 more cycles of RCHOP for a total of 4 to 6 cycles or ISRT if a PET scan was positive for disease after 3 cycles of RCHOP.
- If disease progresses, you'll have another biopsy and be treated for refractory disease as discussed in *Chapter 6: Relapsed and refractory DLBCL*.

Stages 1 and 2 bulky (limited)

Bulky disease is a lesion 7.5 cm or larger. Treatment for stage 1 or 2 limited bulky disease is often 6 total cycles of RCHOP. This is called first-line chemoimmunotherapy. A type of radiation called involved-site radiation therapy (ISRT) might be added.

Lymph node regions are based on the Ann Arbor Staging System

Adapted from: Lymph_node_regions.jpg: https://commons.wikimedia.org/wiki/File:Lymph_node_regions.svg



DLBCL is restaged using PET/CT after 3 to 4 cycles of RCHOP and again after the last (6th) cycle.

- For a complete response, you'll finish the planned course of treatment. If you're in remission, then you'll enter surveillance and be monitored for relapse.
- For a partial response, you'll complete the planned course of treatment.
- For no response or if disease has progressed, you'll have another biopsy and be treated for refractory disease as discussed in *Chapter 6: Relapsed and refractory DLBCL*.

Stages 3 and 4 (advanced)

For stages 3 and 4, RCHOP or Pola-R-CHP chemoimmunotherapy is recommended and preferred. Chemotherapy regimens, such as DA-EPOCH-R, might be used for people with certain types of DLBCL and in those with HIV. A CT or PET scan might be done after 2 to 4 cycles to restage your lymphoma. For all first-line therapy options, see **Guide 4**.

Guide 4
First-line therapy options

Preferred therapies	• CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) plus Rituximab (or RCHOP) • Pola-R-CHP (Polatuzumab vedotin-piiq plus Rituximab plus Cyclophosphamide, Doxorubicin, Prednisone)
Other recommended therapies	• Dose-adjusted EPOCH (Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin) plus Rituximab (or DA-EPOCH-R)
Therapies for people with heart issues	• DA-EPOCH plus Rituximab • CDOP (Cyclophosphamide, Liposomal Doxorubicin, Vincristine, Prednisone) plus Rituximab • CEOP (Cyclophosphamide, Etoposide, Vincristine, Prednisone) plus Rituximab • GCVP (Gemcitabine, Cyclophosphamide, Vincristine, Prednisone) plus Rituximab
Therapies or people who are unwell or over 80 years of age with other health concerns	• CDOP plus Rituximab • Mini-CHOP plus Rituximab • GCVP plus Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

- For a complete or partial response, you'll finish the remaining cycles of treatment for a total of 6 cycles. Then you'll enter surveillance to be monitored for relapse.
- For no response or if disease has progressed, you'll have another biopsy and be treated for refractory disease as discussed in *Chapter 6: Relapsed and refractory DLBCL*.

Follow-up testing

After you've completed all cycles of treatment, a PET/CT scan will be done. Radiation therapy might be considered based on the initial stage of disease or response to treatment. Surveillance is a period of testing that begins after remission to monitor for the return of DLBCL. It includes a physical exam, health history, and blood tests every 3 to 6 months for 5 years. After 5 years, testing is done once a year or as needed.

Surveillance imaging may be considered for monitoring people without symptoms (asymptomatic). This may include a chest/abdomen/pelvis CT no more than every 6 months for 2 years. After 2 years, imaging is done as needed. Discuss with your care team if surveillance imaging is right for you.

Key points

- Chemoimmunotherapy, such as RCHOP and Pola-R-CHP, is the standard treatment for diffuse large B-cell lymphoma (DLBCL). Other treatments may include some or all of the drugs in RCHOP.
- A type of radiation called involved-site radiation therapy (ISRT) might be added to treatment. ISRT treats a small region or 1 area of your body.
- Treatment for non-bulky stage 1 or 2 disease is often 4 to 6 cycles of RCHOP.
- Bulky disease is 7.5 cm or larger. Treatment for bulky stage 1 or 2 disease is often 6 cycles of RCHOP.
- For stages 3 and 4, the recommended and preferred option is 6 cycles of RCHOP or Pola-R-CHP. Other chemoimmunotherapy regimens might be used.
- Surveillance is a period of testing that begins after remission to monitor for relapse or the return of DLBCL.

Questions to ask

- How large are the areas of lymphoma and where are they located in my body?
- Which treatment do you recommend and why?
- Will I spend time in the hospital?
- Are you planning for a hematopoietic cell transplant (HCT) or CAR T-cell therapy in the future?
- What side effects can I expect from this treatment?



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What's next?

The next chapter explains treatment options for DLBCL that returns after treatment or progresses during treatment.

6

Relapsed and refractory DLBCL

46 Relapse – Under 12 months

49 Relapse – Over 12 months

50 Refractory disease

51 2 or more relapses

52 Follow-up testing

52 Key points

52 Questions to ask

Diffuse large B-cell lymphoma (DLBCL) that returns is called relapse. The goal of treatment is to achieve remission again. When DLBCL progresses during treatment, it's called refractory. In relapsed and refractory disease, treatment options are based on if a hematopoietic cell transplant (HCT) or CAR T-cell therapy is planned.

In relapsed and refractory disease, the order, or sequence, of treatment is very important. It's based on the timing of relapse, and options like if you're able and want to have a hematopoietic cell transplant (HCT) or CAR T-cell therapy, and if treatment, such as CAR T-cell therapy or a clinical trial, is available in your area. Some treatments are done at specialized centers and require time and planning to access. Multiple factors are considered when choosing which treatment to give, at what time, and in what order.

Relapse – Under 12 months

Treatment options for relapsed disease are based on the time since finishing your last treatment. If DLBCL returned less than 12 months after your last treatment, then treatment options depend on if CAR T-cell therapy is or isn't planned. A clinical trial is also an option.

CAR T-cell therapy is planned

CD19-targeting CAR T-cell therapy is an option for relapses that occurred less than 12 months since treatment ended. CD19-targeting CAR T-cell therapy options include axicabtagene ciloleucel and lisocabtagene maraleucel.

