

Understanding Lymphoma: Relapsed/Refractory Follicular Lymphoma

Follicular lymphoma (FL) is the most common indolent (slow-growing) form of B-cell non-Hodgkin lymphoma (NHL), accounting for 1 out of 5 lymphomas in the United States.

Common symptoms of FL include:

- Enlargement of the lymph nodes (bean-shaped structures that help the body fight infection, Figure 1) in the neck, underarms, abdomen, or groin
- Fatigue (extreme tiredness)

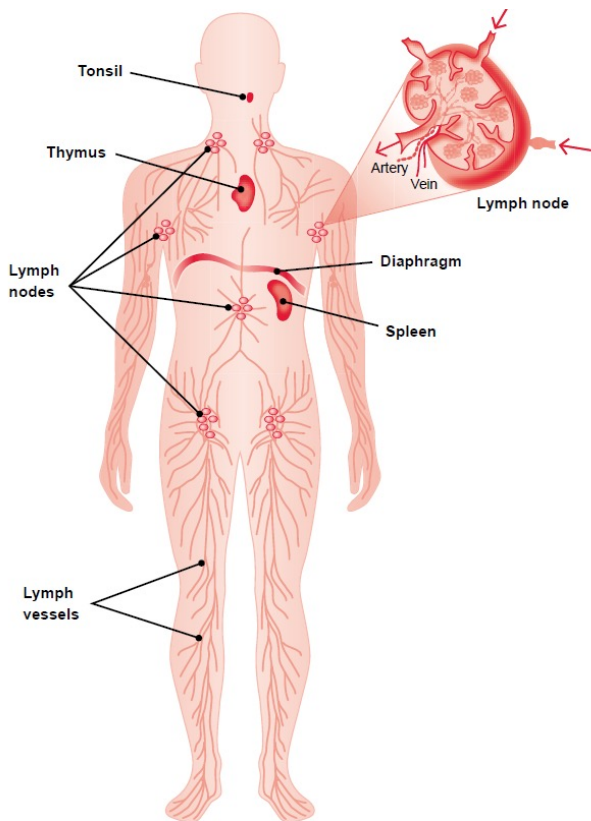


Figure 1. The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and the lymph nodes.

Typically, patients with FL have no obvious symptoms of the disease at diagnosis. Patients often present only with an enlarged lymph node on exam or found by chance on an imaging study (such as computed tomography [CT] scans).

Determining how far the lymphoma has spread (staging) is important to define the best treatment for each patient. The results of the different tests (such as biopsies [doctors collect a sample of the affected lymph node to observe the lymphoma cells under the microscope] and scans) are used to determine

the severity of the disease and the appropriate treatment. The Lugano staging system is used for FL and is depicted in Figure 2 below. This system categorizes FL from Stage I (limited disease) to IV (advanced disease), based on whether the disease is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs). Because FL is an indolent disease and might not cause any symptoms initially, it is often advanced (Stage III or IV) when it is diagnosed.

