Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Immunotherapy and Other Targeted Therapies

Lymphoma Research Foundation

Immunotherapy, also called biological response modifier therapy, works with the body's normal cell functions to fight cancer. The action of these therapies is more focused on specific targets, whereas conventional chemotherapy generally kills any rapidly multiplying cell in the body.

The term "biologics" refers to complex molecules that may occur naturally in the body or be made in a laboratory (using bacteria, yeast cells, or purified mammalian cells). Biologic agents may be given alone (*monotherapy*) or with other anti-cancer agents (*combination therapy*). Types of biological therapy include immunotherapy (like antibodies, cytokines and cell therapy), growth factors and some targeted therapies:

- Immunotherapy consists of treatments that use the body's immune system to treat cancer, like the following:
  - Monoclonal antibodies are proteins made in the laboratory that bind to cancer cells and help the immune system destroy them.
  - Immune checkpoint inhibitors are monoclonal antibodies that recognize immune checkpoint proteins. Checkpoint proteins (such as PD-1/PD-L1) regulate (activate or slow down) the immune responses against the body's own cells.
  - Antibody-drug conjugates (ADC) are monoclonal antibodies attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication.
  - Radioimmunotherapy (RIT) consists of a targeted antibody attached to a radioisotope (a particle that emits radiation). RIT acts as a "guided missile" to destroy lymphoma cells by attaching to them and delivering small doses of radiation.
  - Immunomodulatory agents are drugs that regulate the immune system by activating or slowing down the activity of specific proteins. They cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate the immune system to help destroy cancer cells.
  - Chimeric antigen receptor (CAR) T-cell therapies are a special type of immunotherapy, that use the patients' T-cells or donor T-cells to treat cancer. Briefly, T-cells are collected from patients or donors and genetically modified to produce a special molecule called CAR, which recognizes antigens in the surface of cancer cells. The genetically modified CAR T-cells are grown in the laboratory until they number in the billions and are then infused into the patient after a short course of chemotherapy, where they recognize and destroy cancer cells.
    - Autologous T-cells (patients receive their own T-cells)
    - Allogeneic T-cells (patients receive T-cells from a donor)
  - Bispecific Antibodies (bsAbs) recognize two different antigens, which can be on the same cell or two different cells. BsAbs used to treat lymphoma are called T-cell engagers and work by linking cancer cells to healthy immune cells.
  - Cytokines are proteins that coordinate cell-to-cell communication and help regulate the body's immune response.
- Growth factors are proteins (such as hormones) that promote cell growth and differentiation.
- Targeted therapies are generally small molecules that affect the biological processes of cancer cells (how they grow, multiply, and spread). This includes inhibitors of proteins involved in cell signaling and growth like kinases and other proteins.

For more information on immunotherapy, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit **lymphoma.org/publications**).

Immunotherapy

The immune system is made of various cells, tissues, and organs that work together to fight off harmful pathogens (like bacteria and viruses), as well as cancers. The term immunotherapy refers to treatments that use the immune system response to treat cancer, including lymphoma.

Immunotherapy in Lymphoma

Lymphoma occurs when white blood cells of the immune system called lymphocytes grow and multiply uncontrollably. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B-cells) and T lymphocytes (T-cells). While the immune system monitors the body to find and eliminate lymphoma cells, sometimes lymphoma cells are able to "hide" from, deceive, or even shut down this response. By improving or replacing parts of the immune response, immunotherapy helps to eliminate lymphoma cells from the body. Lymphoma cells tend to be sensitive to changes in the immune system, although this differs between patients and depends on the lymphoma subtype. Ultimately, how lymphomas respond to immunotherapy depends on how well the immune system can target the lymphoma cells.

Most immunotherapy drugs are given to patients in the same way as chemotherapy: *subcutaneously* (injection under the skin) or *intravenously* (injection directly into a vein; IV). Some immunomodulatory drugs are administered orally. Patients who have received IV lines like a peripherally inserted central catheter (PICC) or port for chemotherapy may as well receive their immunotherapy through the same intravenous line. Immunotherapy is often given in combination with chemotherapy, and this regimen is called *chemoimmunotherapy*.