The entire CAR T-cell process can take several weeks. This includes the appointment to have your T cells removed, the time it takes the lab to create your CAR T-cell therapy, and the appointment to have the T cells infused into your body. While waiting for CAR T-cell therapy, systemic therapy or radiation therapy might be given to prevent DLBCL from progressing.

- **Holding therapy** is systemic or radiation therapy given before T cells are removed from your body (prepheresis).
- **Bridging therapy** is systemic or radiation therapy given after the T cells are removed from your body (postpheresis) and while waiting for your CAR T cells to be created in the lab.

After completing CAR T-cell therapy, you'll have follow-up testing to monitor for relapse.

Holding therapy options can be found in **Guide 5A**.

Bridging therapy options can be found in **Guide 5B**.

Guide 5A Holding therapy options (before T cells are removed)
DHA (dexamethasone and cytarabine) plus platinum-based chemotherapy (Carboplatin, Cisplatin, or Oxaliplatin) with or without Rituximab
GDP (Gemcitabine, Dexamethasone, Carboplatin, or Cisplatin) plus Rituximab
GemOx (Gemcitabine, Oxaliplatin) with or without Rituximab
ICE (Ifosfamide, Carboplatin, Etoposide) with or without Rituximab
Polatuzumab vedotin-piiq with or without Rituximab
Involved-site radiation therapy (ISRT)

Guide 5B Bridging therapy options (after T cells are removed)
DHA (dexamethasone and cytarabine) plus platinum-based chemotherapy (Carboplatin, Cisplatin, or Oxaliplatin) with or without Rituximab
GDP (Gemcitabine, Dexamethasone, Carboplatin, or Cisplatin) plus Rituximab
GemOx (Gemcitabine, Oxaliplatin) with or without Rituximab
ICE (Ifosfamide, Carboplatin, Etoposide) with or without Rituximab
Polatuzumab vedotin-piiq with or without Rituximab with or without Bendamustine
Involved-site radiation therapy (ISRT)

CAR T-cell therapy not planned

If CAR T-cell therapy isn't planned, then options include:

- Clinical trial
- Second-line therapy, see **Guide 6**.
- Palliative involved-site radiation therapy (ISRT) to treat lymph nodes where lymphoma was originally found, or lymphoma located in a small region or 1 area of your body
- Best supportive care to improve quality of life

Guide 6
Second-line therapy options: CAR T-cell therapy not planned

Preferred therapies	• GemOx plus Epcoritamab-bysp • GemOx plus Glofitamab-gxbm • GemOx plus Polatuzumab vedotin-piiq plus Rituximab • Lenalidomide plus Tafasitamab-cxix • Polatuzumab vedotin-piiq with or without Bendamustine with or without Rituximab • Mosunetuzumab-axgb plus Polatuzumab vedotin-piiq • Glofitamab-gxbm plus Polatuzumab vedotin-piiq
Other recommended therapies	• CEOP plus Rituximab • DHA (Dexamethasone and Cytarabine) plus platinum-based chemotherapy (Carboplatin, Cisplatin, or Oxaliplatin) with or without Rituximab • ESHAP (Etoposide, Methylprednisolone, Cytarabine, Cisplatin) with or without Rituximab • GDP with or without Rituximab • GemOx with or without Rituximab (if can't have Epcoritamab-bysp, Glofitamab-gxbm, or Polatuzumab vedotin-piiq) • ICE with or without Rituximab
Therapies used in certain cases	• Brentuximab vedotin • Ibrutinib (for non-germinal center B-cell DLBCL) • Lenalidomide with or without Rituximab (for non-germinal center B-cell DLBCL)

An FDA-approved biosimilar might be used in place of some therapies.

After a complete response, you'll have follow-up testing.

After a partial response, no response, or disease progression, see treatment options explained under "2 or more relapses" on page 51.

Relapse – Over 12 months

Treatment options for DLBCL that returned more than 12 months since treatment ended are described next.

HCT is planned

If autologous (self) hematopoietic cell transplant (HCT) is planned, then see second-line therapy in **Guide 7**.

After a complete response, next options include:

- Autologous HCT (also called HDT/ASCR
- Clinical trial
- In some cases, an allogeneic (donor) HCT
- ISRT might be added

After a partial response, next options include:

- CAR T-cell therapy (axicabtagene ciloleucel or lisocabtagene maraleucel)
- Autologous (self) HCT
- Clinical trial
- In some cases, an allogeneic (donor) HCT
- ISRT might be added

If there's no response or disease progresses, then see "2 or more relapses" on page 51.

Guide 7
Second-line therapy options: HCT planned

Preferred therapies	• DHA plus platinum-based chemotherapy (Carboplatin, Cisplatin, or Oxaliplatin) with or without Rituximab • GDP with or without Rituximab • ICE with or without Rituximab
Other recommended therapies	• ESHAP with or without Rituximab • GemOx with or without Rituximab

An FDA-approved biosimilar might be used in place of some therapies.

HCT not planned

If you aren't receiving a hematopoietic cell transplant (HCT), then options include:

- Clinical trial
- Second-line therapy, see **Guide 8**
- Palliative ISRT
- Best supportive care

After a complete response, you'll have follow-up testing.

After a partial response, no response, or disease progression, see "2 or more relapses" on page 51.

Refractory disease

Refractory disease might be treated with CAR T-cell therapy. While waiting for CAR T-cell therapy, you might have holding and bridging therapy shown in **Guide 5A** and **Guide 5B**.

Guide 8
Second-line therapy options: HCT not planned

Preferred therapies	• CD19-targeting CAR T-cell therapy (Lisocabtagene maraleucel) (with holding therapy and bridging therapy as needed) • GemOx plus Epcoritamab-bysp • GemOx plus Glofitamab-gxbm • GemOx plus Polatuzumab vedotin-piiq plus Rituximab • Lenalidomide plus Tafasitamab-cxix • Polatuzumab vedotin-piiq with or without Bendamustine with or without Rituximab • Mosunetuzumab-axgb plus Polatuzumab vedotin-piiq • Glofitamab-gxbm plus Polatuzumab vedotin-piiq
Other recommended therapies	• CEOP with or without Rituximab • GDP with or without Rituximab • GemOx with or without Rituximab (if can't have Epcoritamab-bysp, Glofitamab-gxbm, or Polatuzumab vedotin-piiq) • Rituximab alone
Therapies used in certain cases	• Brentuximab vedotin • Ibrutinib (for non-germinal center B-cell DLBCL) • Lenalidomide with or without Rituximab (for non-germinal center B-cell DLBCL)

An FDA-approved biosimilar might be used in place of some therapies.

