

Understanding Lymphoma: T-Cell Lymphoma

T-cell lymphomas can develop in lymphoid tissues such as the lymph nodes (small bean-shaped structures that help the body fight disease, Figure 1) and spleen, or outside of lymphoid tissues such as the gastrointestinal tract (digestive system which includes esophagus, stomach, and intestines), liver, nasal cavity, skin, bone marrow (the spongy tissue inside the bone), and others.

T-cell lymphomas develop from white blood cells called T-lymphocytes (also called T-cells) or natural killer (NK) cells (a type of T-cell), and account for less than 15% of all non-Hodgkin lymphomas (NHLs) in the United States. T-cells direct the immune response by binding and signaling the cancer cells, while NK cells directly and rapidly kill cancer cells.

Most T-cell lymphomas appear from mature T-cells (T-cells that are fully developed). T-cell lymphomas can be aggressive (fast-growing) or indolent (slow-growing) and are mainly found in the skin (cutaneous T-cell lymphomas, CTCL) or throughout the body (peripheral T-cell lymphomas, PTCL):

- PTCL accounts for 6%-10% of all cases of NHL.
- CTCL accounts for about 4% of all NHL.

In rare cases (about 1% of all lymphomas), T-cell lymphoma develops from immature (early stages of development) T-cells in the thymus and is called T-lymphoblastic lymphoma. When cancer develops from NK cells (which share many characteristics with T-cells), it is called NK or NK/T-cell lymphoma and is generally grouped with other T-cell lymphomas. Some subtypes of T-cell lymphoma are listed in Figure 2 on the next page.

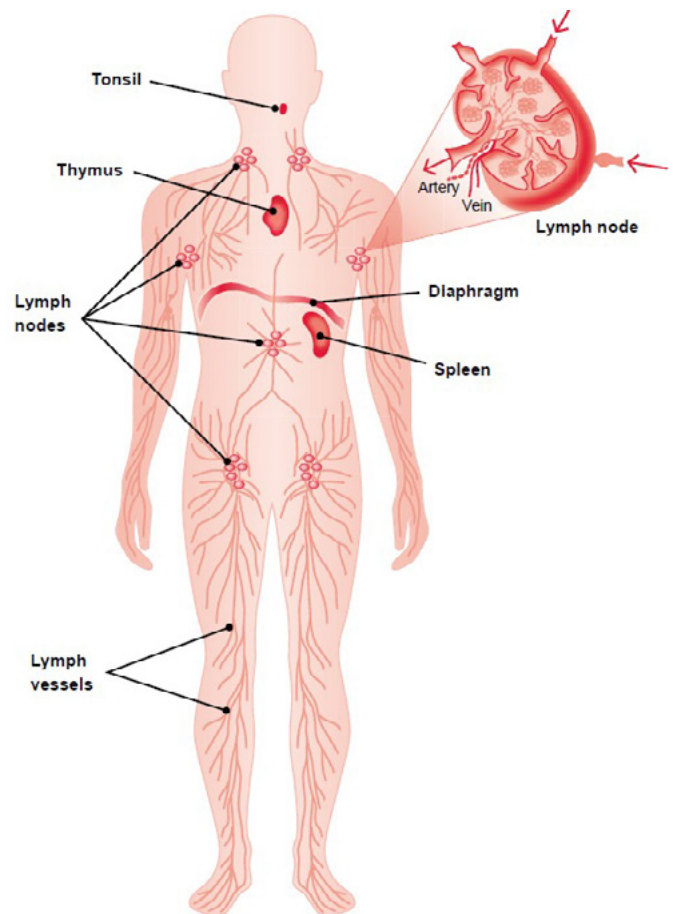


Figure 1. The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and the lymph nodes.

