

Understanding Lymphoma

Diffuse Large B-Cell Lymphoma: Relapsed/Refractory

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for about 1 out of every 3 lymphomas in the United States.

DLBCL occurs in both men and women, although it is slightly more common in men. DLBCL can occur in childhood, however its incidence generally increases with age, and roughly half of patients are over the age of 60 years.

DLBCL is an *aggressive* (fast-growing) lymphoma that can arise in lymph nodes and often the spleen, liver, bone marrow, or other organs are also affected. Often, the first sign of DLBCL is a painless, rapid swelling in the neck, underarms, or groin that is caused by enlarged lymph nodes. For some patients, the swelling may be painful. Other symptoms may include night sweats, fever, and unexplained weight loss. Patients may notice fatigue, loss of appetite, shortness of breath, or pain.



SUBTYPES OF DLBCL

There are several subtypes of DLBCL that may affect a patient's *prognosis* (how well a patient will do with standard treatment) and treatment options. Doctors determine the subtype based on testing of the tumor tissue as well as the clinical presentation (e.g., location). Each DLBCL subtype has a different prognosis and may be treated differently. The most common subtype of DLBCL is called diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS), and it can further be subdivided into germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes, which refers to the cell of origin (i.e., the origin of the cell that turned into a lymphoma). Increasingly, doctors are recognizing the biological complexity of DLBCL, and new subtypes may emerge in the near future. In some cases, lymphomas that were previously considered to be a subtype of DLBCL are now considered separately from DLBCL; e.g., high-grade B-cell lymphoma (HGBL) demonstrates specific genetic abnormalities that may affect outcomes. For more information, patients should view the *High-Grade B-Cell Lymphoma* fact sheet on the Lymphoma Research Foundation's (LRF's) website (lymphoma.org/publications).



RELAPSED OR REFRACTORY DISEASE

Although DLBCL is often cured, up to 40% of patients can relapse (disease returns after treatment) or become refractory (disease does not respond to treatment). These patients are eligible for *second-line* treatment, which can reduce symptoms, control cancer growth, provide a second chance at cure, and extend life.



TREATMENT OPTIONS

Early evaluation at a specialized lymphoma management center is recommended for patients with relapsed/refractory DLBCL. Treatment options will depend on whether or not you are eligible for a stem cell transplant (see Table 1).

Patients Who Are Refractory to First-Line Chemoimmunotherapy or Relapsed within 1 Year of First-Line Chemoimmunotherapy

Preferred second-line treatment is CAR T cell therapy | Axicabtagene ciloleucel (Yescarta)

Patients Who Are Candidates for a Stem Cell Transplant

Preferred second-line treatment is chemotherapy | DHAP +/- rituximab (Rituxan)
 DHAX +/- rituximab (Rituxan)
 GDP +/- rituximab (Rituxan)
 ICE +/- rituximab (Rituxan)
 ESHAP +/- rituximab (Rituxan)
 GemOx +/- rituximab (Rituxan)
 MNE +/- rituximab (Rituxan)

Patients Who Are Not Candidates for a Stem Cell Transplant

Preferred second-line treatment is chemotherapy | GemOx +/- rituximab (Rituxan)
 CEPP +/- rituximab (Rituxan)
 CEOP +/- rituximab (Rituxan)
 Dose-adjusted EPOCH +/- rituximab (Rituxan)
 GDP +/- rituximab (Rituxan)
 Gemcitabine and vinorelbine +/- rituximab (Rituxan)

Other second-line regimens | Tafasitamab-cxix (Monjuvi) and lenalidomine (Remvidil)

After ≥ 2 lines of systemic therapy | Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)
 Loncastuximab tesirine (Zynlonta)
 Axicabtagene ciloleucel (Yescarta)
 Tisagenlecleucel (Kymriah)
 Lisocabtagene maraleucel (Breyanzi)
 Selinexor (Xpovio)

CAR T cell: chimeric antigen receptor T cell; CEPP: cyclophosphamide, etoposide, prednisone and procarbazine; CEOP: cyclophosphamide, etoposide, vincristine and prednisone; DHAP: dexamethasone, cisplatin and cytarabine; DHAX: dexamethasone, cytarabine and oxaliplatin; DLBCL: diffuse large B-cell lymphoma; GDP: gemcitabine, dexamethasone and cisplatin or carboplatin; ICE: ifosfamide, carboplatin and etoposide; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; ESHAP: etoposide, methylprednisolone, cytarabine and cisplatin; GemOx: gemcitabine and oxaliplatin.