Other options include:

- Clinical trial
- Second-line therapy, see **Guide 6**
- Palliative ISRT
- Best supportive care
- RT with or without chemoimmunotherapy followed by autologous HCT may be an option in some people with localized disease

After a complete response, you'll have follow-up testing.

After a partial response, no response, or disease progression, see treatment options listed next under "2 or more relapses."

2 or more relapses

For a partial response, second or third relapse, or disease progression, then treatment options include:

- Third-line therapy, see **Guide 9**
- A systemic therapy not used before
- Clinical trial
- Palliative ISRT
- Best supportive care

For a complete or partial response to treatment, an allogeneic (donor) HCT with or without ISRT might be an option in some cases.

Guide 9
Third-line and next-line therapy options

Second-line therapies not used before are options.

Preferred therapies	CD19-targeting CAR T-cell therapy (preferred) (in alphabetical order) • Axicabtagene ciloleucel • Lisocabtagene maraleucel • Tisagenlecleucel
	Bispecific antibody therapy (including people with disease progression after HCT or CAR T-cell therapy) (in alphabetical order) • Epcoritamab-bysp • Glofitamab-gxbm
Other recommended therapies	• Lenalidomide plus Brentuximab vedotin plus Rituximab • Loncastuximab tesirine-lpyl • Selinexor (including people with disease progression after HCT or CAR T-cell therapy)

An FDA-approved biosimilar might be used in place of some therapies.

Follow-up testing

After completing treatment, you'll have the following tests to monitor for relapse:

- A physical exam, health history, and blood tests every 3 to 6 months for 5 years. After 5 years, these tests are done once a year or as needed.
- Surveillance imaging may be considered for people without symptoms (asymptomatic). This may include a chest/abdomen/pelvis CT no more than every 6 months for 2 years. After 2 years, imaging is done as needed. Discuss with your care team if surveillance imaging is right for you.

It's important to keep any follow-up doctor visits and imaging test appointments. Seek good routine medical care, including regular doctor visits for preventive care and cancer screening.

Key points

- Diffuse large B-cell lymphoma (DLBCL) that returns is called relapse. Treatment options for relapsed disease are based on the time since treatment was completed. The goal of treatment is to achieve remission again.
- If DLBCL returned less than 12 months since treatment ended, treatment is based on if CAR T-cell therapy is planned.
- If DLBCL returned more than 12 months since treatment ended, treatment is based on if a hematopoietic cell transplant (HCT) is planned.
- When DLBCL progresses during treatment, it's called refractory. Refractory disease might be treated with CAR T-cell therapy. Other treatment options are available.
- After completing treatment, you'll be monitored for the return of cancer. Keep all follow-up doctor visits and imaging test appointments.

Questions to ask

- Which treatment do you recommend and why?
- Why are some treatment options preferred over others?
- Does this treatment offer a cure? If not, how well can treatment stop DLBCL from growing?
- Does the order of treatments matter?
- Is HCT, CAR T-cell therapy, or clinical trial an option for me?

What's next?

The next chapter explains treatment for lymphomas with a specific rearrangement in the *ALK* gene, called ALK-positive large B-cell lymphomas.

7

ALK-positive large B-cell lymphomas

54 Overview

54 Treatment

56 Key points

56 Questions to ask

ALK-positive large B-cell lymphoma (ALK+ LBCL) is caused by a rearrangement in the *ALK* gene. ALK+ LBCL is usually treated with radiation therapy and chemotherapy.

Overview

ALK-positive large B-cell lymphoma (ALK+ LBCL) is caused by a rearrangement in the anaplastic lymphoma kinase (*ALK*) gene. *ALK* tells your body how to make proteins that help cells talk to each other. ALK+ LBCL expresses the ALK protein but usually lacks CD20 (is CD20-). A gene fusion called *CLTC::ALK* is common in ALK+ LBCL. It's written as t(2;17)(p23;q23). The ALK rearrangement makes this lymphoma difficult to treat.

Most persons with ALK+ LBCL have advanced disease with lymphoma found inside (nodal) and outside (extranodal) the lymph nodes. ALK+ LBCL is more commonly seen in people around 40 years of age, assigned male at birth.

Treatment

Currently, there's no standard of care or agreement on treatment for ALK+ LBCL. It's usually treated with chemotherapy. Involved-site radiation therapy (ISRT) is preferred when treating localized disease. A clinical trial is recommended if available and it's what you want. Since this lymphoma is often CD20-, rituximab isn't given.

"Drug treatment for DLBCL was intense and strong. And, I had unusual side effects. I told my care team right away when I noticed a side effect. This really helped. They were very good at treating it!"



First-line treatment options include:

- Clinical trial (recommended if available)
- ISRT (preferred for localized disease)
- DA-EPOCH
- CHOEP
- CHOP
- Mini-CHOP
- HyperCVAD
- CODOX-M/IVAC

Treatment options for relapsed or refractory disease include:

- Clinical trial (recommended if available).
- A platinum-based chemotherapy followed by an autologous (self) hematopoietic cell transplant (HCT). Platinum-based chemotherapy includes carboplatin, cisplatin, or oxaliplatin.
- ALK inhibitors (targeted therapy), such as alectinib and lorlatinib, followed by an allogeneic (donor) HCT.
- If CD19+, consider CD19-directed CAR T-cell therapy (axicabtagene ciloleucel, lisocabtagene maraleucel, or tisagenlecleucel).

Chemoimmunotherapy regimens for ALK-positive large B-cell lymphoma

Some regimens might be preferred over others, depending on your age and other factors.

- **DA-EPOCH** is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.
- **CHOEP** is cyclophosphamide, doxorubicin, etoposide, and prednisone.
- **CHOP** is cyclophosphamide, doxorubicin, vincristine, and prednisone.
- **Mini-CHOP** is a lower-dose combination of cyclophosphamide, doxorubicin, vincristine, and prednisone.
- **HyperCVAD** is cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine.
- **CODOX-M/R-IVAC** is cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with rituximab, ifosfamide, etoposide, and cytarabine.