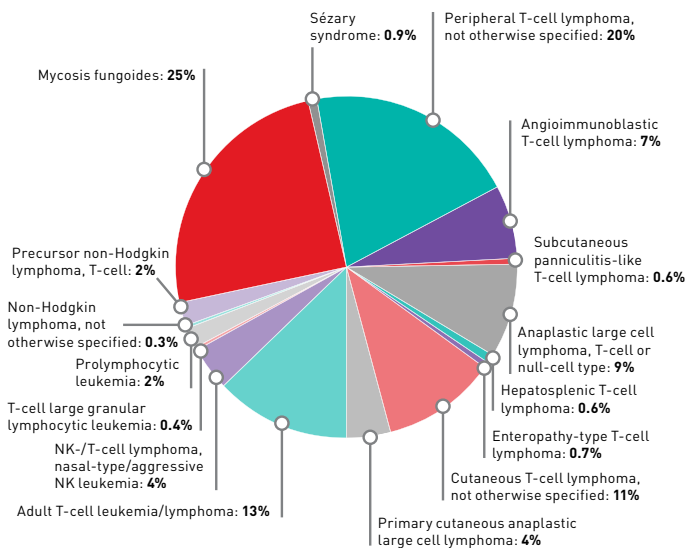


Figure 2. Relative frequencies (probability of T-cell lymphoma happening relative to all lymphomas) of T-cell lymphomas in the U.S. Percentages are based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER; an official source for cancer statistics) data, 2008–2017. Some very rare types are not shown in the graph. NK, natural killer.

SUBTYPES OF T-CELL LYMPHOMA

COMMON PERIPHERAL T-CELL LYMPHOMAS

Peripheral T-Cell Lymphomas, Not Otherwise Specified (PTCL-NOS) refers to a group of diseases that do not fit into any of the other PTCL subtypes. PTCL-NOS accounts for 30% of PTCL and is the most common PTCL subtype. Although most patients with PTCL-NOS are diagnosed when the disease is only in the lymph nodes, extranodal sites (outside of the lymph nodes) such as the liver, bone marrow, gastrointestinal tract, and skin, may also be involved. This subtype of PTCL is generally aggressive and patients will frequently have symptoms such as fever, night sweats, and unexplained weight loss. For more information, view the *Understanding Peripheral T-Cell Lymphoma* fact sheet on the Lymphoma Research Foundation’s (LRF’s) website (visit lymphoma.org/publications).

Anaplastic Large Cell Lymphoma (ALCL) accounts for around 15% of all T-cell lymphomas. There are several different subtypes of ALCLs. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, itching, skin rash, and tiredness. All patients with ALCL have a protein called CD30 on the surface of cancer cells, which helps detect and diagnosing ALCL. CD30 is characteristic of some forms of NHLs, while the majority of Hodgkin lymphoma cells are positive for CD30.

ALCL can be either systemic (occurring throughout the body), cutaneous (limited to the skin), or can rarely be seen around breast implants. Systemic ALCL is typically in an advanced stage (disease has grown in size and/or spread throughout the body) at diagnosis and can progress (grow and/or spread)

rapidly. Patients with systemic ALCL are divided into two groups, depending on whether or not the surface of their cells have an abnormal form of a protein called anaplastic lymphoma kinase (ALK):

- ALK-positive (ALK protein is present in cancer cells) disease can respond well to treatment and is potentially curable.
- ALK-negative (ALK protein is not present in cancer cells) disease may require stronger treatments, and relapse (disease returns after treatment) occurs more frequently than in ALK-positive disease.

Primary cutaneous ALCL appears only on the skin and is often less aggressive. A rare type of ALCL called breast implant-associated (BIA)-ALCL has been observed in some patients who have or had breast implants, especially implants with textured (non-smooth) surfaces. Most patients with BIA-ALCL may be treated with surgery alone. For more information on ALCL, please view the *Understanding Lymphoma: Anaplastic Large Cell Lymphoma* fact sheet (visit lymphoma.org/publications).

Angioimmunoblastic T-Cell Lymphoma (AITL) is a rare and aggressive type of T-cell lymphoma, accounting for about 20% of all patients with PTCL in the U.S. AITL is more common in older adults (median [average] age at diagnosis of around 65 years) and is usually diagnosed in an advanced stage. Initial symptoms often include fever, night sweats, skin rash, itching, and some autoimmune disorders (the body’s own immune system attacks its healthy cells), such as autoimmune hemolytic anemia. For more information, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on LRF’s website (visit lymphoma.org/publications).

