LYMPHOMA RESEARCH • FOUNDATION

Understanding Immunotherapy and Lymphoma

The term immunotherapy refers to treatments that capitalize on the immune response to treat cancer.

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. Immunotherapies may either enhance or replace parts of the immune system, enabling it to once again eliminate unwanted cells.

INTRODUCTION TO IMMUNOTHERAPY

IMMUNOTHERAPY AND CANCER

The immune system patrols the body for cancer cells. When a cancer cell is detected, the immune system launches an attack to eliminate it. However, some cancer cells are able to "hide" from, deceive, or even shut down the immune system. Immunotherapies help fight cancer by enhancing or replacing parts of the immune response so that it can do its job and eliminate cancer cells from the body. Immunotherapy agents have been approved for the treatment of many types of cancer, including lymphoma.

IMMUNOTHERAPY AND LYMPHOMA

Immunotherapies have been used for the treatment of lymphoma for decades. 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). Lymphoma cells tend to be sensitive to changes in the immune system, although this differs depending on the lymphoma subtype and between patients. Ultimately, how lymphomas respond to immunotherapy depends on how well the immune system can target the lymphoma cells.

IMMUNOTHERAPY AS A TREATMENT OPTION

BACKGROUND

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). Some immunomodulatory drugs are administered orally. Patients who have received catheters for chemotherapy may receive their immunotherapy through their catheter as well. Immunotherapy drugs may be given by themselves or with other anti-cancer agents. For example, the immunotherapy drug rituximab is often given in combination with the CHOP chemotherapy regimen. For more information on chemotherapy regimens, view the fact sheet titled *Getting The Facts – Chemotherapy* on the Lymphoma Research Foundation's (LRF's) website (click **here**).

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

Depending on the type of lymphoma, immunotherapies may be used 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 immunotherapy medications and treatment regimens are being evaluated and may be given to patients in clinical trials. This fact sheet reviews immunotherapies that are currently used or being evaluated in the treatment of lymphoma.

OVERVIEW OF SPECIFIC THERAPIES

MONOCLONAL ANTIBODIES

Many of the immunotherapies used to treat lymphoma are monoclonal antibodies. An antibody is a protein that binds to a single type of molecule, such as another protein. Each type of antibody therefore has a unique target. Many of the anti-lymphoma antibodies used to treat lymphoma were designed to recognize and bind to proteins on the surface of lymphoma cells (like CD20 and CD52). When they do, they either destroy the cell directly or recruit the individual's own immune system to destroy lymphoma cells. All monoclonal antibodies are given either intravenously or subcutaneously. Common side effects of monoclonal antibodies include allergic reactions, fever, chills, weakness, headache, nausea/vomiting, diarrhea, low blood pressure, chest tightness, and rashes. FDA-approved antibodies to treat lymphoma include:

Rituximab (Rituxan) and rituximab biosimilars

Rituximab is a CD20-directed antibody indicated for the treatment of adult patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to rituximab in combination with chemotherapy, as single-agent maintenance therapy
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, prednisone (CVP) chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimen
- Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide

Rituximab and Hyaluronidase Human (Rituxan Hycela)

A subcutaneous form of rituximab combined with human hyaluronidase was approved for use in adult patients with previously untreated DLBCL, and those with previously untreated and relapsed or refractory follicular lymphoma or CLL. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of intravenous rituximab.

Obinutuzumab (Gazyva)

Obinutuzumab is a CD20-directed antibody indicated:

- In combination with chlorambucil (Leukeran) for the treatment of patients with previously untreated CLL
- In combination with bendamustine (Treanda) followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab (Rituxan)-containing regimen
- In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III or IV follicular lymphoma

Ofatumumab (Arzerra)

Ofatumumab is a CD20-directed antibody indicated for the treatment of CLL:

- In combination with chlorambucil, 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)

Tafasitamab-cxix (Monjuvi)

Tafasitamab is a CD19-directed antibody indicated in combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for stem cell transplant.

Alemtuzumab (Campath)

Alemtuzumab is a CD52-directed antibody indicated for the treatment of B-cell CLL in patients who have been treated with alkylating agents and who have failed fludarabine therapy.