Key points

- ALK-positive large B-cell lymphoma (ALK+ LBCL) is caused by a rearrangement in the *ALK* gene.
- A gene fusion called *CLTC::ALK* is common in ALK+ LBCL. It's written as t(2;17)(p23;q23).
- Most people with ALK+ LBCL have advanced disease with lymphoma found inside and outside the lymph nodes.
- ALK+ LBCL is usually treated with radiation therapy and chemotherapy.
- A clinical trial is recommended if available and it's what you want.
- Treatment for relapse or refractory disease might be a hematopoietic cell transplant (HCT).

Questions to ask

- Which treatment do you recommend and why?
- Does this treatment offer a cure? If not, how well can treatment stop the lymphoma from growing?
- What side effects can I expect from this treatment?
- Does the order of treatments matter?
- Is a hematopoietic cell transplant (HCT), CAR T-cell therapy, or a clinical trial an option for me?

What's next?

The next chapter explains treatment for a type of large B-cell lymphoma, called primary mediastinal large B-cell lymphoma, that develops in the area behind the sternum (breastbone).

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Primary mediastinal large B-cell lymphomas

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60 Follow-up testing

60 Relapsed or refractory disease

60 Key points

60 Questions to ask

Primary mediastinal large B-cell lymphoma (PMBL) develops in the area of the chest behind the breastbone called the mediastinum. Treatment is chemoimmunotherapy.

Overview

In primary mediastinal large B-cell lymphoma (PMBL), a tumor forms most often behind the breastbone (sternum). This can cause a cough, shortness of breath, chest discomfort, or swelling of the head and neck, due to the tumor pressing on the windpipe and the large veins above the heart (superior vena cava syndrome). Enlarged lymph nodes in this area can also be found. PMBL can spread to organs and tissues such as the lungs, pericardium (sac around the heart), liver, gastrointestinal tract, ovaries, adrenal glands, and central nervous system.

PMBL is more commonly seen in people 30 to 40 years of age, assigned female at birth.

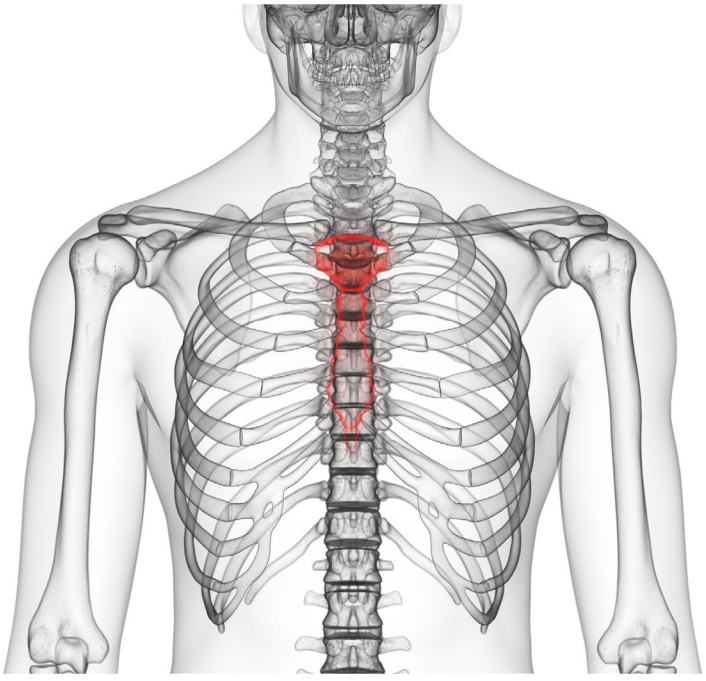
Treatment

Currently, the most used treatment options are:

- 6 cycles of DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin with rituximab).
- 4 to 6 cycles of RCHOP-14 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).
- 6 cycles of RCHOP-21 (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Mediastinum

Mediastinal lymphomas are growths found in the area of the chest that separates the lungs, called the mediastinum. In primary mediastinal large B-cell lymphoma (PMBL), a tumor often forms behind the breastbone (sternum).



A PET/CT scan is done after treatment to restage the lymphoma. Some of the tumor can remain after treatment, and a PET/CT helps find any residual masses. A biopsy might be done.

After a complete response

If there's a complete response:

- After DA-EPOCH-R, you'll enter observation.
- After 6 cycles of RCHOP-14, you'll enter observation.
- After 6 cycles of RCHOP-21, you might have involved-site radiation therapy (ISRT) to treat lymphoma found in a area of your body.
- After 4 cycles of RCHOP-14, you may have 3 cycles of ifosfamide, carboplatin, and etoposide (ICE). Rituximab might be added.

After a partial response or lymphoma progresses

If there's a partial response or lymphoma progresses, a biopsy may be done before treatment with

- ISRT
- Pembrolizumab
- Nivolumab with or without brentuximab vedotin
- Options found in *Chapter 6: Relapsed and refractory DLBCL*

"My diagnosis was sudden and unexpected. I am a non-smoker and runner and had just completed a half marathon before diagnosis. My only symptom was a persistent cough. My tumor was causing fluid to back up in my heart and lungs."



Follow-up testing

After a complete response (remission), you'll be monitored for relapse with the following tests:

- A physical exam, health history, and blood tests every 3 to 6 months for 5 years. After 5 years, these tests are done once a year or as needed.
- Surveillance imaging may be considered for monitoring people without symptoms (asymptomatic). This may include a chest/abdomen/pelvis CT no more than every 6 months for 2 years. After 2 years, imaging is done as needed. Discuss with your care team if surveillance imaging is right for you.

Relapsed or refractory disease

Lymphoma that returns is called relapse. When lymphoma progresses during treatment, it's called refractory. Treatment options vary by type of DLBCL, whether disease was refractory to initial therapy, and timing of relapse.

- Treatment may include a different chemoimmunotherapy than used before, CAR-T therapy, or hematopoietic cell transplant.
- Or it may be treated as discussed in *Chapter 6: Relapsed and refractory DLBCL*.