UNCOMMON PERIPHERAL T-CELL LYMPHOMAS

Adult T-Cell Leukemia/Lymphoma (ATLL) is a rare and often aggressive form of T-cell lymphoma that can be found in the blood (leukemia), lymph nodes (lymphoma), skin, or other areas of the body. ATLL has been linked to infection with human T-lymphotropic virus type 1 (HTLV-1). However, not all individuals that are positive for HTLV-1 will develop ATLL.

This virus is commonly found in people from the Caribbean, parts of Japan, and some areas of South and Central America, Africa, Middle East, and more rarely in Australia and Asia. The HTLV-1 virus is believed to be passed through sexual contact or contact with blood, but it is most often passed from mother to child through the placenta, at childbirth, and during breastfeeding. Only 5% of those who carry the virus will develop lymphoma. Treatment commonly includes chemotherapy and antivirals to treat the underlying HTLV-1 infection. In some patients, stem cell transplantation (SCT) may be appropriate following remission (disappearance of signs and symptoms). For more information, view the *Understanding Lymphoma: Adult T-Cell Leukemia/Lymphoma* fact sheet and the *Understanding Cellular Therapy* guide on LRF’s website (visit lymphoma.org/publications).

Enteropathy-Associated T-Cell Lymphoma and Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma are extremely rare and aggressive subtypes of T-cell lymphoma that appear in the intestines. Patients with enteropathy-associated T-Cell lymphoma frequently have chronic diarrhea, gluten sensitivity (feeling sick after eating gluten), and celiac disease (autoimmune disease where the ingestion of gluten leads to damage of the small intestine). Monomorphic epitheliotropic intestinal T-cell lymphoma is not generally associated with celiac disease. Other Symptoms include abdominal pain and weight loss. Both require aggressive treatment that frequently is followed by SCT, in selected patients.

Hepatosplenic Gamma-Delta T-Cell Lymphoma is an extremely rare and aggressive disease that affects the liver and/or spleen. It can spread into the blood and bone marrow. It most often occurs in adolescents and young adults and is more common in males. This lymphoma is associated with immunosuppressive treatments (drugs that lower the activity of the immune system). Patients, especially children, who have been treated with immunosuppressants such as azathioprine and infliximab (Remicade) for Crohn's disease (a type of inflammatory bowel disease), may be more susceptible to this type of lymphoma.

Extranodal NK/T-Cell Lymphomas develop from natural killer (NK) cells. This aggressive lymphoma is relatively rare in the United States, but common in Asia and parts of Latin America. It typically develops in the interior of the nose or upper airway (nose, nasal cavity, mouth, throat, and larynx) at the back of the throat (in which case it is referred to as nasal type), but may appear in the gastrointestinal tract, skin, and other organs. The NK/T-cell lymphomas seem to be related to infections with Epstein-Barr virus.

Treatment-Related T-Cell Lymphoma, sometimes referred to as post-transplant lymphoproliferative disorder (PTLD), appears in patients who received immunosuppressants (medication that weakens the immune system) after an organ or bone marrow transplant (to prevent rejection of the transplanted organ). These treatments put patients at risk for this type of lymphoma. While PTLD is more commonly from B-cells, it can sometimes come from T-cells.

Lymphoblastic Lymphoma can appear from either immature B-cells or T-cells (B- or T-cells that are not fully developed), but more commonly comes from T-cells, making up to 90% of all lymphoblastic lymphomas. This type of lymphoma is most often diagnosed in adolescents and young adults and is a bit more common in males.

This lymphoma can progress rapidly, if not properly treated, and frequently appears in the middle of the chest, or mediastinum (area between the lungs, including heart, throat, thymus, and lymph nodes). In this type of lymphoma, immature white blood cells (called lymphoblasts) can appear in the lymph nodes, bone marrow, or spleen.

Lymphoblastic lymphomas, like other subtypes of lymphoma, can result in opportunistic infections (infections that happen more often or are more serious in patients with a weaker immune system) and affect the body's ability to make blood cells.