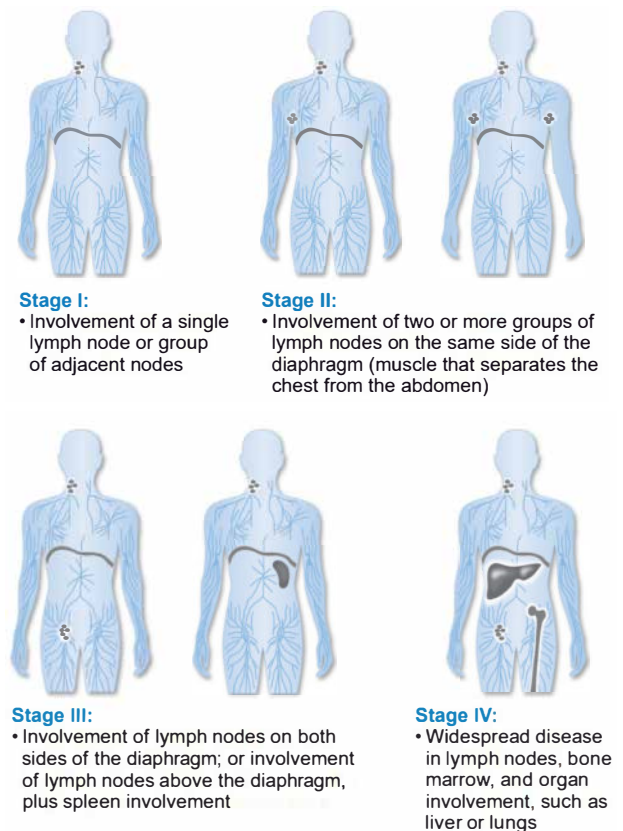


Figure 2. Staging of FL according to the Lugano staging system.

Many patients may not need treatment initially and can be actively monitored for some time through an approach called active surveillance (also known as “watchful waiting” or “careful observation”). This consists in monitoring patients’ overall health and disease through regular physical and laboratory exams and periodic imaging tests. For more information on active surveillance, view the *Active Surveillance* fact sheet on Lymphoma Research Foundation’s (LRF’s) website (lymphoma.org/publications). Treatment is started if the patient begins to develop symptoms or there are signs that the disease is progressing.

FL is generally very responsive to first-line therapies like radiation, immunotherapy, and chemotherapy, and many patients go into durable remission (disappearance of disease signs and symptoms of cancer for a long time). However, the disease often relapses (returns after treatment) or becomes refractory (no longer responds to current treatment). In this case, second-line therapies (treatment given when initial therapy does not work or stops working) are often successful in providing another remission. Some patients who relapse do not need treatment right away and are monitored through active surveillance. For those who need treatment, the same therapies used for newly diagnosed FL can often be used, but additional treatments are also available (see section below).

TREATMENT OPTIONS

Treatment for relapsed/refractory FL is based on different factors, including:

- Patient’s age and overall health
- Presence and type of symptoms
- Type of prior treatment
- Response to prior treatment

Patient preference also may play a role in treatment choice. Treatment options include chemotherapy, radiation, and monoclonal antibodies (proteins made in the laboratory that bind to markers at the surface of lymphoma cells and help the body fight cancer). The most used monoclonal antibodies for treating relapsed/refractory FL bind to a protein called CD20, and examples include:

- Rituximab (Rituxan, given by injection)
- Rituximab and hyaluronidase human (Rituxan Hycela, a rituximab product that is administered under the skin)
- Obinutuzumab (Gazyva)

Mosunetuzumab-axgb (Lunsumio), a bispecific antibody (a drug that binds to two different proteins at the same time), was recently approved for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy (treatment delivered throughout the body). Mosunetuzumab (Lunsumio) works by binding to CD20 at the surface of cancer cells and to CD3 in healthy T cells. This is called a T-cell engager, which means it links cancer cells to healthy immune cells that fight cancer. To learn more about bispecific antibodies, view the *Bispecific Antibodies* fact sheet on the LRF website (visit lymphoma.org/publications).

Common second- or later-line regimens for relapsed/refractory FL include:

- Bendamustine hydrochloride (Treanda) ± rituximab (Rituxan) or obinutuzumab (Gazyva), if not used for first-line treatment
- Lenalidomide (Revlimid) in combination with rituximab (Rituxan) (often referred to as R2 (R-squared))
- R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone)
- R-CVP (rituximab [Rituxan], cyclophosphamide, vincristine, and prednisone)
- Rituximab (Rituxan)
- Tazemetostat (Tazverik) for patients with an EZH2 mutation (permanent change in the gene EZH2 that results in a more aggressive type of cancer) or for patients who have no satisfactory alternative treatment option
- Copanlisib (Aliqopa)

A special type of immunotherapy (drugs that help the body’s immune system fight cancer) called chimeric antigen receptor (CAR) T-cell therapy has recently been approved for the treatment of relapsed or refractory FL. These include the following:

- Axicabtagene ciloleucel (Yescarta)
- Lisocabtagene maraleucel (Breyanzi)
- Tisagenlecleucel (Kymriah)

To learn more about CAR T cell therapy, view the *Understanding Cellular Therapy Guide* on the LRF’s website (lymphoma.org/publications).