Key points

- In primary mediastinal large B-cell lymphoma (PMBL), a tumor most often forms in the chest area behind the breastbone (sternum).
- Treatment is chemoimmunotherapy.
- After a complete response (remission), you'll be monitored for relapse.
- Immunotherapy, such as pembrolizumab or nivolumab with or without brentuximab vedotin (an antibody-drug conjugate), CAR-T therapy, or a hematopoietic cell transplant (HCT), might be used to treat lymphoma that progresses, relapses, or is refractory.

Questions to ask

- Which treatment do you recommend and why?
- Does this treatment offer a cure? If not, how well can treatment stop the lymphoma from growing?
- What order of treatments are you considering and why?
- Am I a candidate for a clinical trial, CAR T-cell therapy, or an HCT?
- What is the likelihood the lymphoma will return?

What's next?

The next chapter explains treatment for high-grade B-cell lymphomas.

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High-grade B-cell lymphomas

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63 HGBL with *MYC* and *BCL2*

63 HGBL with *MYC* and *BCL6*

63 HGBL, not otherwise specified

64 Relapsed and refractory disease

64 Key points

64 Questions to ask

High-grade B-cell lymphomas (HGBLs) are very aggressive, fast-dividing tumors. This chapter provides information on HGBL with gene rearrangements and HGBL, not otherwise specified (HGBL, NOS).

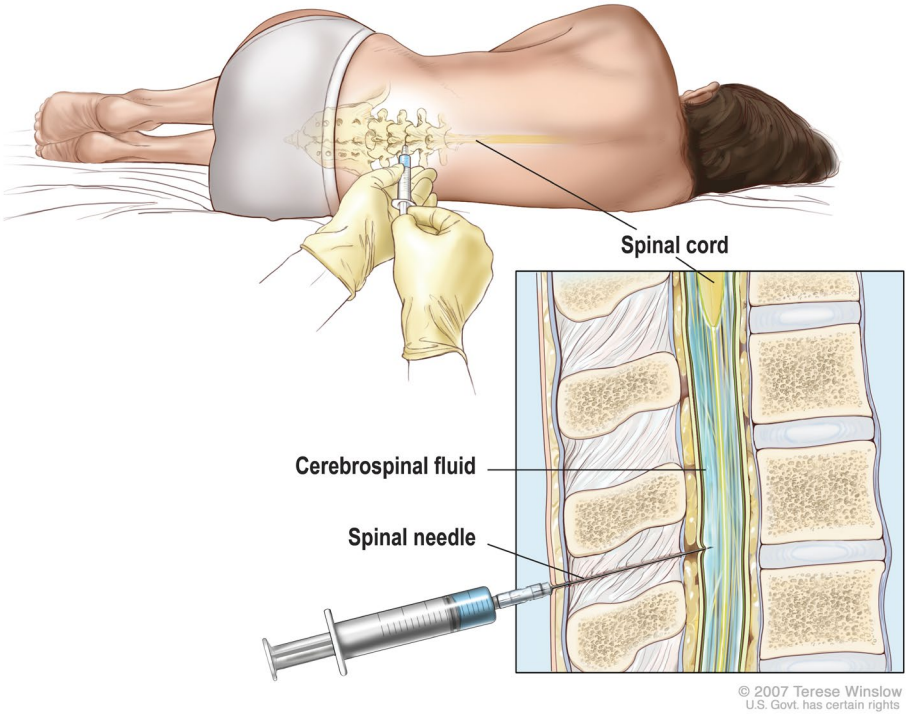
Overview

High-grade B-cell lymphomas (HGBLs) have gene rearrangements, such as MYC, or other high-risk features that make treatment a challenge. People with HGBL often have elevated lactate dehydrogenase (LDH), bone marrow and central nervous system (CNS) involvement, and a high International Prognostic Index (IPI) score. Since lymphoma is often found in the bone marrow and central nervous system, a lumbar puncture might be done. In addition, intrathecal chemotherapy might be given at the time of a lumbar puncture to prevent CNS disease.

Currently, there's no standard of care or agreement on treatment for HGBLs. Treatment is usually chemoimmunotherapy. Radiation therapy might be given. A clinical trial is recommended, if available and it's what you want.

Lumbar puncture

A lumbar puncture is a procedure that removes spinal fluid.



HGBL with *MYC* and *BCL2*

People who have HGBL with gene rearrangements of *MYC* and *BCL2* are treated as follows:

- Clinical trial (recommended)
- ISRT after chemoimmunotherapy (preferred for localized disease)
- DA-EPOCH-R
- RCHOP
- R-mini-CHOP
- R-HyperCVAD
- R-CODOX-M/R-IVAC

HGBL with *MYC* and *BCL6*

HGBL with gene rearrangements of *MYC* and *BCL6* is often treated with DA-EPOCH-R or other systemic therapies used for DLBCL.

HGBL, not otherwise specified

HGBL, not otherwise specified (HGBL-NOS), includes tumors that aren't well defined or don't fall into another HGBL category.

Treatment options include:

- Clinical trial (recommended)
- ISRT chemoimmunotherapy for early-stage disease
- DA-EPOCH-R
- Pola-R-CHP
- RCHOP
- R-mini-CHOP
- R-HyperCVAD
- R-CODOX-M/R-IVAC

High-grade B-cell lymphoma chemoimmunotherapy regimen definitions

- **DA-EPOCH-R** is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab.
- **Pola-R-CHP** is polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone.
- **RCHOP** is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
- **Mini-RCHOP** is a modified, lower-dose version of RCHOP.
- **R-HyperCVAD** is rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine.
- **R-CODOX-M/R-IVAC** is rituximab, cyclophosphamide, vincristine, doxorubicin, and methotrexate alternating with rituximab, ifosfamide, etoposide, and cytarabine.

Relapsed and refractory disease

For relapsed and refractory disease treatment options, see *Chapter 6: Relapsed and refractory DLBCL*.

Key points

- High-grade B-cell lymphomas (HGBLs) are aggressive, fast-dividing tumors.
- People with HGBL have elevated lactate dehydrogenase (LDH), bone marrow and central nervous system involvement, and a high International Prognostic Index (IPI) score.
- A clinical trial is recommended for people with HGBL. Treatment options may include radiation therapy for localized disease and chemoimmunotherapy.
- HGBL, not otherwise specified (HGBL-NOS) includes tumors that aren't well defined or don't fall into another HGBL category.

