

## Oral Agents in Lymphoma

### Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

Currently, there are a number of chemotherapy and targeted anticancer drugs approved or under investigation for the treatment of lymphoma that can be taken by mouth, either in liquid or tablet/capsule form. Oral agents are just as effective and can have similar side effects as anticancer drugs that are given intravenously.

Oral agents are a convenient option for patients because 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 the dosage, which can compromise the effectiveness of the anticancer therapy. **It is critical that patients take all medications as prescribed to maximize the effectiveness of the treatment and to minimize toxicity and negative therapeutic outcomes.** Additionally, patients may feel isolated from their healthcare team when taking their anticancer medications at home, compared with

going to a cancer treatment center where they have direct interaction with the healthcare staff. Side effects may also go unnoticed or unreported to the healthcare team, and patients may also be afraid of managing side effects on their own. Many of the side effects of oral medications can be alleviated by supportive care, so it is important for patients to stay connected with their healthcare team, carefully track all potential side effects of their treatment, and report them back to their healthcare team so they can receive the best of care. Since keeping track of medications can be complicated, particularly when a combination medication regimen is prescribed in which agents may have different dosing schedules, drug diaries are available that can be helpful, as well as online reminders and apps for smartphones and devices. (see *Resources* section for information on smartphone apps).

Some oral agents are targeted therapies. Targeted therapies are directed against specific molecules needed for tumor growth, whereas standard chemotherapy agents are directed against any rapidly dividing cell, both normal and tumor cells. Because chemotherapy agents cannot tell the difference between cancer cells and normal cells, normal rapidly dividing cells like blood cells; cells in the mouth, stomach, and intestines; and hair follicles are affected. As a result, the side effects of chemotherapy are usually low blood cell counts, mouth sores, nausea, vomiting, diarrhea, and/or hair loss. In contrast, targeted therapies usually affect fewer normal cells and typically result in fewer serious side effects.

**Table. Targeted and Immunomodulatory Agents: Oral Agents in Lymphoma**

Agent	Class	How it Works	Indications
Panobinostat (Farydak)	Targeted therapy; HDAC inhibitor	Inhibits HDAC enzymes needed for expression of genes in DNA to inhibit cancer cell growth and division	Under investigation for patients with relapsed (disease returns after treatment) or refractory (disease does not respond to treatment) HL or NHL
Vorinostat (Zolinza)	Targeted therapy; HDAC inhibitor	Inhibits HDAC enzymes needed for expression of genes in DNA to inhibit cancer cell growth and division	Treatment of patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic (spread throughout the entire body) therapies  Under investigation in patients with B-cell NHL and CLL
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor	Inhibits B-cell receptor pathway needed for tumor cell survival and replication	Treatment of patients with MCL and CLL after receiving at least one prior treatment, CLL with 17p deletion, and Waldenström macroglobulinemia

Abbreviations: BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; FL, follicular lymphoma; HDAC, histone deacetylase; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma.

**Table. Targeted and Immunomodulatory Agents: Oral Agents in Lymphoma (continued)**

Agent	Class	How it Works	Indications
Spebrutinib (AVL-292; CC-292)	Targeted therapy; BTK inhibitor	Inhibits B-cell receptor pathway needed for tumor cell survival and replication	Under investigation for patients with B-cell NHL and CLL
Idelalisib (Zydelig)	Targeted therapy; phosphoinositide 3-kinase delta inhibitor	Inhibits B-cell receptor pathway needed for tumor cell survival and replication	Treatment of relapsed CLL in combination with rituximab, or when rituximab alone would be considered appropriate therapy; relapsed follicular B-cell NHL (FL) or SLL in patients who have received at least two prior systemic therapies
TGR-1202	Targeted therapy; phosphoinositide 3-kinase delta inhibitor	Inhibits B-cell receptor pathway needed for tumor cell survival and replication	Under investigation for B-cell malignancies
Lenalidomide (Revlimid)	Immunomodulatory and antiangiogenic agent	Not clear; may act by inhibiting growth of new blood vessels (angiogenesis) in tumors, enhancing status of immune system, or decreasing cytokines	Relapsed/refractory MCL after receipt of two prior therapies, one of which included bortezomib (Velcade) Under investigation for treatment of HL and NHL
Bexarotene (Targretin)	Retinoid	Selectively binds and activates retinoid X receptors, resulting in expression of genes that control cell growth and replication	To treat skin problems arising from CTCL after at least one prior systemic therapy
Venetoclax (formerly ABT-199)	Targeted therapy; inhibitor of B-cell lymphoma-2 (BCL-2)	Targets proteins thought to prevent cancer cells from dying	In 2015, the Food and Drug Administration (FDA) granted Breakthrough Therapy Designation for the treatment of previously treated (relapsed/refractory) patients with CLL who have 17p deletion Under investigation in patients with B-cell NHL
Navitoclax (formerly ABT-263)	Targeted therapy; inhibitor of BCL-2	Targets proteins thought to prevent cancer cells from dying	Under investigation for relapsed/refractory CLL Under investigation for NHL
Everolimus (Afinitor)	Targeted therapy; mammalian target of rapamycin (mTOR) inhibitor	Targets molecules in the biochemistry pathway involved in cell growth and division	Under investigation for treatment of HL and NHL
Alisertib (MLN8237)	Aurora A kinase inhibitor	Inhibits the serine/threonine protein kinase aurora A kinase, which may result in disruption of chromosomes and cell division	Under investigation in relapsed/refractory B- and T-cell lymphomas
Entospletinib (GS-9973)	Spleen tyrosine kinase inhibitor	Interferes with B-cell signaling	Under investigation for treatment of CLL, FL, and other forms of NHL