Mogamulizumab-kpkc (Poteligeo)

Mogamulizumab is a CC chemokine receptor type 4 (CCR4)-directed monoclonal antibody indicated for the treatment of adult patients with rare types of NHL, including relapsed or refractory mycosis fungoides or Sézary syndrome after at least one prior systemic therapy.

IMMUNE CHECKPOINT INHIBITORS

Immune Checkpoint inhibitors are monoclonal antibodies that recognize immune checkpoint proteins. Checkpoints (i.e. proteins like CTLA-4/B7-1/B7-2 and PD-1/PD-L1) normally regulate the immune responses against the body's own cells. Some cancers can activate signaling via checkpoint proteins and evade detection by the immune system. Checkpoint inhibitors block this evading mechanism, thereby restoring the immune system's ability to launch an attack against the cancer cells and rid them from the body. They are given intravenously. The most common side effects associated with checkpoint inhibitors include fatigue, upper respiratory tract infection, fever, diarrhea, and cough. FDA-approved checkpoint inhibitors indicated for the treatment of lymphoma include:

Nivolumab (Opdivo)

- Nivolumab is a PD-1 checkpoint inhibitor indicated for the treatment of adult patients with classical HL that has relapsed or progressed after auto-HSCT and brentuximab vedotin (Adcetris) or 3 or more lines of systemic therapy that includes auto-HSCT.

Pembrolizumab (Keytruda)

- Pembrolizumab is a PD-1 checkpoint inhibitor indicated for the treatment of adult patients with relapsed or refractory classical HL, and for pediatric patients with refractory classic HL or classic HL that has relapsed after 2 or more prior lines of therapy.

Radioimmunotherapy

Radioimmunotherapy (RIT) consists of a monoclonal antibody attached to a source of radiation. RIT acts as a "guided missile" to destroy lymphoma cells by attaching to a specific molecule on the surface of the lymphoma cell and delivering small doses of radioactivity. RIT is given intravenously. Side effects of RIT include fever/chills, pneumonia, lung inflammation, arrhythmias, and low blood counts.

Ibritumomab Tiuxetan (Zevalin)

Ibritumomab tiuxetan is a CD20-directed radiotherapeutic antibody indicated for the treatment of adult patients with:

- Relapsed or refractory low-grade or follicular B-cell NHL
- Previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy

ANTIBODY-DRUG CONJUGATES

An antibody-drug conjugate (ADC) is a monoclonal antibody attached to a chemotherapy drug. These agents target lymphoma cells by attaching to a protein on the cancer cell surface. The ADC then enters the cell, where the chemotherapy drug separates from the antibody portion and kills the cell by targeting a critical cell function, such as cell division. Similar to monoclonal antibodies, ADC is given intravenously. Side effects are caused both by the antibody and the chemotherapy portion of the drug, and may include low blood cell counts, nerve damage leading to neuropathy, fatigue, and nausea. Examples of FDA-approved ADCs include:

Brentuximab Vedotin (Adcetris)

Brentuximab Vedotin is a CD30-directed ADC indicated for treatment of adult patients with:

- Previously untreated Stage III or IV classical Hodgkin lymphoma (HL), in combination with doxorubicin, vinblastine, and dacarbazine
- Classical HL after failure of autologous hematopoietic stem cell transplantation (auto-HSCT) or after failure of at least two combination chemotherapy regimens in patients who are not auto-HSCT candidates.
- Classical HL at high risk of relapse or progression after auto-HSCT consolidation.
- 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.
- Systemic ALCL after failure of at least one combination chemotherapy regimen.
- Primary cutaneous ALCL or CD30-expressing mycosis fungoides who have received prior systemic therapy.

Polatuzumab vedotin-piiq (Polivy)

- Polatuzumab vedotin is a CD79b-directed ADC indicated in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after at least two prior therapies.
- Polatuzumab vedotin is currently being evaluated in clinical trials for its efficacy in treating other types of lymphoma and chronic lymphocytic leukemia (CLL).

Loncastuximab tesirine (Zynlonta, Lonca)

- Loncastuximab tesirine is a CD19-directed ADC for relapsed or refractory DLBCL granted accelerated approval by the FDA in April 2021.
- Loncastuximab teserine is undergoing clinical trials to evaluate its safety and efficacy in the treatment of mantle cell lymphoma (MCL) and follicular lymphoma.