Questions to ask

- What do the test results tell you about my lymphoma?
- Which treatment do you recommend and why?
- How many rounds of treatment do you think I'll need?
- Are you planning for a hematopoietic cell transplant (HCT) or CAR T-cell therapy in the future?
- Am I a candidate for a clinical trial?

What's next?

The next chapter provides information about a type of lymphoma called mediastinal gray zone lymphoma. It's treated with chemotherapy.

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Mediastinal gray zone lymphomas

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67 Key points

67 Questions to ask

Mediastinal gray zone lymphoma (MGZL) has overlapping features of primary mediastinal B-cell lymphoma and Hodgkin lymphoma. Treatment is usually chemotherapy. Radiation therapy might be added.

Overview

Gray zone lymphomas have overlapping features of primary mediastinal large B-cell lymphoma and classic Hodgkin lymphoma. This means that the cells are large but can vary in size and might look like Hodgkin cells (Reed-Sternberg cells). Reed-Sternberg cells are large, abnormal lymphocytes that may contain more than 1 nucleus.

Mediastinal gray zone lymphomas

Mediastinal lymphomas are found behind the breastbone (sternum) in the part of the chest that separates the lungs and holds the heart. Mediastinal gray zone lymphomas (MGZLs) and primary mediastinal large B-cell lymphomas aren't the same. They are treated differently. Primary mediastinal lymphomas are discussed in Chapter 8.

MGZLs are more commonly seen in people between 20 to 40 years of age, assigned male at birth. They are characterized by the presence of a large mediastinal mass. Lymph nodes above the collar bone (supraclavicular) may be involved.

An expert hematopathologist review is essential to confirm the diagnosis of MGZL.

"Be your own advocate. Talk to someone who has gone through the same thing as you. Ask a lot of questions, even the ones you are afraid to ask. You have to protect yourself and ensure you make the best decisions for you, and get the best care for your particular situation."



Treatment

Since MGZL has features of both classical Hodgkin lymphoma and non-Hodgkin PMBL, treatment is a challenge. Currently, there's no standard of care or agreement on treatment. MGZL is usually treated with an anthracycline-based chemotherapy. Anthracyclines include doxorubicin and liposomal doxorubicin. If the tumor cells are CD20+, rituximab might be added to chemotherapy. This is called chemoimmunotherapy. Involved-site radiation therapy (ISRT) may be added for localized disease. Pola-R-CHP is not recommended for MGZL.

Key points

- Gray zone lymphomas have overlapping features of primary mediastinal large B-cell lymphoma and classic Hodgkin lymphoma.
- Mediastinal lymphomas are found behind the breastbone (sternum) in the part of the chest that separates the lungs and holds the heart.
- An expert hematopathologist review is essential to confirm the diagnosis of mediastinal gray zone lymphoma (MGZL).
- MGZL is usually treated with chemotherapy. Rituximab might be added to chemotherapy if the tumor cells are CD20+. Involved-site radiation therapy (ISRT) may be added for localized disease.

People with gray zone lymphomas are best managed in cancer centers with experience in treating this type of lymphoma.

Questions to ask

- Where do you think we should start with treatment?
- How many rounds of treatment do you think I'll need?
- Will I spend time in the hospital?
- Does this treatment offer a cure?
- What side effects should I look for and when should I contact my care team?

What's next?

The next chapter provides information about a type of diffuse large B-cell lymphoma that causes skin lesions.

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Primary cutaneous DLBCL, leg type

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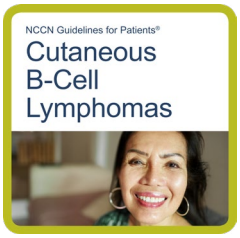
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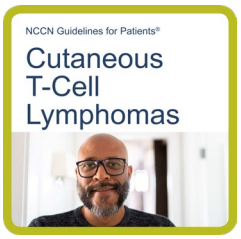
In primary cutaneous diffuse large B-cell lymphoma (PC-DLBCL), leg type, abnormal B-cell lymphocytes cause skin lesions. Although the skin is involved, the skin cells themselves aren't cancerous. Despite its name, PC-DLBCL, leg type can be found anywhere on the body. Treatment options are based on many factors.

Overview

Primary cutaneous diffuse large B-cell lymphoma (PC-DLBCL), leg type consists of large, transformed B cells that typically appear as red or bluish-red tumors on the skin. Despite its name, the disease can involve the torso, arms, legs, buttocks, or anywhere on the body. PC-DLBCL, leg type can also spread to areas other than the skin. An expert hematopathologist review is essential to confirm the diagnosis of PC-DLBCL, leg type. A skin biopsy is done to distinguish between PC-DLBCL, leg type from other types of primary cutaneous lymphomas (lymphomas of the skin).

More information on other types of primary cutaneous lymphomas can be found in the *NCCN Guidelines for Patients: Cutaneous B-Cell Lymphomas* and *NCCN Guidelines for Patients: Cutaneous T-Cell Lymphomas*, available at NCCN.org/patientguidelines and on the NCCN Patient Guides for Cancer app.





Treatment

Treatment is based on the number of skin lesions and their location. This is called staging. Skin lesions/tumors will be measured by their depth, height, size, and region of the body. Lesions are often measured in centimeters (cm). Body regions are based on regional lymph node drainage patterns. Body regions include head/neck, chest, upper arm, lower arm and hand, abdomen and genitals, upper leg, lower leg and feet, upper back, and lower back and buttocks.

Disease may be solitary, regional, generalized skin only, or outside the skin (extracutaneous). PC-DLBCL is a non-germinal center B-cell DLBCL which influences the type of initial therapy. At the end of treatment, imaging tests are needed to assess response.

