Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for about 23 percent of newly diagnosed cases of B-cell NHL 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.

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. For instance, primary mediastinal B-cell lymphoma is a subtype of DLBCL that occurs mainly in younger patients and grows rapidly in the mediastinum (a division of the thoracic cavity in the chest). Another example is DLBCL that only affects the brain, called primary central nervous system (CNS) lymphoma, which is treated differently than DLBCL that affects areas outside of the brain. For more information about CNS lymphoma, patients should view the CNS Lymphoma fact sheet on LRF’s website (click here).

Most cases do not fall into one of these categories, and they are considered diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS). However, these NOS cases can be grouped into subtypes of DLBCL according to genetic markers on the surface of cancer cells. These subtypes are named according to their cell of origin and include germinal center B-cell-like (GCB) and activated B-cell-like (ABC). Each disease subtype has a different prognosis with treatment. Additionally, an aggressive type of DLBCL, called “double-hit” lymphoma (DHL), demonstrates specific genetic abnormalities that may affect outcome. For more information about DHL, patients should view the Double-Hit Lymphoma fact sheet on LRF’s website (click here).

A tissue biopsy is needed for a definitive diagnosis of DLBCL. A biopsy is a small surgical procedure to remove part or all of an affected lymph node or other abnormal area to look at it under a microscope. This can be done under local or general anesthesia. Once the diagnosis of DLBCL is confirmed, the next step is to understand the progression and location of the disease in the body (disease staging). Because DLBCL is a blood cancer, it is important to look for any signs of lymphoma across the entire body. This is usually done with a whole-body computed tomography (CT) scan, which is a series of computerized x-rays. A combination positron emission tomography (PET)/CT scan, in which a small amount of radioactive dye is injected to better identify areas of disease activity, may also be used. Staging may also include a bone marrow biopsy to look for lymphoma cells in the bone and sometimes a spinal tap (lumbar puncture) to determine if there are lymphoma cells in the brain and spinal cord. The physician will use the results of these tests to assess the stage of the lymphoma. NHL is categorized as Stages I to IV. Limited-stage disease (Stages I and II) represents lymphoma affecting only one area of the body, while advanced-stage disease (Stages III and IV) indicates that lymphoma has spread to several organs. Staging is needed to choose an appropriate course of treatment. It is common for patients with DLBCL to have advanced-stage disease, and treatment can still be very effective in this scenario.

Patients interested in learning more about scans and staging should view the Understanding NHL booklet on LRF’s website (click here).
TREATMENT OPTIONS

Since DLBCL often causes symptoms, treatment is typically begun shortly after diagnosis. A combination of chemotherapy and a monoclonal antibody targeting CD20 remains the backbone of most treatments. CD20 is a molecule expressed on the cell surface of lymphoma cells, and antibodies such as rituximab (Rituxan [for intravenous infusion]) target this molecule. Rituxan Hycale, a form of rituximab that is injected subcutaneously (under the skin), may be an option for some patients. The most widely used combination chemotherapy regimen for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), that is usually given in 21-day cycles. Sometimes etoposide (VePesid, Toposar, Etopophos) is added to the R-CHOP regimen, resulting in a drug combination called R-EPOCH. Sometimes treatment may involve radiation therapy. For many patients with DLBCL, the initial treatment can lead to disease remission (disappearance of signs and symptoms). However, for patients in whom the disease becomes refractory (no longer responds to treatment) or relapses (returns after treatment), secondary therapies may be successful.

Chemotherapy is typically used for second-line treatment. In patients who are able to achieve a second remission, high-dose chemotherapy coupled with 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).

Relapsed/refractory patients who are not candidates for stem cell transplant, or who choose not to have a stem cell transplant, do have other treatment alternatives. Chemotherapies such as bendamustine (Treanda) or gemcitabine (Gemzar), or targeted drugs like lenalidomide (Revlimid) or ibrutinib (Imbruvica) may be used in these patients in combination with rituximab 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 recently approved monoclonal anti-CD19 antibody. Patients may also be candidates for chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), or liso-cel [Lisocabtagene maraleucel]. For more information, view the CAR T-cell Therapy in Lymphoma fact sheet on LRF’s website [click here]. Most importantly, early evaluation at a specialized lymphoma management center is recommended.

TREATMENTS UNDER INVESTIGATION

Many novel individual and combination therapies are currently being studied in clinical trials for the treatment of patients with both newly diagnosed and relapsed/refractory DLBCL. Loncastuximab tesirine is an investigational CD19-directed antibody-drug conjugate for relapsed or refractory DLBCL granted priority review status by the FDA. Other investigational drugs under development for DLBCL are listed below (Table 1).

<table>
<thead>
<tr>
<th>AGENT</th>
<th>CLASS</th>
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<tbody>
<tr>
<td>Abexinostat (PCI-24781)</td>
<td>Targeted therapy; HDAC inhibitor</td>
</tr>
<tr>
<td>ALLO-501A</td>
<td>CAR T cell; anti-CD19</td>
</tr>
<tr>
<td>AUTO3</td>
<td>Dual target CAR T cell; anti-CD19 and CD22</td>
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<tr>
<td>Blinatumomab (Blincyto)</td>
<td>Immunotherapy; bispecific antibody</td>
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<tr>
<td>CX-2029</td>
<td>Probody drug conjugate; anti-CD71</td>
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<tr>
<td>DTRM-555</td>
<td>Targeted therapy; BTK inhibitor</td>
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<tr>
<td>Fimepinostat (CU20-907)</td>
<td>Targeted therapy; dual PI3K and HDAC inhibitor</td>
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<tr>
<td>Iberdomide (CC-220)</td>
<td>Targeted therapy; cereblon E3 ligase modulator</td>
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<tr>
<td>Panobinostat (Farydak)</td>
<td>Targeted therapy; HDAC inhibitor</td>
</tr>
<tr>
<td>Parsaclisib (INCB050465)</td>
<td>Targeted therapy; PI3K inhibitor</td>
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<tr>
<td>PBCAR0191</td>
<td>CAR T cell; anti-CD19</td>
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<tr>
<td>PBCAR20A</td>
<td>CAR T cell; anti-CD20</td>
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<tr>
<td>Odonextamab</td>
<td>Immunotherapy; bispecific antibody</td>
</tr>
<tr>
<td>Relmacabtagene autoleucel (Relma-cel, JWCAR029)</td>
<td>Autologous CAR T cell; anti-CD19</td>
</tr>
<tr>
<td>Tislelizumab</td>
<td>Immune checkpoint inhibitor; anti-PD1</td>
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Clinical trials are investigating the use of these agents at various treatment stages (frontline, maintenance, etc.) and for specific patient populations, including newly diagnosed patients, patients with relapsed/refractory disease, the elderly, and patients with specific molecular subtypes. 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 DHL are also being actively investigated; view the Double-Hit Lymphoma fact sheet on LRF’s website for more information [click here]. 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 [click here], 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 program, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with 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.

**Resources**

LRF offers a wide range of 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, from in-person meetings to webinars for people with lymphoma, as well as DLBCL e-updates that provide the latest disease-specific news and treatment options. 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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