CELLULAR THERAPY

CAR T-CELL THERAPY

Adoptive cellular therapies include the chimeric antigen receptor (CAR) T-cell therapies. These directly provide engineered molecules called chimeric antigen receptors (CARs). T cells are removed from patients and genetically modified to produce CARs. The genetically engineered CAR T cells are grown in the laboratory until they number in the billions and are then infused back into the patient, where they recognize and destroy cancer cells with specific antigens on their surface. The most prominent safety concern of CAR T cells is cytokine release syndrome, a group of symptoms including fever and hypotension, caused by cytokines released by the infused CAR T cells. FDA-approved CAR T cell therapies target CD19 and include the following:

Axicabtagene Ciloleucel (Yescarta)

- Axicabtagene ciloleucel was approved in October 2017 for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic (throughout the body) therapy, including DLBCL (not otherwise specified), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. In March 2021, the FDA granted accelerated approval for those with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Tisagenlecleucel (Kymriah)

- Tisagenlecleucel was approved in May 2018 for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL (not otherwise specified), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- Tisagenlecleucel is also indicated for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Brexucabtagene autoleucel (Tecartus)

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

Lisocabtagene maralaucel (Breyanzi)

- Lisocabtagene maralaucel was approved in February 2021 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), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

Several CAR T cell therapies are in development through clinical trials for patients with lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The studies are also evaluating innovative approaches, including dual targeted and allogeneic CAR T cell therapies. For additional information regarding CAR T cell therapy, visit https://lymphoma.org/aboutlymphoma/treatments/cartcell/

IMMUNOMODULATORY DRUGS

Immunomodulatory drugs have many ways of working against tumor cells. They actively kill tumor cells, keep tumors from getting blood and microenvironment nutrients, and stimulate the immune system.

Lenalidomide (Revlimid)

- Lenalidomide is indicated for treatment of adult patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade), and for relapsed or refractory follicular and marginal zone lymphoma in combination with rituximab, also known as the R-squared regimen.
- The most common side effects of lenalidomide are low white blood cell and platelet counts, fatigue, diarrhea, nausea, cough, fever, rash, shortness of breath, itching, constipation, and swelling, with a small increase in the risk of blood clots.

IMMUNOTHERAPIES UNDER INVESTIGATION FOR LYMPHOMA

Several other classes of immunotherapies are currently in clinical trials:

- Antibodies that target CD19 include inebilizumab
- Antibodies that target CD20 include ublituximab
- Antibodies that target OX40 include MEDI6469
- Antibodies that target CD47 include magrolimab, granted Fast Track Designation by the FDA for the treatment of myelodysplastic syndrome, acute myeloid leukemia (AML), DLBCL, and follicular lymphoma
- Bispecific antibodies include blinatumumab (Blincyto)
- Checkpoint inhibitors include atezolizumab (Tecentriq), toripalimab, cosibelimab, PDR001, CX-072 and CA-170
- Radioimmunotherapy that targets CD37 with 177Lu-lilotomab satetraxetan
- Radioimmunotherapy that targets CD45 with apamistamab-I-131
- Anti-CD19 CAR T Cells that use donor T cells
- Anti-CD19 CAR T cells include relmacabtagene autoleucel
- Anti-CD22 CAR T cells
- Anti-CD20 CAR T cells
- Anti-CD30 CAR T cells
- Dual target (anti-CD19 and CD20) CAR T cells
- CARs in NK cells

VACCINES

Cancer vaccines that stimulate the immune system to fight lymphoma cells are also being evaluated in clinical trials, including:

- *In situ* vaccines include Flt3L/CDX-301 and Poly-ICLC
- Imprime PGG

QUESTIONS TO ASK YOUR DOCTOR

- What is the goal of my immunotherapy treatment?
- What are the risks, possible side effects, and benefits of the immunotherapy 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 (eg, 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 immunotherapy impact potential future treatment decision?

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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Supported through grants from: Bristol Myers Squibb | Genentech | Biogen

Last updated 2021

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