Solitary or regional disease

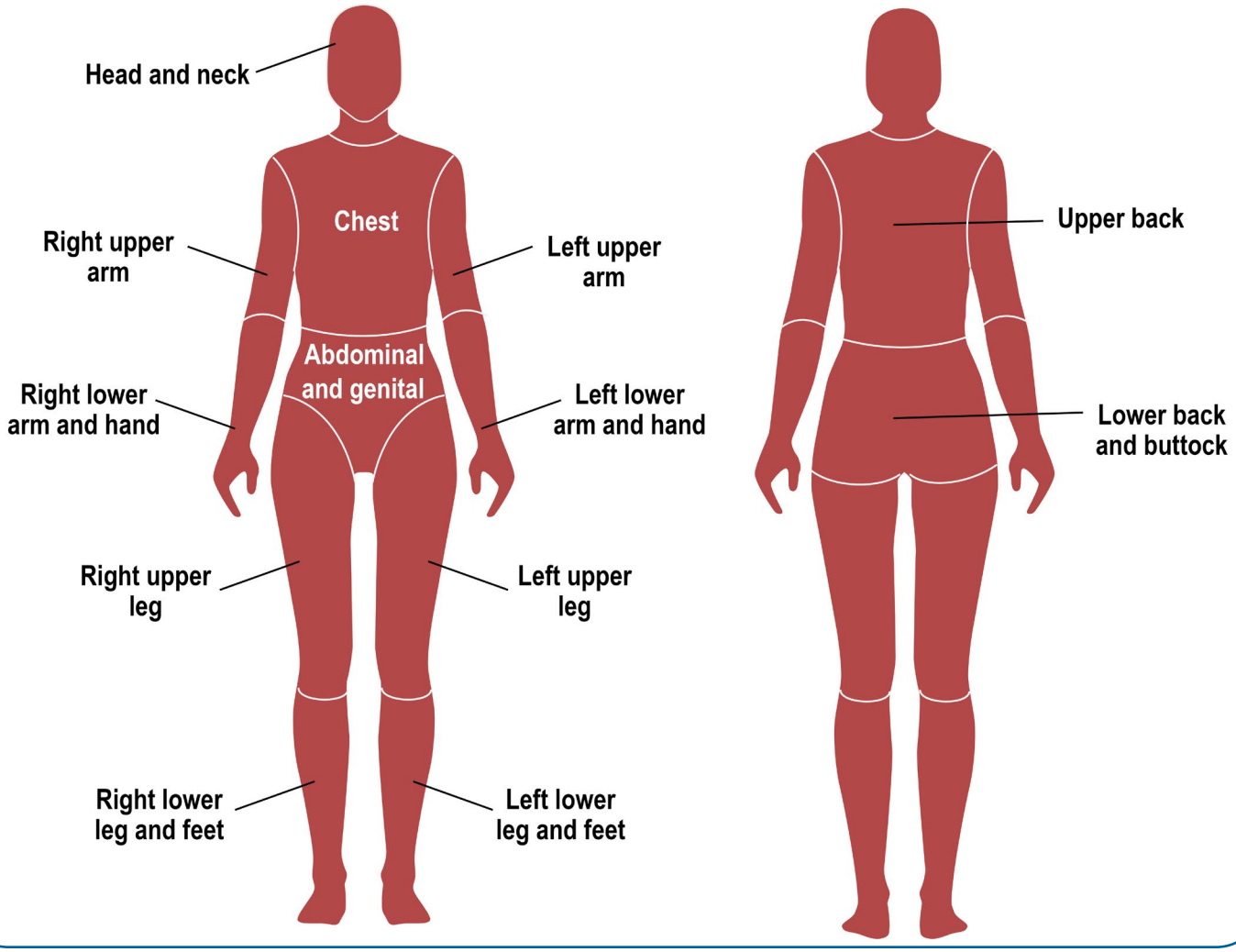
A solitary lesion is 1 lesion. Regional disease can be multiple lesions limited to 1 body region or 2 adjoining regions. Disease area will be measured.

Options include:

- Pola-R-CHP (polatuzumab vedotin-piiq, rituximab, cyclophosphamide, doxorubicin, and prednisone) with local involved-site radiation therapy (ISRT)
- Local ISRT
- Clinical trial

After a complete response, you'll have follow-up testing to monitor for relapse.

Body regions are based on regional lymph node drainage patterns.



Generalized, skin-only disease

Generalized, skin-only disease covers a larger area of the body than regional disease. There are multiple lesions that involve 2 or more body regions not next to one another. Disease isn't found in lymph nodes, blood, or other organs. Treatment works inside the body to target the skin lesions. ISRT might be used to target a specific area of skin.

Skin-only disease is initially treated with Pola-R-CHP. ISRT might be added to treat the skin lesions. A clinical trial is also an option.

After a complete response, you'll have imaging tests and be monitored for relapse with follow-up testing.

Extracutaneous disease

Extracutaneous disease is found outside the skin. It might be found in the lymph nodes, blood, or organs. Treatment is based on the stage of diffuse large B-cell lymphoma (DLBCL) as discussed in *Chapter 5: DLBCL stages 1, 2, 3, and 4*.

Follow-up testing

After a complete response, you'll be monitored for relapse with the following tests:

- A physical exam, health history, and blood tests every 3 to 6 months for 5 years. After 5 years, these tests will be done once a year or as needed.
- Surveillance imaging may be considered for monitoring those without symptoms (asymptomatic). This may include a chest/abdomen/pelvis CT no more than every 6 months for 2 years. After 2 years, imaging will be done as needed. Discuss with your care team if surveillance imaging is right for you.

Relapsed and refractory disease

For a relapse, if not given before, you might be treated with Pola-R-CHP or local radiation therapy (ISRT). Other treatment options are based on if relapse occurred less than 12 months or more than 12 months since your initial treatment ended. For more information, see *Chapter 6: Relapsed and refractory DLBCL*.

Key points

- Primary cutaneous diffuse large B-cell lymphoma (PC-DLBCL), leg type consists of large, transformed B cells that typically appear as red or bluish-red tumors on the skin. It isn't skin cancer.
- Despite its name, PC-DLBCL, leg type can be found anywhere on the body. Treatment is based on the number of skin lesions and their location. This is called staging.
- Disease may be solitary, regional, generalized skin only, or outside the skin (extracutaneous).
- A solitary lesion is 1 lesion.
- Regional lesions can be multiple lesions limited to 1 body region or 2 adjoining regions.
- Generalized skin-only disease covers a larger area of the body than regional disease. There are multiple lesions that involve 2 or more body regions not next to one another.
- Extracutaneous (outside the skin) disease might be found in the lymph nodes, blood, or organs.