This subtype of T-cell lymphoma spreads to the central nervous system (brain and spinal cord) more often than other T-cell lymphomas. It behaves similarly to acute lymphoblastic leukemia (lymphoblasts are found in the bone marrow and blood) and is often treated with intensive (high-dose or over several months) chemotherapy, which is associated with a very high rate of complete remission and cure.

COMMON CUTANEOUS T-CELL LYMPHOMAS

Cutaneous T-Cell Lymphoma (CTCL) describes a group of typically indolent lymphomas that appear on, and most often only affect, the skin. Some patients may develop lymphoma in their blood, lymph nodes and, more rarely, other organs.

Mycosis Fungoides is the most common subtype of CTCL (50%-65% of all cases). It usually appears as skin patches (flat and often scaly rashes), plaques (thick, raised, and often itchy lesions, similar to those found in eczema, psoriasis, or dermatitis), or tumors (raised bumps or nodules with a diameter or height \geq 1cm, which may turn into an open sore). More than one type of lesion may be present at any time.

Sézary Syndrome is a less common and more aggressive form of CTCL that affects both the skin and the blood. Most individuals with Sézary syndrome are adults between the ages of 55 and 60 years. The most common symptoms are swollen lymph nodes and a red, very itchy rash that covers large portions of the body. Cancer T-cells, called Sézary cells, can be seen under a microscope and are present in both the skin and blood. There are other rarer forms of CTCL as well. For more information, view the *Understanding Lymphoma: Cutaneous T-Cell Lymphoma* fact sheet on LRF's website (visit lymphoma.org/publications).



TREATMENT OPTIONS

Because there are so many different subtypes of T-cell lymphoma, treatment varies widely. Standard lymphoma therapies include:

- Chemotherapy (drugs that stop the growth of or kill cancer cells)
- Targeted therapy (drugs that target molecules that cancer cells use to grow and spread)
- Immunotherapy (drugs that use the body's immune system to fight cancer)
- Immunomodulatory agents (drugs that work on the immune system directly by regulating [activating or slowing down] the activity of specific proteins)
- Radiation (treatment that uses high-energy radiation to kill cancer cells)

Patients diagnosed with rare forms of lymphoma should consult their medical team to find new promising therapies or to enroll into clinical trials.

Treatments vary depending on the subtype of lymphoma, but initial treatment for the more common types of PTCL typically includes combination chemotherapy regimen, usually for curative intent:

- CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone)
- CHOEP (CHOP plus etoposide)
- BV-CHP (brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone)
- Dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone)

Three histone deacetylase inhibitors (a type of targeted therapy) have been approved by the U.S. Food and Drug Administration (FDA) in the past decade: belinostat (Beleodaq) for PTCL and romidepsin (Istodax) and vorinostat (Zolinza) for CTCL.

In some cases, allogeneic (patients receive stem cells from a familiar or unrelated donor) or autologous (patient receives own stem cells) SCT is recommended for either relapsed disease or to increase the chance of cure from some forms of PTCL.

For more information about stem cell transplantation, please view the *Understanding Cellular Therapy* guide on LRF's website (lymphoma.org/publications).

Therapy for CTCL often includes treatments directed at the skin (also called topical therapies), to improve quality of life. Topical (applied directly to the skin) treatments include corticosteroids, retinoids, chemotherapy, phototherapy (use of ultraviolet light to kill cancer cells on the skin), or electron beam radiation therapy (a type of radiation therapy that does not reach the internal organs). When skin-directed therapies do not provide sufficient disease control or when the disease affects other areas of the body, systemic therapy is considered. For some patients with CTCL that has spread to the bloodstream, a procedure called extracorporeal photopheresis (ECP) is approved. During this procedure, blood is removed from the patient and treated with ultraviolet light and drugs that become active when exposed to ultraviolet light. Once the blood has been treated, it is then returned back into the patient's body.

