LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma
Oral Agents in Lymphoma

In the past, most treatments for lymphoma had to be given intravenously (IV) at a hospital or cancer center. However, today there are many chemotherapeutic drugs and targeted anticancer drugs for the treatment of lymphoma that can be taken by mouth, either in liquid or tablet/capsule form. Oral agents can be very effective at suppressing 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 the dosage, which can reduce the effectiveness and safety of the anticancer therapy. Taking all medications as prescribed is important to maximize the effectiveness of the treatment and to minimize serious side effects.

Patients are typically monitored closely in the early weeks and months after starting an oral agent, but after being on a medication for a longer period of time, they may follow up with their healthcare team only every two to four months. Blood work and tests may be obtained less frequently for patients on an oral agent compared with 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 adjustments, 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 medications prescribed 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 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 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, to make reviewing progress with their physician or nurse easier. *Focus On Lymphoma* is 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 **lymphoma.org/mobileapp**.

ORAL TREATMENT OPTIONS

Oral agents include targeted therapies, chemotherapy agents, and immunomodulatory drugs. 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 do not distinguish between cancer cells and normal cells, they also damage normal rapidly dividing cells like those in the hair follicles, mouth, and blood. This leads to side effects such as low blood cell counts, mouth sores, nausea, vomiting, diarrhea, and hair loss. In contrast, targeted therapies usually affect fewer normal cells, resulting in fewer of these types of serious side effects. *Immunomodulatory agents* stimulate or suppress the immune system and may also have antiangiogenic properties, which means they prevent cancer cells from getting nutrients from the blood.

United States Food and Drug Administration (FDA) approved and investigational oral chemotherapy agents are listed in **Table 1** on the next page. Targeted and *immunomodulatory agents* (drugs that cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate the immune system to destroy cancer cells) for lymphoma are listed in **Table 2**. In describing the indications, the term "relapsed" refers to cancer that returns after treatment and "refractory" means that the cancer does not respond to treatment.

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 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 **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**.

Table 1. Chemotherapy Treatment Options: Oral Agents in Lymphoma

Agent	Class	Indications
Cyclophosphamide	Alkylating agent (mustard gas derivative)	Approved for HL, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, MM, mycosis fungoides and leukemias
Chlorambucil (Leukeran)	Alkylating agent (nitrogen mustard)	Approved for CLL, lymphosarcoma, FL, and HL
Lomustine (Gleostine)	Alkylating agent (nitrosurea)	Approved for relapsed or refractory HL, used in combination therapy
Methotrexate	Antimetabolite	Approved for advanced mycosis fungoides and advanced-stage 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
Azacitidine (CC-486)	Antimetabolite	Under investigation for treatment of HL, DLBCL, FL and AITL

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; RNA, ribonucleic acid.

Table 2. Oral Targeted and Immunomodulatory Agents for Lymphoma

Agent	Class	Indications
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor	Approved for MCL after at least one prior therapy and for 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 and FL after at least two prior therapies
Ibrutinib (Imbruvica)	Targeted therapy; BTK inhibitor	Approved for treatment of adult patients with MCL after at least one prior treatment, CLL/SLL with or without a 17p deletion, MZL who require systemic therapy and after at least one prior anti-CD20-based therapy, and WM

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; Bcl-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CK, casein kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; FDA, food and drug administration; FL, follicular lymphoma; GPER, G protein-coupled estrogen receptor; HL, Hodgkin lymphoma; HDAC, histone deacetylase; HL, hodgkin lymphoma; IAP, inhibitors 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.

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

Agent	Class	Indications
Idelalisib (Zydelig)	Targeted therapy; PI3K-γ inhibitor	Approved for treatment of relapsed CLL in combination with rituximab, when rituximab alone would be considered appropriate therapy, and in relapsed FL or SLL after at least two prior systemic therapies
Lenalidomide (Revlimid)	Immunomodulatory and antiangiogenic agent	Approved for relapsed or refractory MCL after two prior therapies including bortezomib and for previously treated FL or MZL in combination with rituximab
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 relapsed or refractory FL with an EZH2 mutation or for patients with FL who have no satisfactory alternative treatment options
Umbralisib (Ukoniq)	Targeted therapy; multiple kinase inhibitor (PI3Kδ and CK1ε)	Approved for relapsed or refractory MZL after at least one prior anti-CD20-based regimen and relapsed or refractory FL after at least 3 prior lines of systemic therapy
Venetoclax (Venclexta)	Targeted therapy; Bcl-2 inhibitor	Approved for treatment of CLL/SLL
Vorinostat (Zolinza)	Targeted therapy; HDAC inhibitor	Approved for treatment of patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Approved for the treatment of MCL after at least one prior therapy
Abexinostat (PCI-24781)	Targeted therapy; HDCA inhibitor	Under investigation for HL, FL, DLBCL and MCL
APG-2575	Targeted therapy; Bcl-2 inhibitor	Under investigation for CLL/SLL
DTRM-555	Targeted therapy; BTK inhibitor	Under investigation for relapsed or refractory CLL/SLL, DLBCL, FL
Entospletinib (GS-9973)	Spleen tyrosine kinase inhibitor	Under investigation for treatment of CLL, FL, and other forms of NHL
Fimepinostat (CUDC-907)	Targeted therapy; dual PI3K and HDAC inhibitor	Under investigation for relapsed and refractory lymphoma. Granted FDA Fast Track designation for adult patients with relapsed or refractory DLBCL.
Iberdomide (CC-220)	Targeted therapy; cereblon E3 ligase modulator	Under investigation for NHL, FL and DLBCL

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; Bcl-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CK, casein kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; FDA, food and drug administration; FL, follicular lymphoma; GPER, G protein-coupled estrogen receptor; HL, Hodgkin lymphoma; HDAC, histone deacetylase; HL, hodgkin lymphoma; IAP, inhibitors 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.

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

Agent	Class	Indications
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
Panobinostat (Farydak)	Targeted therapy; HDAC inhibitor	Under investigation for patients with relapsed/ refractory HL or NHL
Parsaclisib (INCB050465)	Targeted therapy; PI3Kδ inhibitor	Under investigation for FL, MCL, relapsed or refractory DLBCL, CLL/SLL, NHL
Tenalisib (RP6530)	Targeted therapy; PI3K inhibitor	Under investigation for NHL and T cell lymphoma
Tolinapant (ASTX660)	Targeted therapy; IAP antagonist	Under investigation for relapsed or refractory PTCL, CTCL and ATLL
Zandelisib (ME-401)	Targeted therapy; PI3Kδ inhibitor	Under investigation for NHL, FL and MZL

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; Bcl-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CK, casein kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EZH2, enhancer of zeste homolog 2; FDA, food and drug administration; FL, follicular lymphoma; GPER, G protein-coupled estrogen receptor; HL, Hodgkin lymphoma; HDAC, histone deacetylase; HL, hodgkin lymphoma; IAP, inhibitors 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.

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, 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 or late side effects, which can vary based on the 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 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 lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one 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 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 CLL/SLL including our award-winning mobile app. LRF also provides many educational activities, including our in-person meetings, podcasts, webinars for people with lymphoma, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options. To learn more about any of these resources, visit our website at **ww.lymphoma.org**, or contact the LRF Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

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