For patients who do not respond to first-line chemoimmunotherapy (e.g., R-CHOP) or who progress within 12 months of first-line chemoimmunotherapy, chimeric antigen receptor T cells (CAR T cells) may be an option. For patients who experience a recurrence of lymphoma beyond 12 months, second-line chemoimmunotherapy is typically used. In patients who are able to achieve a good response to chemoimmunotherapy, high-dose chemotherapy with autologous stem cell transplantation may be recommended to consolidate their successful second-line treatment.

Patients in complete remission undergoing a stem cell transplant commonly receive their own stem cells (*autologous stem cell transplant*). Occasionally, a patient will receive stem cells from a donor (*allogeneic stem cell transplant*). After a stem cell transplant, patients may also receive involved-site radiation therapy (ISRT) to treat a specific area.

Relapsed/refractory patients who are not candidates for or who choose not to have a stem cell transplant have other treatment alternatives. Chemotherapies such as bendamustine (Treanda) or gemcitabine (Gemzar), or targeted drugs like lenalidomide (Revlimid) may be used in these patients in combination with rituximab (Rituxan) or other monoclonal antibodies. Patients with relapsed or refractory DLBCL after two prior therapies may also be eligible for treatment with polatuzumab vedotin-piiq (Polivy) or selinexor (Xpovio). Relapsed/refractory disease in adult patients can also be treated with tafasitamab-cxix (Monjuvi), a monoclonal anti-CD19 antibody, or loncastuximab tesirine (Zynlonta), a CD19-directed antibody-drug conjugate. Patients may also be candidates for second-line CAR T-cell therapy with axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), or lisocabtagene maraleucel (Breyanzi). For more information, view the *CAR T-cell Therapy in Lymphoma* fact sheet on LRF’s website (lymphoma.org/publications).

TREATMENTS UNDER INVESTIGATION

Many novel individual and combination therapies are currently being studied in clinical trials for the treatment of patients with relapsed/refractory DLBCL. Some of the investigational drugs under development are listed below (Table 2).

Table 2. Selected Agents Under Investigation for DLBCL in Phase 2-3 Clinical Trials

Agent	Class
Copanlisib (Aliqopa)	Targeted therapy; PI3K inhibitor
DTRM-555	Targeted therapy; BTK inhibitor
PBCAR0191	CAR T cell; anti-CD19
PBCAR20A	CAR T cell; anti-CD20
Odronextamab	Immunotherapy; bispecific antibody
Glofitamab	Immunotherapy; bispecific antibody
Epcoritamab (GEN3013)	Immunotherapy; bispecific antibody
Relmacabtagene autoleucel (Relma-cel, JWCAR029)	Autologous CAR T cell; anti-CD19
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor
Zilovertamab vedotin (MK-2140)	Immunotherapy; antibody-drug conjugate

Abbreviations: BCL-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; HDAC, histone deacetylase; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase.

Clinical trials are investigating the use of these agents at various treatment stages and for specific patient populations, including patients with relapsed/refractory disease. For example, because patients with the GCB subtype may have a better response to standard R-CHOP chemotherapy treatment than those with the ABC subtype, researchers are exploring new treatments that specifically improve outcomes for patients with ABC DLBCL. Optimal treatment strategies for HGBL are also being actively investigated; view the High-Grade B-Cell Lymphoma fact sheet on LRF's website for more information (lymphoma.org/publications). Clinical trials investigating these drugs are in various phases of development. It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved, so it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the

Understanding Clinical Trials fact sheet on LRF's website (lymphoma.org/publications), talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing helpline@lymphoma.org.

FOLLOW-UP

Patients with lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they have received. Medical tests (CT scans and PET scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) and *Lymphoma Care Plan* (lymphoma.org/publications) can help patients manage this documentation.



LRF'S HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with relapsed/refractory DLBCL, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.



MOBILE APP

Focus On Lymphoma is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype, including relapsed/refractory DLBCL, and tools to help manage their lymphoma such as, keep track of medications and blood work, track symptoms, and document treatment side effects. The *Focus On Lymphoma* mobile app is available for download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit **FocusOnLymphoma.org**. To learn more about any of these resources, visit our website at **lymphoma.org**, or contact the LRF Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and DLBCL. LRF also provides many educational activities, including our in-person meetings, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at **lymphoma.org/DLBCL** or **lymphoma.org**, or contact the LRF Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

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