Oncology nurses are usually responsible for giving the immunotherapy prescribed by the doctor. Most patients receive their immunotherapy in an outpatient clinic, hospital outpatient department, or doctor's office. Sometimes patients must stay in the hospital for treatment.

Depending on the type of lymphoma, immunotherapies may be used as monotherapy or in combination therapy as initial treatment for patients, and for those with *relapsed* (disease returns) or *refractory* (disease no longer responds to treatment) disease. Several agents are approved by the U.S. Food and Drug Administration (FDA) for different lymphoma subtypes, and new unapproved immunotherapies are being evaluated and may be given to patients in clinical trials. Below are listed types of immunotherapies that are approved to treat lymphoma.

Monoclonal Antibodies

Monoclonal antibodies are the most common biologic agents used for lymphoma treatment. Scientists can now develop monoclonal antibodies in the laboratory that are designed to recognize antigens (specific molecules such as CD19, CD20 or CD52) that are present on the surface of certain cancer cells.

Once in the bloodstream, monoclonal antibodies travel throughout the body and bind to their specific target antigens. All monoclonal antibodies are given either intravenously or subcutaneously.

Infusion reactions usually occur with the first infusion and can be treated with antiallergic medications. It is unlikely to have these reactions with the infusions that follow the first. Other common side effects are fever, chills, weakness, headache, nausea/vomiting, diarrhea, low blood pressure, chest tightness, and rashes.

Rituximab (Rituxan) and Biosimilars

Rituximab was the first monoclonal antibody approved by the FDA for cancer. Rituximab targets the antigen CD20 and is indicated for the treatment of adult patients in certain cases of non-Hodgkin lymphoma (NHL) or chronic lymphocytic leukemia (CLL) as a single agent or in combination with specific chemotherapy regimens.

Rituximab (Rituxan) is also approved for use in pediatric patients aged 6 months and older with mature B-cell NHL, including previously untreated, advanced stage, CD20-positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL) and Burkitt-like lymphoma (BLL) in combination with chemotherapy.

Biosimilars is the term used to describe products that copy biologics. Biosimilars must undergo review by regulatory agencies such as the FDA or the European Medicines Agency (EMA) to demonstrate that they closely resemble the original reference drug and are as safe and effective. FDA-approved rituximab biosimilars for the treatment of lymphoma include rituximab-abbs (Truxima), rituximab-pvvr (Ruxience) and rituximab-arrx (Riabni).

Rituximab and Hyaluronidase Human (Rituximab Hycela)

A subcutaneous form of rituximab (Rituxan Hycela or "rituximab and hyaluronidase human") includes the same monoclonal antibody as IV rituximab (Rituxan) in combination with hyaluronidase human, an enzyme that helps to deliver rituximab under the skin. Rituxan Hycela was approved by the FDA in 2017 for use in patients with follicular lymphoma (FL), DLBCL and CLL as a single agent or in combination with specific chemotherapy regimens.

Obinutuzumab (Gazyva)

Obinutuzumab is another monoclonal antibody administered by IV infusion that targets CD20 on the surface of B-cells. Obinutuzumab is approved in the following conditions:

- In combination with chlorambucil (Leukeran) for the treatment of patients with previously untreated CLL.
- In combination with bendamustine (Treanda) followed by obinutuzumab (Gazyva) monotherapy for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen.
- In combination with chemotherapy followed by obinutuzumab (Gazyva) monotherapy in patients achieving at least a partial remission (decrease in tumor size and/or spread cancer in the body), for the treatment of adult patients with previously untreated stage II bulky, III or IV FL.

Tafasitamab-cxix (Monjuvi)

Tafasitamab is an antibody that targets CD19 and is indicated in combination with lenalidomide (Revlimid) for the treatment of adult patients with relapsed or refractory DLBCL (not otherwise specified), including DLBCL arising from low grade lymphoma, and who are not eligible for autologous (patient receives own stem cells) stem cell transplant (SCT). Autologous SCT is commonly given after the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells and consists of receiving their own healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells.

