LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma: High-Grade B-Cell Lymphoma

High-grade B-cell lymphoma (HGBL) is a new category of B-cell non-Hodgkin lymphoma (NHL) introduced in 2008 by the World Health Organization (WHO). This type of lymphoma is aggressive (fast-growing) and can be grouped in two subtypes:

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

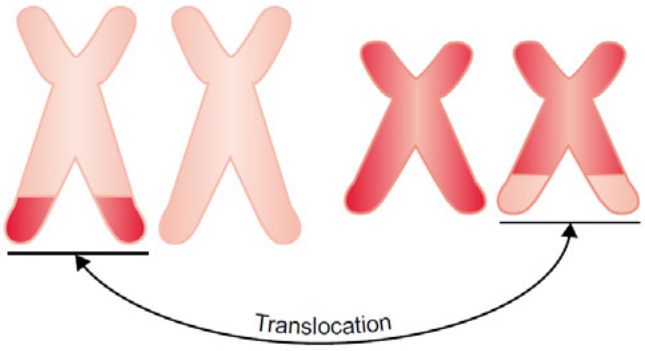

Figure 1. Example of a translocation, where a chromosome (a structure made of DNA and proteins found inside the cell) breaks, and part of it reattaches to another chromosome.

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

- Painless rapid swelling in the neck, underarms, or groin, that is caused by enlarged lymph nodes. For some patients, the swelling may be painful
- Night sweats
- Fever
- Unexplained weight loss
- Fatigue (extreme tiredness)
- Loss of appetite
- Shortness of breath
- Pain

TREATMENT OPTIONS

HGBL is treatable, but more likely to relapse (come back after treatment) than DLBCL. These lymphomas are generally treated with one of the following chemoimmunotherapy (chemotherapy combined with immunotherapy [drugs that use the body's immune system to fight cancer]) regimens:

- **DA-EPOCH-R** (dose-adjusted etoposide/VP-16 [VePesid, Toposar, Etopophos], prednisone [Deltasone and others], vincristine [Oncovin and others], cyclophosphamide [Cytoxan, Neosar], and doxorubicin/hydroxydaunorubicin [Rubex, Adriamycin PFS] plus rituximab [Rituxan])
- **R-Hyper-CVAD/MA** (rituximab [Rituxan] plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [Decadron and others], alternating with high-dose methotrexate [Mexate and others] and cytarabine/high-dose Ara-C [Cytosar-U, Tarabine PFS])
- **R-CODOX-M/R-IVAC** (rituximab plus cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with rituximab plus ifosfamide [Ifex], etoposide, and cytarabine)
- **R-CHOP** (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)
- **Pola-R-CHP** (polatuzumab, rituximab, cyclophosphamide, doxorubicin, prednisone)
- **R-mini-CHOP** (rituximab and reduced-dose CHOP) may be considered for patients who are older or frail
- **Biosimilar therapy** (a biologic therapy [molecules that are created inside living cells] that is modeled after an existing biologic therapy or reference product already approved by the FDA) may be an option for patients who are taking rituximab (Rituxan). Some biosimilar therapies for rituximab (Rituxan) include rituximab-abbs and rituximab-pvvr. For more information about biosimilars, please see the *Biosimilar Therapies* publication on Lymphoma Research Foundation's (LRF's) website (**lymphoma.org/publications**)

Patients with HGBL that relapses or becomes refractory (does not respond to treatment) may undergo high-dose chemotherapy followed by an autologous stem cell transplant (patient's own stem [blood-forming] cells are infused after high-dose chemotherapy with or without radiation). Treatment options can include:

- Autologous stem cell transplant
- Allogeneic stem cell transplant (patients receive stem cells from a donor)
- Chimeric antigen receptor (CAR) T-cell therapy (a special form of immunotherapy that uses the patient's own white blood cells, which are modified in a lab to fight cancer), including lisocabtagene maraleucel (Breyanzi), tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta)
- Loncastuximab tesirine (Zynlonta)

For more information on stem cell transplantation and CAR T-cell therapy, view the *Understanding Cellular Therapy* publication on LRF's website (**lymphoma.org/publications**).