Abbreviations: BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; FL, follicular lymphoma; HDAC, histone deacetylase; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma.

**Table. Chemotherapy Treatment Options: Oral Agents in Lymphoma**

Agent	Class	How it Works	Indications
Cyclophosphamide (Cytoxan)	Alkylating agent (mustard gas derivative)	Chemically modifies DNA to cause death of growing cells	Burkitt lymphoma; CLL; HL; NHL; mycosis fungoides; conditioning regimens for bone marrow transplantation
Etoposide (Vepesid)	Topoisomerase II inhibitor	Interferes with topoisomerase enzymes that control manipulation of the structure of DNA necessary for replication	NHL; cutaneous T-cell lymphomas
Fludarabine (Oforta)	Adenosine deaminase inhibitor	Interferes with cancer cell's process of duplicating itself and causes cell death	CLL, including relapsed/refractory CLL; NHL
Chlorambucil (Leukeran)	Alkylating agent (nitrogen mustard)	Chemically modifies DNA to cause death of growing cells	CLL, HL, and NHL
Methotrexate (Rheumatrex)	Antimetabolite	Interferes with DNA synthesis and cell growth	Advanced mycosis fungoides, advanced stage NHL

Abbreviations: CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

## Treatments Under Investigation

Some of the agents listed above 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 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 the Lymphoma Research Foundation (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 [www.lymphoma.org](http://www.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](mailto:helpline@lymphoma.org).

## Follow-up

Patients with lymphoma 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 and CAT scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term effects or late 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 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 effects resulting from treatment or potential disease recurrences.

#### National Headquarters

115 Broadway, Suite 1301  
New York, NY 10006  
(212) 349-2910  
(212) 349-2886 fax

Helpline: (800) 500-9976  
helpline@lymphoma.org

Website: [www.lymphoma.org](http://www.lymphoma.org)

Email: [LRF@lymphoma.org](mailto:LRF@lymphoma.org)

#### Medical reviewer:

Michael E. Williams, MD, ScM  
University of Virginia School of Medicine

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## Support

A lymphoma diagnosis often triggers a range of feelings and raises concerns. In addition, cancer treatment can cause physical discomfort. Support groups and online message boards can help patients connect with other people who have lymphoma. One-to-one peer support programs, such as the LRF Lymphoma Support Network, match lymphoma patients (or caregivers) with volunteers who have gone through similar experiences.

## Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts, as well as disease-specific websites, videos, and eNewsletters for current lymphoma information and treatment options. To learn more about any of these resources, visit our website at [www.lymphoma.org](http://www.lymphoma.org), or contact the LRF Helpline at (800) 500-9976 or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

Although oral therapy can be conveniently taken by mouth at home, patients may have higher out-of-pocket financial costs compared with patients on intravenous therapy receiving treatment in a doctor's office or healthcare facility. LRF can assist patients to identify sources of financial support. It is important for patients to understand their health insurance coverage and their payment responsibility for oral chemotherapies. Patients may find that their financial responsibility, reflected in co-pay and co-insurance contributions, is higher for an oral agent. Numerous public and private resources, and sometimes even manufacturers' programs, exist to assist patients with these expenses. LRF's financial assistance programs can also assist eligible patients in need of financial support.

LRF has also launched a new application for smartphones and tablets to help patients keep track of oral chemotherapy agents. *Focus on Lymphoma* is the first mobile app that provides patients and caregivers 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 suite 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 device 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, to make reviewing progress with their physician or nurse easier.

The *Focus on Lymphoma* mobile app is now available for free download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit [www.FocusOnLymphoma.org](http://www.FocusOnLymphoma.org).