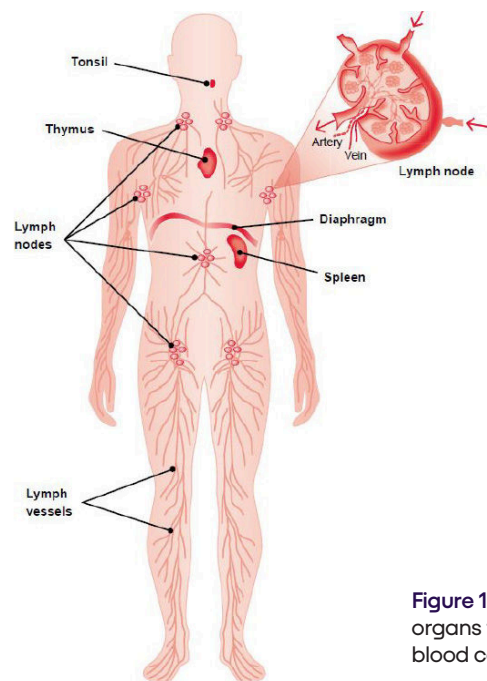


Follicular lymphoma (FL) is the most common *indolent* (slow-growing) form of B-cell non-Hodgkin Lymphoma (NHL), accounting for 1 out of 5 lymphomas in the US.

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).



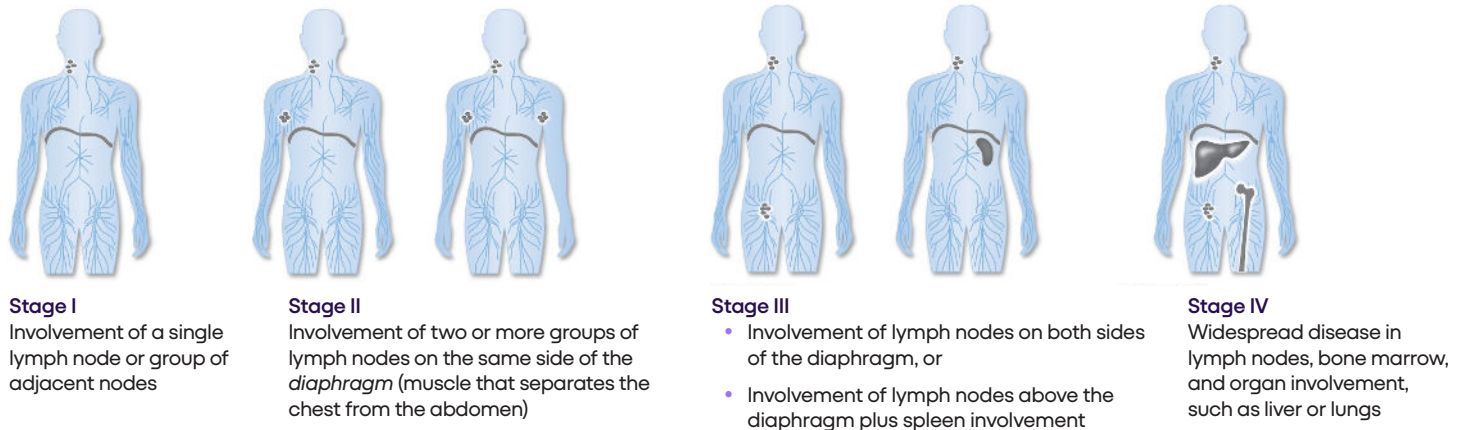
**Figure 1:** The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

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 where in the body the lymphoma is present (staging) is important to define the best management plan for each patient. The results of the different tests (such as biopsies [doctors collect a sample of an 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 plan. 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 involves the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs). Because FL is a slow-growing disease and might not cause any symptoms initially, it is often advanced (stage III or IV) when it is diagnosed.

Many patients, including those with advanced stage disease, 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 the Lymphoma Research Foundation website (visit [lymphoma.org/publications](http://lymphoma.org/publications)). Treatment is started if the patient begins to develop symptoms and/or there are signs that the disease is progressing.

**Figure 2:** Staging of NHL according to the Lugano system.



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, *additional 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).

For more information on relapsed and refractory FL diagnosis and disease staging, please view the *Understanding Lymphoma and CLL Guide* on the Foundations website (visit [lymphoma.org/publications](http://lymphoma.org/publications)).

## Treatment Options

Treatment for relapsed/refractory FL is based in 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 for relapsed/refractory FL include:

- *Chemotherapy* (drugs that stop the growth of or kill cancer cells).
- *Radiation therapy* (treatment that uses high-energy radiation to kill cancer cells).
- *Immunotherapy* (drugs that help the body's immune system to fight cancer).
  - *Monoclonal antibodies* (proteins made in the laboratory that bind to markers at the surface of lymphoma cells and help the body fight cancer).
    - Rituximab (Rituxan, given by injection).
    - Rituximab and hyaluronidase human (Rituxan Hycela, a rituximab product that is administered under the skin).
    - Obinutuzumab (Gazyva).

- *Bispecific antibodies* (antibodies that recognize two different antigens).
  - Mosunetuzumab (Lunsunio) and Epcoritamab (Epkincy) are 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). This drug is a T-cell engager, and it works by binding to CD20 at the surface of cancer B-cells and to CD3 in healthy T-cells. To learn more about bispecific antibodies, view the *Bispecific Antibodies* fact sheet on the Lymphoma Research Foundation website (visit [lymphoma.org/publications](http://lymphoma.org/publications)).
- Chimeric antigen receptor (CAR) T-cell therapy is a special type of immunotherapy that uses the patient's immune cells to fight cancer. Common CAR T-cell therapies are axicabtagene ciloleucel (Yescarta), lisocabtagene maraleucel (Breyanzi), and tisagenlecleucel (Kymriah). To learn more about CAR T-cell therapy, view the *Understanding Cellular Therapy Guide* on the Lymphoma Research Foundation website (visit [lymphoma.org/publications](http://lymphoma.org/publications)).

