LYMPHOMA RESEARCH • FOUNDATION

Understanding Follicular Lymphoma: Relapsed/Refractory

Follicular lymphoma (FL) is the most common *indolent* (slow-growing) form of non-Hodgkin Lymphoma (NHL), accounting for just over 10 percent of all B-cell NHLs.

Common symptoms of FL include swelling of the lymph nodes in the neck, underarms, abdomen, or groin; fatigue and much less commonly, fevers, night sweats, and weight loss. Often, patients with FL have no obvious symptoms of the disease and the diagnosis is found incidentally during routine annual checkup or following imaging studies for unrelated reasons. Many patients may not need treatment initially and can be actively monitored for some time.

FL is generally very responsive to radiation and chemotherapy and many patients go into a *remission* (disappearance of disease signs and symptoms) that lasts for years after their initial treatment; however, the disease often returns. For patients who *relapse* (disease returns after treatment) or become *refractory* (disease no longer responds to treatment), *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 an *active surveillance* (also known as "watchful waiting" or "careful observation") approach might be used. With this strategy, patients' overall health and disease are monitored through regular physical and laboratory exams and sometimes periodic imaging tests. Active treatment is started if the patient begins to develop lymphoma-related symptoms or there are signs that the disease is progressing based on testing during follow-up visits. For those who need treatment, the same therapies used for newly diagnosed patients can often be used in patients with relapsed/refractory FL, but additional treatments are also available.

TREATMENT OPTIONS

Treatment for relapsed/refractory FL is based on a patient's age, overall health, symptoms, prior therapy or therapies, and the duration of remission from the last treatment they received. Chemotherapy, radiation, and monoclonal antibodies such as rituximab (Rituxan [for intravenous infusion] and Rituxan Hycela [for subcutaneous injection after the first IV infusion of Rituxan]) and obinutuzumab (Gazyva) may be used to treat relapsed/refractory FL.

Common second line regimens include:

- Bendamustine (Treanda) with or without rituximab (Rituxan), if not used for first line treatment
- Copanlisib (Aliqopa)
- Idelalisib (Zydelig)
- Duvelisib (Copiktra)
- Umbralisib (Ukoniq)
- Lenalidomide (Revlimid) with or without rituximab (often referred to as R^2 (R-squared) when used in combination with rituximab)
- Obinutuzumab (Gazyva) with bendamustine, if bendamustine was not used in first line treatment
- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)
- R-CVP (rituximab, cyclophosphamide, vincristine, and prednisone)
- Rituximab alone
- Tazemetostat (approved for relapsed/refractory FL with an EZH2 mutation or for patients with FL who have no satisfactory alternative treatment option)

The immunotherapy approach, called Chimeric antigen receptor (CAR) T cell therapies have recently been approved for the treatment of relapsed or refractory FL. Axicabtagene ciloleucel (Yescarta) and lisocabtagene maraleucel (Breyanzi) are indicated for adult patients with relapsed or refractory FL after two or more lines of systemic therapy. Mosunetuzumab-axgb (Lunsumio), a bispecific antibody, is now approved for treatment of relapsed/refractory follicular lymphoma (FL) after two or more lines of prior therapy. To learn more about CAR T cell therapies, view the *Understanding Cellular Therapy* guide on the Lymphoma Research Foundation website (click **here**).

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 the Stem Cell Transplantation Process* publication on LRF's website (click **here**).

RESPONSE TO RETREATMENT

With newer therapeutic regimens, many patients can achieve remissions after second line or third line treatments. Remissions are frequently shorter with each round of therapy however, remissions in the range of one year and longer can be seen with some of the treatments.

TRANSFORMED FL

Some patients with FL may eventually develop a transformed lymphoma, which occurs at a rate of three percent per year and is often more aggressive and usually requires more intensive types of treatment similar to aggressive lymphomas. 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 LRF's website at lymphoma.org/publications.

TREATMENTS UNDER INVESTIGATION

Many treatments are currently being studied in clinical trials alone or as part of a combination therapy regimen in patients with relapsed/refractory FL. Some of these treatments include:

- Abexinostat (PCI-24781)
- Acalabrutinib (Calquence)
- Atezolizumab (Tecentriq)
- BGB-3111
- Buparlisib
- Cerdulatinib
- Durvalumab (Imfinzi)
- Entospletinib
- Iberdomide
- Ibrutinib (Imbruvica)
- Ixazomib (Ninlaro)
- Loncastuximab tesirine
- Nivolumab (Opdivo)
- Parsaclisib
- Pembrolizumab (Keytruda)
- PLX2853
- Romidepsin (Istodax)
- Relmacabtagene autoleucel
- SAIT101
- SD-101
- Tafasitamab (Monjuvi)
- Tisagenlecleucel (Kymriah)
- Ublituximab
- Venetoclax (Venclexta)
- Zandelisib (ME-401)

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. Therefore, 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 at lymphoma.org/publications (click **here**), 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 a physician who is familiar with their medical history and the treatments they have received. Medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required at various times during *remission* (disappearance of signs and symptoms) 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 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 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) 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 FL, 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 FL, 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 FL. LRF also provides many educational activities, including our in- person meetings, podcasts, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at lymphoma.org/FL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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Supported through grants from: Bristol Myers Squibb, Genentech, Biogen, Kite

Last updated 2022

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