Questions to ask

- What can I expect from treatment and what are the risks?
- How can I find a dermatologist or oncologist that specializes in lymphomas of the skin?
- What side effects should I look for and when should I contact my care team?
- How can I prepare for the possibility of relapse?
- Will the treatment I choose today affect my choices if lymphoma relapses or is refractory?

What's next?

The next chapter provides information about resources and where you can get support.

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Other resources

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Want to learn more? Here's how you can get additional help.

What else to know

This guide helps you know your options so you can make informed decisions and improve your cancer care. But it's not the only resource that you have.

Ask for as much information and help as you need. Many people are interested in learning more about:

- Finding an oncologist who's an expert in treating lymphoma
- Making treatment decisions, including participating in a clinical trial
- The details of treatment and possible side effects
- Getting financial help
- Coping with the stress of having lymphoma

What else to do

Your health care center can help you with next steps. It often has on-site resources to help meet your needs and find answers to your questions. Health care centers can also inform you of resources in your community.

In addition to help from your providers, the resources listed in the next section provide support for many people like yourself.

Where to get help

Look through the list below and visit the provided websites to learn more about these organizations.

AnCan Foundation
ancan.org

Blood & Marrow Transplant Information Network
bmtinfonet.org

Blood Cancer United
bloodcancerunited.org

Cancer*Care*
cancercare.org

Cancer Hope Network
cancerhopenetwork.org

GRACE
cancergrace.org

HealthTree Foundation
healthtree.org

Imerman Angels
imermanangels.org

Lymphoma Research Foundation
lymphoma.org

National Bone Marrow Transplant Link (nbmtLINK)
nbmtlink.org

NMDP
nmdp.org

Stupid Cancer
stupidcancer.org

Triage Cancer
triagecancer.org

Questions to ask

- Who can I talk to about help with housing, food, and other basic needs?
- What help is available for transportation, childcare, and home care?
- What other services are available to me and my caregivers?
- How can I connect with others and build a support system?
- Who can I talk to if I don't feel safe at home, at work, or in my neighborhood?



Let us know what you think!

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



Words to know

allogeneic hematopoietic cell transplant (allogeneic HCT)
Cancer treatment that replaces a person's bone marrow and immune system with donor cells to fight the lymphoma.

autologous hematopoietic cell transplant (autologous HCT)
Cancer treatment that destroys a person's bone marrow then rebuilds it with their own healthy stem cells. Also called high-dose therapy with autologous stem cell rescue (HDT/ASCR).

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

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

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

biosimilar
A drug that's almost identical to a drug made by another company. It's been approved by the U.S. FDA and must be used in the same way and at the same dose as the other drug.

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

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

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

chromosome
Structures within cells that contain coded instructions for cell behavior.

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

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

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

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

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

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

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

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

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

hematopoietic cell transplant (HCT)
A cancer treatment that replaces a person's bone marrow and immune system with healthy cells to fight the lymphoma.

high-grade B-cell lymphoma (HGBL)
A type of lymphoma that grows and spreads quickly and has severe symptoms.

histology
The study of tissues and cells under a microscope.

imaging test
A test that makes pictures of areas inside the body.

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

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

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

involved-site radiation therapy (ISRT)
Radiation therapy that treats cancer found in a small region or 1 area of the body.

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

lymph
A clear fluid containing white blood cells.

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

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

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

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

mediastinal gray zone lymphoma (MGZL)
A type of lymphoma with overlapping features of Hodgkin lymphoma and primary mediastinal large B-cell lymphoma found in the mediastinum (the area behind the breastbone).

monitoring
A period of testing for changes in lymphoma status.

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

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

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

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

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

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

primary mediastinal large B-cell lymphoma (PMBL)
A fast-growing type of lymphoma that develops from B cells in the mediastinum (the area behind the breastbone).

prognosis
The likely course a disease will take.

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

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

recurrence
Return of lymphoma after a cancer-free period.

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

refractory cancer
Lymphoma that doesn't improve with treatment.

relapse
Return or worsening of lymphoma after a period of improvement.

remission
Minor or no signs of disease.

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

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

translocation
A switching of parts between 2 chromosomes.

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

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



We want your feedback!

Our goal is to provide helpful and easy-to-understand information on cancer. Take our survey to let us know what we got right and what we could do better.
NCCN.org/patients/feedback

NCCN Contributors

This patient guide is based on the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for B-Cell Lymphomas, Version 4.2026. It was adapted, reviewed, and published with help from the following people:

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Cleveland, Ohio

City of Hope National Medical Center
Duarte, California

Dana-Farber Cancer Institute
Boston, Massachusetts

Duke Cancer Institute
Durham, North Carolina

Fox Chase Cancer Center
Philadelphia, Pennsylvania

Fred & Pamela Buffett Cancer Center
Omaha, Nebraska

Fred Hutchinson Cancer Center
Seattle, Washington

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Salt Lake City, Utah

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Johns Hopkins Kimmel Cancer Center
Baltimore, Maryland

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Boston, Massachusetts

Mayo Clinic Comprehensive Cancer Center
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Jacksonville, Florida
Rochester, Minnesota

Memorial Sloan Kettering Cancer Center
New York, New York

Moffitt Cancer Center
Tampa, Florida

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Chicago, Illinois

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Buffalo, New York

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St. Louis, Missouri

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Memphis, Tennessee

Stanford Cancer Institute
Stanford, California

The Ohio State University Comprehensive Cancer Center -
James Cancer Hospital and Solove Research Institute
Columbus, Ohio

The UChicago Medicine Comprehensive Cancer Center
Chicago, Illinois

The University of Texas MD Anderson Cancer Center
Houston, Texas

UC Davis Comprehensive Cancer Center
Sacramento, California

UC San Diego Moores Cancer Center
La Jolla, California

UCLA Jonsson Comprehensive Cancer Center
Los Angeles, California

UCSF Helen Diller Family Comprehensive Cancer Center
San Francisco, California

University of Colorado Cancer Center
Aurora, Colorado

University of Michigan Rogel Cancer Center
Ann Arbor, Michigan

University of Wisconsin Carbone Cancer Center
Madison, Wisconsin

UT Southwestern Simmons
Comprehensive Cancer Center
Dallas, Texas

Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

Yale Cancer Center/Smilow Cancer Hospital
New Haven, Connecticut

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