Mogamulizumab-kpkc (Poteligeo)

Mogamulizumab is a monoclonal antibody directed at CC chemokine receptor type 4 (CCR4) and is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome after at least one prior systemic therapy (treatments that travel through the bloodstream, reaching cells all over the body).

Ofatumumab (Arzerra)

Ofatumumab is a monoclonal antibody that also targets the CD20 antigen. Ofatumumab is approved for patients with CLL:

- In combination with chlorambucil (Leukeran), for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate.
- In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL.
- For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL.
- For the treatment of patients with CLL refractory to fludarabine and alemtuzumab (Campath).

However, it is only provided through the Arzerra Oncology Access Program and is no longer commercially available. For more information visit the manufacturer's website (**https://www.us.arzerra.com/**) or call **1-800-282-7630**.

Alemtuzumab (Campath)

Alemtuzumab is a monoclonal antibody that targets the CD52 antigen on the surface of cancerous lymphocytes. Alemtuzumab is approved for the treatment of B-cell CLL and is administered by IV infusion. However, it is provided only through the Campath Distribution Program and is no longer commercially available. For more information about the Campath Distribution Program, call **877-422-6728**.

Antibody-Drug Conjugates

Similar to monoclonal antibodies, ADCs are given intravenously. Side effects may include low blood cell counts, infection, nerve damage leading to neuropathy, fatigue, and nausea. FDA-approved ADCs to treat lymphoma are listed below.

Brentuximab Vedotin (Adcetris)

Brentuximab vedotin (Adcetris) is an ADC that targets CD30 and is indicated for the treatment of:

- Adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL), in combination with doxorubicin, vinblastine, and dacarbazine.
- Adult patients with cHL at high risk of relapse or progression as consolidation therapy after autologous SCT.
- Adult patients with cHL after failure of autologous SCT or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not candidates for autologous SCT.
- Adult patients with previously untreated systemic anaplastic large cell lymphoma (ALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone.
- Adult patients with systemic ALCL after failure of at least one prior multiagent chemotherapy regimen.
- Adult patients with primary cutaneous ALCL or CD30-expressing MF who have received prior systemic therapy.
- Pediatric patients 2 years of age or older with previously untreated high-risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.

Polatuzumab Vedotin-piiq (Polivy)

Polatuzumab vedotin (Polivy) is an ADC that targets CD79b and is indicated:

- In combination with rituximab product, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients who have previously untreated DLBCL, not otherwise specified, or high-grade B-cell lymphoma (HGBCL) and who have an International Prognostic Index score of 2 or greater.
- In combination with bendamustine (Treanda) and a rituximab product for the treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, after at least two prior therapies.

Loncastuximab Tesirine (Zynlonta)

Loncastuximab tesirine is an antibody directed at CD19 conjugated with an alkylating agent indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, DLBCL arising from low-grade lymphoma, and HGBCL.

Radioimmunotherapy

Ibritumomab Tiuxetan (Zevalin)

Ibritumomab tiuxetan consists of the monoclonal antibody ibritumomab, a radioisotope, and a molecule called tiuxetan that links them together. Like rituximab (Rituxan), ibritumomab tiuxetan targets CD20-expressing B-cells. Once the ibritumomab component of the drug binds to an NHL B-cell that expresses CD20, the radioactive component damages the cell, activating its destruction. Ibritumomab tiuxetan (Zevalin) is approved to treat patients with:

- Low-grade NHL or FL when the disease relapses or is refractory.
- Newly diagnosed FL who have achieved partial or complete responses to frontline (initial) chemotherapy.

Ibritumomab tiuxetan is given through an IV infusion in combination with two rituximab treatments. The most common side effects of ibritumomab tiuxetan include low blood cell counts, fatigue (tiredness), nasopharyngitis (inflammation of the nose), and nausea.

Immunomodulatory Drugs

Lenalidomide (Revlimid)

Lenalidomide is an immunomodulatory drug that slows down the growth and induces the death of some types of malignant blood cells, including MCL cells. Lenalidomide should not be taken by pregnant women. Lenalidomide is approved by the FDA for patients with:

- Refractory or relapsed MCL after two prior treatments (one of which includes bortezomib [Velcade]).
- Previously treated FL, in combination with a rituximab product.
- Previously treated marginal zone lymphoma (MZL), in combination with a rituximab product.

