

Understanding Lymphoma: Oral Agents For Lymphoma

In the past, most treatments for lymphoma had to be given through a needle inserted directly into a vein (intravenously [IV]) at a hospital or cancer center. However, today there are many anticancer drugs for the treatment of lymphoma that can be taken by mouth (also called *oral agents*), in tablet/capsule form. Oral agents can be very effective at slowing down cancer cell growth and at maintaining long-term *remission* (disappearance of signs and symptoms). Although oral agents are pills that you can take at home, they can have side effects.

Oral agents may be beneficial for patients who have to travel a long distance to their treatment center, since they can be taken at home. However, as patients are typically responsible for ensuring they take their pills, there may be an increased risk of medication errors, such as forgetting/skipping pills or self-adjusting (changing) the dosage, which can reduce the effectiveness (drug's effect on the body) and safety of the anticancer therapy. Taking all medications as prescribed is important to increase the benefits of the treatment and to reduce serious side effects.

Patients are typically followed closely in the early weeks and months after starting an oral agent. After being on a medication for a longer period of time, they may see their healthcare team only once every two to four months. Blood work (measuring the amount of blood cells and certain substances in a sample of blood) and other tests may be done less frequently for patients on an oral agent compared to IV therapy. For these reasons, patients may feel less connected to their healthcare team than they would if they were receiving IV medications at a cancer treatment center, where they would have more frequent interaction with the healthcare staff. Side effects of oral anticancer therapies may also go unnoticed or unreported to the healthcare team, and patients may be uncertain about how to manage side effects on their own. Many of the side effects of oral medications can be managed with medication or lifestyle changes, so patients should carefully track all side effects of their treatment and report them to their healthcare team on a regular basis so they can receive the best care.



MEDICATION TRACKING

Keeping track of medications and side effects can be complicated, particularly when they have different dosing schedules. Keeping drug diaries can be helpful, as well as setting online reminders and using apps for smartphones and devices. To assist with this, the Lymphoma Research Foundation's (LRF's) award-winning *Focus on Lymphoma* mobile app provides patients and caregivers with comprehensive content based on their lymphoma subtype and tools to help manage their diagnosis, including a medication manager and side effects tracker. Users can access a full range of tools to help manage a patient's healthcare. The medication manager allows users to easily view all of their medications and track medicine schedules, including when to take an oral cancer therapy. Patients and caregivers can also set reminders on their mobile devices and keep track of dosages and progress in the calendar. In addition, users can

track the severity of side effects/symptoms as often as needed, which makes it easier for their physician or nurse to review disease progress. *Focus On Lymphoma* is available for free download on iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit lymphoma.org/mobileapp.



ORAL TREATMENT OPTIONS

Oral agents for the treatment of lymphoma include:

- **Chemotherapy agents:** These are drugs directed against any rapidly dividing cell, both normal and tumor cells. Because of this, they may also damage normal rapidly dividing cells like those in the hair follicles, mouth, and blood. This can lead to side effects such as low blood cell counts, mouth sores, diarrhea, and hair loss.

- Targeted therapies: These are drugs directed against specific molecules that cancer cells use to survive and/or spread. Targeted therapies usually affect fewer normal cells when compared to chemotherapy, resulting in fewer serious side effects.
- Immunomodulatory agents: These are drugs that activate or slow down the immune system and may also have antiangiogenic properties, which means they can prevent cancer cells from getting nutrients from the blood, eventually causing their death.

United States Food and Drug Administration-(FDA-) approved and investigational oral chemotherapy agents are listed in **Table 1** below. Targeted and immunomodulatory agents for lymphoma are listed in **Table 2**. In describing the indications, the term “relapsed” refers to cancer that has returned after treatment and “refractory” means that the cancer did not respond to treatment.

Table 1. Chemotherapy Treatment Options: Oral Agents in Lymphoma

Agent (Drug)	Class (Type of Treatment)	Uses
Cyclophosphamide	Alkylating agent (mustard-gas derivative)	Approved for HL, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt lymphoma, mycosis fungoides and leukemias
Chlorambucil (Leukeran)	Alkylating agent (nitrogen mustard)	Approved for CLL, lymphosarcoma, FL, and HL
Lomustine (Gleostine)	Alkylating agent (nitrosourea)	Approved for relapsed or refractory HL, used in combination therapy
Methotrexate	Antimetabolite	Approved for mycosis fungoides and relapsed or refractory NHL
Procarbazine hydrochloride (Matulane)	Not defined; may act by inhibition of protein, RNA, and DNA synthesis	Approved for combination therapy in stage III and IV HL

Abbreviations: CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid;; FL, follicular lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; RNA, ribonucleic acid.