Radiation therapy can be effective in some patients with relapsed/refractory FL who have localized disease. Often very low doses of radiation can be quite beneficial.

For some patients with relapsed/refractory FL, high-dose chemotherapy followed by stem cell transplantation may be an option. For more information on transplantation, view the *Understanding Cellular Therapy Guide* on LRF’s website (lymphoma.org/publications).

RESPONSE TO RETREATMENT

With newer therapeutic regimens, many patients can achieve remission after second- or third-line treatments. Although remission in the range of one year or longer can be seen with some of the treatments, it may be shorter with each round of therapy.

TRANSFORMED FL

Some patients with FL may eventually develop a transformed lymphoma (when a slow-growing lymphoma changes into a fast-growing one) at a rate of 2%-3% per year. A transformed lymphoma is often more aggressive and usually requires more intensive treatment. The risk of developing a transformed lymphoma increases each year, from the time of diagnosis until approximately 10 years afterward, after which point transformations become rare. For more information on transformed lymphomas, view the *Transformed Lymphomas* fact sheet on LRF’s website at (lymphoma.org/publications).

TREATMENTS UNDER INVESTIGATION

Many treatments (also referred to as investigational drugs) are currently being studied in clinical trials alone or as part of a combination therapy regimen in patients with relapsed/refractory FL. 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 (below) 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* publication on the Lymphoma Research Foundation's (LRF's) website (lymphoma.org/publication).

It is critical 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. It is also very important that all patients consult with an FL specialist to answer any questions.

Table 1. Treatments Under Investigation for Relapsed/Refractory Follicular Lymphoma

Agent (Drug)	Class (Type of Treatment)
Abexinostat (PCI-24781)	Targeted therapy; HDAC inhibitor
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor
Atezolizumab (Tecentriq)	Immune checkpoint inhibitor; anti-PD-1
Durvalumab (Imfinzi)	Immune checkpoint inhibitor; anti-PD-1
Epcoritamab (GEN3013)	Bispecific monoclonal antibody; anti-CD20
Glofitamab (RO7082859)	Bispecific monoclonal antibody; anti-CD20
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor
Loncastuximab tesirine-lpyl (Zynlonta)	Antibody-drug conjugate; anti-CD19
Nivolumab (Opdivo)	Immune checkpoint inhibitor; anti-PD-1 receptor
Odronektamab (REGN1979)	Immunotherapy; bispecific antibody
Parsaclisib (INCB050465)	Targeted therapy; PI3K δ inhibitor
Pembrolizumab (Keytruda)	Immune checkpoint inhibitor; anti-PD-1 receptor
Relmacabtagene autoleucel (Relma-cel, JWCAR029)	Autologous CAR T cell; anti-CD19
SD-101	Immunotherapy; TLR9 agonist
Tafasitamab-cxix (Monjuvi)	Monoclonal antibody; anti-CD19
Ublituximab (TG-1101)	Immunotherapy; anti-CD20 antibody
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor
Zandelisib (ME-401)	Targeted therapy; PI3K δ inhibitor
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor

BCL2, B-cell lymphoma-2 protein; BTK, Bruton tyrosine kinase; CAR, chimeric antigen receptor; HDAC, histone deacetylase; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; TLR9, Toll-like receptor 9.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and optimal 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 (lymphoma.org/publications) and the *Clinical Trials Search Request Form* at lymphoma.org, 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

Since FL is generally characterized by multiple disease relapses after responses to a variety of treatments, patients should have regular visits with their physician. During these visits, medical tests (such as blood tests, CT scans, and positron emission tomography [PET] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause side effects that are long-term (occur **during** treatment and continue for months or years) or late side effects (appear only months, years, or decades **after** treatment has ended). The presence of side effects 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 side 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. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. LRF's award-winning *Focus on Lymphoma* mobile app (lymphoma.org/mobileapp) 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. It provides convenient and comprehensive lymphoma management 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 Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about 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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