Lenalidomide is a capsule which is taken by mouth once daily, with or without food. Some of the most common side effects of lenalidomide include low blood cells or platelets, fatigue, diarrhea, nausea, and coughing.

CAR T-Cell Therapy

FDA-approved CAR T-cell therapies target CD19 and are listed below.

Axicabtagene Ciloleucel (Yescarta)

Axicabtagene ciloleucel was first approved in October 2017 and is indicated for the treatment of:

- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL (not otherwise specified), primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from FL.
- Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- Adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

Tisagenlecleucel (Kymriah)

Tisagenlecleucel was first approved in May 2017 and is indicated for the treatment of adult patients with:

- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL (not otherwise specified), HGBCL, and DLBCL arising from FL.
- Relapsed or refractory FL after two or more lines of systemic therapy.

Brexucabtagene Autoleucel (Tecartus)

Brexucabtagene autoleucel was approved in July 2020 for the treatment of adults with relapsed or refractory MCL.

Lisocabtagene Maraleucel (Breyanzi)

Lisocabtagene maraleucel was first approved in February 2021 and is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma, including DLBCL (not otherwise specified), DLBCL arising from indolent lymphoma, HGBCL, PMBCL, and FL grade 3B, who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.
- Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for SCT due to comorbidities (other diseases that the patient may have at the same time) or age.
- Relapsed or refractory disease after two or more lines of systemic therapy.
- Relapsed or refractory CLL or SLL who have received at least 2 prior lines of therapy, including a Bruton's tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor.

Important side effects related to CAR T-cells are 1) cytokine release syndrome (CRS, a group of symptoms including fever, hypotension [low blood pressure] and hypoxia [low oxygen levels in the blood], caused by cytokines released by the infused CAR T-cells) and 2) neurological toxicity (damage to the nervous system called immune effector cell-associated neurotoxicity syndrome or ICANS). Both side effects can be effectively managed with the aid of anti-inflammatory medications like steroids and anti-cytokine therapies. Infections and low blood counts can also occur. To learn more about CAR T-cell therapy, please view the *Understanding Cellular Therapy* publication on the Foundation's website (**lymphoma.org/publications**).

Bispecific Antibodies

Like standard monoclonal antibodies, bsAbs can be administered IV or subcutaneously. Once in the bloodstream, bsAbs travel throughout the body and bind to their specific antigens on the surface of the target cells. Safety concerns for bsAbs include CRS and neurological effects (including immune effector cell-associated neurotoxicity syndrome). This condition can be very serious, but it is manageable with medication. Infections and low blood counts can also occur.

Mosunetuzumab (Lunsumio)

Mosunetuzumab is a bsAbs that targets CD20 and CD3 (T-cell engager) and is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

Epcoritamab (Epkinly)

Epcoritamab-bysp is a T-cell engager bsAb that binds to CD20 and CD3 and is indicated for the treatment of adult patients with relapsed or refractory DLBCL (not otherwise specified), including DLBCL arising from indolent lymphoma, and HGBCL after two or more lines of systemic therapy.

Glofitamab (Columvi)

Glofitamab-gxbm is a bsAb that binds to CD20 and CD3 and is indicated for treatment of adult patients with relapsed or refractory DLBCL, not otherwise specified, or large B-cell lymphoma arising from FL, after two or more lines of systemic therapy. The CD20 antibody obinutuzumab is given as part of treatment with glofitamab and is administered one week prior to the first dose of glofitamab.

Immune Checkpoint Inhibitors

Checkpoint proteins (such as CTLA-4/B7-1/B7-2 and PD-1/PD-L1) regulate (activate or slow down) the immune responses against the body's own cells. Some cancers can activate checkpoint proteins and escape the immune system. Checkpoint inhibitors block this mechanism, thereby restoring the immune system's ability to attack the cancer cells and rid them from the body. These drugs are given intravenously. The most common side effects associated with checkpoint inhibitors include fatigue, rash, upper respiratory tract infection, fever, diarrhea, and cough. FDA-approved checkpoint inhibitors indicated for the treatment of lymphoma are listed below.