Table 2. Oral Targeted and Immunomodulatory Agents for Lymphoma

Agent (Drug)	Class (Type of Treatment)	Uses
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor	Approved for MCL after at least one prior therapy and for adult patients with CLL/SLL
Bexarotene (Targretin)	Retinoid	Approved to treat skin problems arising from CTCL after at least one prior systemic therapy
Crizotinib (Xalkori)	Targeted therapy; tyrosine kinase receptor inhibitor	Approved for patients 1 year of age and older and young adults with relapsed or refractory, systemic ALCL that is ALK-positive
Duvelisib (Copiktra)	Targeted therapy; PI3K- δ and PI3K- γ inhibitor	Approved for treatment of adult patients with relapsed or refractory CLL/SLL after at least two prior therapies
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor	Approved for CLL/SLL with or without a 17p deletion, WM, and chronic graft vs host disease in adult and pediatric patients aged 1 year and older following allogeneic stem cell transplantation (stem cells from a donor) after failure of one or more systemic therapies
Idelalisib (Zydelig)	Targeted therapy; PI3K- δ inhibitor	Approved for treatment of relapsed CLL in combination with rituximab (Rituxan)
Lenalidomide (Revlimid)	Immunomodulatory agent	Approved for relapsed or refractory MCL after two prior therapies, including bortezomib (Velcade), and for previously treated FL or MZL in combination with a rituximab product

Table 2. Oral Targeted and Immunomodulatory Agents for Lymphoma (continued)

Agent (Drug)	Class (Type of Treatment)	Uses
Pirtobrutinib (Jaypirca)	Targeted therapy; BTK inhibitor	Approved for adult patients with relapsed or refractory MCL after at least two lines of systemic therapy
Prednisone (Rayos)	Immunomodulatory and anti-inflammatory agent	Approved for palliative treatment of leukemias and lymphomas
Selinexor (Xpovio)	Targeted therapy; XPO1 inhibitor	Approved for treatment of relapsed or refractory DLBCL, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy
Tazemetostat (Tazverik)	Targeted therapy; EZH2 inhibitor	Approved for treatment of adult patients with relapsed or refractory FL with an EZH2 mutation after at least 2 prior systemic therapies or for adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor	Approved for treatment of adult patients with CLL/SLL
Vorinostat (Zolinza)	Targeted therapy; HDAC inhibitor	Approved for treatment of skin problems arising from CTCL in patients who have progressive, persistent, or recurrent disease on or following two systemic therapies
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Approved for the treatment of adult patients with MCL after at least one prior therapy, WM, and relapsed or refractory MZL who have received at least one anti-CD20-based regimen, CLL, and SLL.
Abexinostat (PCI-24781)	Targeted therapy; HDAC inhibitor	Under investigation for NHL, FL, DLBCL, and MCL
Azacitidine (CC-486)	Targeted therapy/ Immunomodulatory agents; hypomethylating agents	Under investigation for treatment of HL, FL, DLBCL, AITL, and other T-cell lymphomas
Lisafotoclax (APG-2575)	Targeted therapy; BCL-2 inhibitor	Under investigation for relapsed or refractory CLL/SLL
LNS8801	Targeted therapy; GPER agonist	Under investigation for lymphoma (subtype not specified)
Nanatinostat (VRx-3996)	Targeted therapy; HDAC inhibitor	Under investigation for Epstein-Barr virus-associated lymphoma
Tolinapant (ASTX660)	Targeted therapy; IAP antagonist	Under investigation for relapsed or refractory PTCL
Zandelisib (ME-401)	Targeted therapy; PI3K δ inhibitor	Under investigation for relapsed or refractory NHL, FL, and MZL

Abbreviations: AITL, angioimmunoblastic t-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BCL-2, B-cell lymphoma 2; ATLL, adult T-cell leukemia/lymphoma; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; GPER, G protein-coupled estrogen receptor; HDAC, histone deacetylase; IAP, inhibitor of apoptosis proteins; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia; XPO1, nuclear export receptor Exportin 1.

TREATMENTS UNDER INVESTIGATION

Some of the agents listed in the tables are being used in clinical trials for various types of lymphoma; some are used alone, and others are being added to existing therapy or used as part of new combination therapy regimens. The list of oral agents being tested in clinical trials is growing.

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 emerged.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and 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 at www.lymphoma.org/publications, 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 their physician. Medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [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 (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 depend 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
- Patient's age and gender
- 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 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 type, amount, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences.

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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