Compared with DLBCL, HGBL may have a higher risk of relapse in the patient's central nervous system (CNS; the brain and spinal cord). To reduce this risk, some patients with HGBL may receive additional chemotherapy drugs to treat the CNS in addition to one of the chemotherapy regimens described above. CNS treatments may include methotrexate and/or cytarabine that is administered either intravenously (as a liquid that is infused directly into a vein), through a lumbar puncture (spinal tap), or both. A lumbar puncture is a procedure where a small needle is inserted into the back, some spinal fluid is withdrawn, and chemotherapy is injected directly into the cerebrospinal fluid surrounding the CNS.

TREATMENTS UNDER INVESTIGATION

Many new treatments (also referred to as investigational drugs) and combination therapies (two or more drugs given at the same time) are currently being studied for the treatment of patients with HGBCL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). Table 1 lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* fact sheet on LRF's website (**lymphoma.org/publications**).

Table 1. Treatments Under Investigation for HGBCL in Phase 2 or 3 Clinical Trials.

Agent (Drug)	Class (Type of Treatment)
Sepantronium bromide (SepB)	Targeted therapy; surviving inhibitor
Devimistat (CPI-613)	Targeted therapy; inhibitor of mitochondrial enzymes
Polatuzumab vedotin (Polivy)	Immunotherapy; antibody-drug conjugate, anti-CD79B
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Glofitamab	Immunotherapy; bispecific antibodies, anti-CD20 and -CD3
Tafasitamab (Monjuvi)	Immunotherapy, monoclonal antibody, anti-CD19
Retifanlimab	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor
Orelabrutinib	Targeted therapy; BTK inhibitor
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor
E7777	Immunotherapy; fusion protein
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Ontorpacept (TTI-621)	Immunotherapy; fusion protein
Maplirpacept (TTI-622)	Immunotherapy; fusion protein
Varlilumab (CDX-1127)	Immunotherapy; monoclonal antibody, anti-CD27
Mosunetuzumab (Lunsumio)	Immunotherapy; bispecific antibody; anti-CD20 and -CD3
Mogamulizumab (Poteligeo)	Immunotherapy; monoclonal antibody, anti-CCR4
Toripalimab	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
CRC01	Immunotherapy; CAR T-cell therapy, anti-CD19
Tislelizumab	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Lenalidomide (Revlimid)	Immunotherapy; immunomodulatory drug
Vorinostat (Zolinza)	Targeted therapy; HDAC inhibitor
Inotuzumab ozogamicin (Besponsa)	Immunotherapy; antibody-drug conjugate, anti-CD22
Epcoritamab (GEN3013)	Immunotherapy; bispecific antibody; anti-CD20 and -CD3

BTK, Bruton's kinase; CAR, chimeric antigen receptor; CCR4, CC chemokine receptor type 4; HDAC, histone deacetylase; HGBCL, high-grade B-cell lymphoma; PD-1, programmed cell death protein 1

It is important to remember that today's scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently appeared.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining the best treatment 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 (visit **lymphoma.org/publications**) or talk to their physician. The LRF Helpline can also be contacted for an individualized clinical trial search by calling **(800) 500-9976**, by emailing **helpline@lymphoma.org**, or by submitting the *Clinical Trials Search Request Form* at **lymphoma.org**.

FOLLOW-UP

Patients with HGBCL should have regular visits with their physician. During these visits, medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur **during** treatment and continue for months or years) or late side effects (appear only months, years, or decades **after** treatment has ended). These can vary depending on the following factors:

- Duration of treatment (how long the treatment lasted)
- Frequency of treatment (how often the treatment was administered)
- Type of treatment given
- Age and gender of the patient
- Patient's overall health at the time of treatment.

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the patient stays in remission (disappearance of signs and symptoms).

Patients and their caregivers are encouraged to keep copies of all medical records. This includes test results as well as information on the type, amount, and duration of time of all treatments received. Medical records are 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 our *Lymphoma Care Plan* (**lymphoma.org/publications**) can help patients manage this documentation.

LYMPHOMA CARE PLAN AND PATIENT EDUCATION PROGRAMS

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. LRF's *Lymphoma Care Plan* document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The *Lymphoma Care Plan* document can be accessed by visiting **lymphoma.org/publications**. LRF also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

LRF Helpline

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

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

LRF FOCUS ON LYMPHOMA MOBILE APP

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype and actionable tools to better manage diagnosis and treatment. Experience comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information first, with resources from the entire LRF content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more this resource, visit our website at **lymphoma.org/mobileapp**, or contact the LRF Helpline at **800-500-9976** or **helpline@lymphoma.org**.

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