Nivolumab (Opdivo)

Nivolumab is a checkpoint inhibitor that binds to the programmed death receptor-1 (PD-1). It is approved for the treatment of adult patients with cHL that has relapsed or progressed after:

- Autologous SCT and brentuximab vedotin (Adcetris).
- 3 or more lines of systemic therapy that includes autologous SCT.

Pembrolizumab (Keytruda)

Pembrolizumab is a checkpoint inhibitor that binds to PD-1. It is approved for the treatment of:

- Adult patients with relapsed or refractory cHL.
- Pediatric patients with cHL that became refractory or have relapsed after 2 or more lines of therapy.
- Adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more lines of therapy. It is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Growth Factors

Filgrastim (Neupogen) and Biosimilars
Filgrastim is a human protein called a granulocyte colony-stimulating factor (G-CSF). G-CSF does not have anticancer properties but is given as supportive care to stimulate production of white blood cells either after chemotherapy or before and during STC. Filgrastim is given by IV infusion or subcutaneously. Side effects include pain, rash, cough, shortness of breath and fever. Filgrastim-sndz (Zarxio) is an FDA-approved biosimilar of filgrastim.

Epoetin Alfa (Epogen, Procrit)
Epoetin alfa stimulates the growth of red blood cells and is used to treat anemia, which can arise after chemotherapy. Epoetin does not have anticancer properties but is given as supportive care in lymphoma. Epoetin alfa is given subcutaneously three times a week (adults) or intravenously once a week (pediatrics) during chemotherapy treatment. The most common side effects in patients with cancer on chemotherapy are nausea and vomiting, but other side effects such as muscle, bone, or joint pain and inflammation in the mouth (stomatitis) may also occur.

Cytokines

Cytokine drugs are synthetic versions of naturally occurring cytokines that boost the body's immune response to lymphoma. They are not commonly used today for the treatment of lymphoma. They may be given subcutaneously or intravenously. Common side effects of cytokines include flu-like symptoms, low white cell counts, rashes, and thinning hair.

Denileukin Diftitox (Ontak)
Denileukin dititox is a cytotoxin directed at CD25 and indicated for the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. This drug was discontinued in 2014 and is no longer available in the US.

Interferon Alfa-2b (Intron A)
Intron A is a recombinant interferon alfa-2b approved for the initial treatment of clinically aggressive follicular NHL in conjunction with anthracycline-containing combination chemotherapy in patients 18 years of age or older. This drug was discontinued in 2022.

Oprelvekin (Neumega)
Oprelvekin is used to stimulate platelet production, which may be decreased by chemotherapy. Platelets are needed to help the blood clot and to prevent bleeding. Oprelvekin is a supportive therapy, meaning it helps patients to tolerate chemotherapy, but it has no anticancer activity itself. Oprelvekin is given subcutaneously. Common side effects include water retention in the hands, feet, and ankles, shortness of breath, increased heart rate, abnormal heart rhythms, and bloodshot eyes.

Targeted Therapies

A list of targeted therapies currently approved to treat lymphoma is presented in **Table 1**.

Table 1: Targeted Therapies in Lymphoma

Agent	Target	Route	Indications	Side Effects
Acalabrutinib (Calquence)	BTK inhibitor	Oral	MCL after at least one prior therapy and CLL/SLL	Low blood cell count, low platelets, upper respiratory tract infection, headache, diarrhea and musculoskeletal pain
Belinostat (Beleodaq)	HDAC inhibitor	IV	r/r PTCL	Nausea, tiredness, fever, anemia, and vomiting
Bexarotene (Targretin)	Retinoid X receptor activator	Oral/topic	CTCL (after at least 1 prior systemic therapy)	High blood fats and cholesterol, low white blood cell count, headache, hypothyroidism, weakness, rash, nausea, infection, peripheral edema, abdominal pain, and dry skin
Bortezomib (Velcade)	Proteosome inhibitor	IV	MCL	Nausea, diarrhea, low platelet and blood cell counts, numbness, tingling, pricking sensations, or sensitivity to touch, constipation, vomiting, rash, fever, and anorexia (eating disorder)
Crizotinib (Xalkori)	Tyrosine kinase receptor inhibitor	Oral	r/r systemic and ALK-positive ALCL in pediatric patients 1 year of age and older and young adults	Diarrhea, vomiting, nausea, vision disorder, headache, musculoskeletal pain, sore mouth, tiredness, decreased appetite, fever, abdominal pain, cough, itching, low blood cell counts