Patients with relapsed or refractory (does not respond to treatment) T-cell lymphomas are usually treated with combination chemotherapy or with other treatments. In some patients with PTCL, SCT is considered as a next step in therapy. However, for some patients, chemotherapy regimens or SCT might not be recommended because of their side effects. Single-agent therapies with less side effects are also available and might cause a long-lasting remission in such patients. These drugs are approved by the FDA for patients who have relapsed or become refractory to first-line chemotherapy:

Table 1.

Agent (Drug)	Indication and Drug Class (Type of Treatment)
Belinostat (Beleodaq)	<ul style="list-style-type: none"> • Indicated for PTCL • Targeted therapy; HDAC inhibitor
Pralatrexate (Folotyn)	<ul style="list-style-type: none"> • Indicated for PTCL • Targeted therapy; Analogue inhibitor
Mogamulizumab (Poteligeo)	<ul style="list-style-type: none"> • Indicated for CTCL • Immunotherapy; monoclonal antibody anti-CCR4
Brentuximab vedotin (Adcetris)	<ul style="list-style-type: none"> • Indicated for both PTCL and CTCL • Immunotherapy; anti-CD30
Crizotinib (Xalkori)	<ul style="list-style-type: none"> • Indicated for relapsed or refractory ALK-positive ALCL • Targeted therapy; ALK inhibitor

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; CCR4, C-C chemokine receptor type 4; CTCL, cutaneous T-cell lymphoma; HDAC, histone deacetylases; PTCL, peripheral T-cell lymphoma.



TREATMENTS UNDER INVESTIGATION

Treatment options for the different types of newly diagnosed and relapsed/refractory T-cell lymphomas are expanding as new treatments are discovered and current treatments are improved. Treatments currently being investigated alone or in combination are described in the table on the next page.

Table 2. Selected Agents Under Investigation for DLBCL in Phase 2-3 Clinical Trials

Agent (Drug)	Class (Type of Treatment)
Azacitidine (CC-486)	Chemotherapy
Bendamustine (Treanda)	Chemotherapy
Bortezomib (Velcade)	Targeted therapy; proteasome inhibitor
Cemiplimab (Libtayo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Devimistat (CPI-613)	Targeted therapy; lipoic acid antagonist
Durvalumab (Imfinzi)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Duvelisib (Copiktra)	Targeted therapy; PI3K inhibitor
Golidocitinib (AZD4205)	Targeted therapy; JAK1 inhibitor
Lacutamab (IPH4102)	Immunotherapy; monoclonal antibody, anti-KIR3DL2
Lenalidomide (Revlimid)	Immunotherapy; immunomodulator drug
MEDI-570	Immunotherapy; anti-ICOS
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Ruxolitinib (Jakafi)	Targeted therapy; JAK1/2 inhibitor
Valemtostat (DS-3201b)	Targeted therapy; EZH1/2 dual inhibitor
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor

BCL-2, B-cell lymphoma 2; EZH1/2, enhancer of zeste homologue 1 and 2; ICOS, inducible T-cell co-stimulator; JAK1/2, Janus kinase 1 and 2; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; KIR3DL2, killer cell immunoglobulin like receptor, three Ig domains and long cytoplasmic tail 2.

In addition, a number of promising clinical trials are studying combinations (two or more drugs given at the same time) of these new treatments which in some cases may be more effective than the single agent (one drug) alone. It is critical to remember that 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 appeared. It is also very important that all patients with T-cell lymphoma consult a specialist to clear up any questions.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and the best treatment doses for patients with relapsed or refractory MCL. Because the optimal initial treatment of MCL is not clear and it is such a rare disease, clinical trial enrollment is important for establishing more-effective and less-toxic treatments. The rarity of the disease also means that the latest treatments are often available only through clinical trials. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website (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 T-cell lymphoma should have regular visits with their physician. During these visits medical tests (such as blood tests, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required 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 vary depending 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 effects during follow-up care. Visits may become less frequent the longer the patient stays 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. LRF's award-winning *Focus on Lymphoma* mobile app (lymphoma.org/mobileapp) can help patients manage this documentation.



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* fact sheet 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* fact sheet 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 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.

LRF Helpline

The LRF Helpline staff is 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).

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