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

- *Chemoimmunotherapy* (a combination of chemotherapy with immunotherapy).
  - Bendamustine (Treanda) ± rituximab (Rituxan) or obinutuzumab (Gazyva), if not used for first line treatment.
  - R-CHOP (rituximab [Rituxan], cyclophosphamide, doxorubicin, vincristine, and prednisone).
  - R-CVP (rituximab [Rituxan], cyclophosphamide, vincristine, and prednisone).
- Immunotherapy.
  - *Immunomodulatory drugs* (drugs that regulate the immune system by activating or slowing the activity of specific proteins).
    - Lenalidomide (Revlimid) ± rituximab (Rituxan) (often referred to as R2 (R-squared) when used in combination with rituximab [Rituxan]).
  - *Monoclonal antibodies* such as rituximab (Rituxan).

- CAR T-cell therapies such as axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah).
- *Targeted therapies* (drugs that target molecules that cancer cells use to grow and spread).
  - Tazemetostat (Tazverik), called an EZH2 inhibitor and interferes with growth of lymphoma cells
  - Zanubrutinib (Brukinsa), called a Bruton's tyrosine kinase (BTK) inhibitor and blocks signals within the lymphoma cells, in combination with obinutuzumab.

Other treatment options for relapsed/refractory FL include:

- 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.
- *Stem cell transplantation* (the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).

For more information on transplantation, view the *Understanding Cellular Therapy Guide* on the Foundation's website (visit [lymphoma.org/publications](http://lymphoma.org/publications)).

### Response to Retreatment

With newer therapeutic regimens, many patients can achieve remissions after second line or third line treatments. Although remissions in the range of one year or longer can be seen with some of the treatments, they 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 afterwards, after which point transformations become rare. For more information on transformed lymphomas, view the *Transformed Lymphomas* fact sheet on the Foundation's website at [lymphoma.org/publications](http://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 regimens 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 website at [lymphoma.org/publication](http://lymphoma.org/publication) (Table 1).

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 the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients consult with a FL specialist to answer any questions.

**Table 1:** Selected Agents Under Investigation for 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-PD1           |
| Chidamide                                       | Targeted therapy; HDAC inhibitor                |
| Glofitamab (RO7082859)                          | Bispecific monoclonal antibody; anti-CD20       |
| Ibrutinib (Imbruvica)                           | Targeted therapy; BTK inhibitor                 |
| Loncastuximab tesirine (Zynlonta)               | Antibody-drug conjugate; anti-CD19              |
| Nivolumab (Opdivo)                              | Immune checkpoint inhibitor; anti-PD-1 receptor |
| Odronextamab (REGN1979)                         | Immunotherapy; bispecific antibody              |
| Pembrolizumab (Keytruda)                        | Immune checkpoint inhibitor; anti-PD-1 receptor |
| Relmacabtagene autoleucel (Relma-cel, JWCAR029) | Autologous CAR T cell; anti-CD19                |
| CTX112  | Allogeneic CAR T cell; anti-CD19                |
| Tafasitamab (Monjuvi)                           | Monoclonal antibody; anti-CD19                  |
| Valemetostat                                    | Targeted therapy; EZH inhibitor                 |
| Venetoclax (Venclexta)                          | Targeted therapy; BCL2 inhibitor                |

BCL2, B-cell lymphoma 2 protein; BTK, Bruton's tyrosine kinase; CAR, chimeric antigen receptor; EZH, enhancer of zeste homolog; HDAC, histone deacetylase; PD-1, programmed cell death protein 1.

## 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 the Foundation's website (visit [lymphoma.org/publications](http://lymphoma.org/publications)), and the *Clinical Trials Search Request Form* at [lymphoma.org](http://lymphoma.org), talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing [helpline@lymphoma.org](mailto: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 ordered 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). These side effects can vary depending on the following factors:

- Duration of treatment (how long was the treatment given).
- Frequency of treatment (how often was the treatment administered).
- Type of treatment given.
- Age and gender of the patient.
- Patient 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.

Patients and their care partners 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. The Foundation's award-winning *Focus on Lymphoma* mobile app ([lymphoma.org/mobileapp](http://lymphoma.org/mobileapp)) or our *Lymphoma Care Plan* ([lymphoma.org/publications](http://lymphoma.org/publications)) can help patients manage this documentation.

## Lymphoma Care Plan

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. The Foundation'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](http://lymphoma.org/publications).

## Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit [lymphoma.org/programs](http://lymphoma.org/programs).

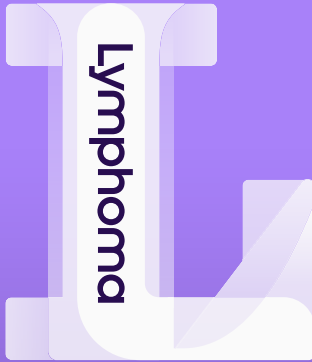
## Helpline

The Foundation's 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. The Foundation 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](http://lymphoma.org), or contact the Helpline at (800) 500-9976 or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

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

## Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. 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 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](http://lymphoma.org/mobileapp), or contact the Foundation's Helpline at (800) 500-9976 or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).



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