Agent	Target	Route	Indications	Side Effects
Duvelisib (Copiktra)	PI3K-δ and PI3K-γ inhibitor	Oral	r/r CLL/SLL in adult patients after at least 2 prior therapies	Diarrhea or colitis, low blood cell count, rash, tiredness, fever, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain
Ibrutinib (Imbruvica)	BTK inhibitor	Oral	Adult CLL/SLL with or without 17p deletion, WM	Diarrhea, muscle and bone pain, rash, nausea, bruising, tiredness, low platelets and blood cell counts
Idelalisib (Zydelig)	PI3K-γ inhibitor	Oral	Relapsed CLL in combination with rituximab (Rituxan)	Diarrhea, pneumonia, fever, tiredness, nausea, cough, and rash
Pirtobrutinib (Jaypirca)	BTK inhibitor	Oral	r/r MCL and r/r CLL/SLL after 2 or more systemic therapies	Tiredness, muscle, joint, and bone pain, diarrhea, swelling, shortness of breath, pneumonia, bruising
Romidepsin (Istodax)	HDAC inhibitor	IV	Adult CTCL after at least 1 prior therapy	Infections, nausea and vomiting, tiredness, anorexia, changes in ECG, abnormal taste, constipation, itching and low blood cell counts.
Selinexor (Xpovio)	XPO1 inhibitor	Oral	r/r DLBCL NOS, including DLBCL arising from FL, after at least 2 lines of systemic therapy	Tiredness, nausea, diarrhea, decreased appetite, weight loss, constipation, vomiting, fever, and low blood cell counts
Tazemetostat (Tazverik)	EZH2 inhibitor	Oral	r/r FL with an EZH2 mutation after 2 prior systemic therapies or who have no satisfactory alternative treatment options	Tiredness, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain
Venetoclax (Venclexta)	Bcl-2 inhibitor	Oral	Adult CLL/SLL	Low blood cell counts, diarrhea, nausea, cough, upper respiratory tract infection, musculoskeletal pain, tiredness, swelling
Vorinostat (Zolinza)	HDAC inhibitor	Oral	Progressive, resistant or relapsed CTCL after taking 2 other systemic therapies	Diarrhea, tiredness, nausea, low platelet counts, anorexia, and abnormal taste
Zanubrutinib (Brukinsa)	BTK inhibitor	Oral	MCL after at least 1 prior therapy, WM, r/r MZL after at least 1 anti-CD20-based regimen, and CLL/SLL.	Low blood cell count, upper respiratory tract infection, hemorrhage, rash and musculoskeletal pain

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; Bcl-2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; ECG, electrocardiogram; EZH2, enhancer of zeste homolog 2; FL, follicular lymphoma; HDAC, histone deacetylase; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NOS, not otherwise specified; PTCL, peripheral T cell lymphoma; PI3K, phosphoinositide 3-kinase; r/r, relapsed or refractory; SLL, small lymphocytic lymphoma; SQ, subcutaneous; WM, Waldenström macroglobulinemia; XPO1, nuclear export receptor Exportin 1.

Novel Therapies Currently Under Investigation

Before approval by the FDA or other regulatory agencies, anticancer drug treatments undergo rigorous testing to show that they are effective and safe. After effectiveness and safety are demonstrated in animals, new treatments must be tested in clinical trials of human patients. The trial results are reviewed by the regulatory agencies before approving the new treatments.

Some patients are able to receive unapproved therapies by participating in a clinical trial, although the treatment given to each participant in the trial is generally randomly assigned. Therefore, participation in the trial does not ensure treatment with the new therapy. Because scientific research is always evolving, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared.

Some therapies are being studied in clinical trials for different diseases or treatment lines. Examples of new therapies under study for lymphoma are listed in the table below. For a comprehensive list of new investigational drugs for lymphoma, visit clinicaltrials.gov.

Table 2: Investigational Drugs in Lymphoma

Type of therapy	Drug	Target	Condition
Monoclonal antibodies	IMT-009	CD161	DLBCL, BL, T-cell lymphoma, HL
	Magrolimab	CD47	HL, r/r HL, NHL, CTCL
Bispecific antibodies	Blinatumumab (Blincyto)	CD19 and CD3	NHL
	Odronextamab (REGN1979)	CD20 and CD3	B-cell NHL, DLBCL, FL, r/r FL, r/r MZL
	AFM-13	CD30 and CD16A	r/r NHL
Antibody-drug conjugates	Belantamab mafodotin (Blenrep)	B-cell maturation antigen	r/r plasmablastic lymphoma, ALK-positive large B-cell lymphoma
	Inotuzumab ozogamicin (Besponsa)	CD22	B-cell lymphoblastic lymphoma, NHL
Immune checkpoint inhibitors	Atezolizumab (Tecentriq)	PD-1/PD-L1	FL, DLBCL, r/r HL, NHL, CLL
	Toripalimab	PD-1	Extranodal NK/T-cell lymphoma (nasal type), HGBCL, FL, DLBCL, ALK-positive ALCL
	Cemiplimab (REGN2810)	PD-1	NK/T-cell lymphoma, lymphoma, CTCL
	Durvalumab (Imfinzi)	PD-L1	CLL/SLL, NK-Cell lymphoma, NHL, CTCL, and PTCL
	Balstilimab (AGEN2034)	PD-1	r/r lymphomas
CAR T-cell therapy	ALLO-501A	Allogeneic (healthy donor derived), CD19	r/r large B-cell lymphoma
	CD19-CD22 CAR T-Cells	Autologous, CD19 and CD22	CD19- and CD22-positive lymphomas
	MB-106	Autologous, CD20	r/r B-cell NHL, FL, MCL, SLL, WM, CLL
	PBCAR0191	Allogeneic, CD19	NHL
Targeted therapies	Abexinostat (PCI-24781)	HDCA inhibitor	FL and DLBCL
	Nanatinostat (VRx-3996)	HDAC inhibitor	EBV-associated lymphoma
	Tofacitinib	JAK inhibitor	DLBCL
	Tolinapant (ASTX660)	IAP antagonist	r/r PTCL
Vaccines *Vaccines that stimulate the immune system to fight lymphoma cells*	CDX-301 (rhuFlt3L)	Flt3	NHL
	Poly-ICLC (Hiltonol)	TLR3	NHL

Abbreviations: ALK, anaplastic lymphoma kinase; BL, Burkitt lymphoma; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; FL, follicular lymphoma; Flt3, Fms-like tyrosine kinase 3; HDAC, histone deacetylase; HGBCL, high-grade B-cell lymphoma; HL, Hodgkin lymphoma; IAP, inhibitor of apoptosis; JAK, janus kinase; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PTCL, peripheral T-cell lymphoma; r/r, relapsed or refractory; SLL, small lymphocytic lymphoma; TLR3, toll-like receptor 3; WM, Waldenström macroglobulinemia.

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 the Foundation's website at **www.lymphoma.org/publications**, talk to their physician, or contact the Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Questions to Ask Your Doctor

- What is the goal of my treatment?
- What are the risks, possible side effects, and benefits of the treatment I will receive?
- What symptoms should I expect? Which of these should prompt me to seek medical attention?
- What side effects should I expect? Which of these should prompt me to seek medical attention?
- What should I do to take care of myself before and during treatment?
- How long will each treatment session last?
- How long will the entire treatment process last?
- What are the chances that the treatment will be successful?
- How will the treatment affect my normal activities (e.g., work, school, childcare, driving, sexual activity, exercise)?
- Will I be able to work during treatment?
- How often will I need a checkup?
- How much will the treatment cost? Will my insurance cover it?
- Will a particular therapy impact potential future treatment decision?

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**.

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**.

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**, or contact the 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**).

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**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

Research. Community. Cure.

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