

**No. 27** in a series providing the latest information for patients, caregivers and healthcare professionals

## Highlights

- Autologous chimeric antigen receptor (CAR) T-cell immunotherapy uses a person's own immune cells (T cells) to identify and attack cancer cells.
- In CAR T-cell therapy, T cells are taken from a patient's blood and sent to a laboratory. There, technologies are used to engineer T cells to express the chimeric antigen receptor, which allows the modified T cells to identify, attack and kill cancer cells. In the laboratory, the number of these engineered CAR T cells is multiplied, and these modified cells are frozen and sent to the patient's treatment center. There, they are re-infused into the patient's bloodstream, where they can seek out and kill cancer cells.
- The following CAR T-cell treatments have been US Food and Drug Administration (FDA) approved: tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), lisocabtagene maraleucel (Breyanzi®), idecabtagene vicleucel (Abecma®) and ciltacabtagene autoleucel (Carvykti™). For prescribing information, see page 3.
- Serious side effects are linked with CAR T-cell therapy, some of which can be life-threatening. Active monitoring of a patient's condition after CAR T-cell infusion is critical to minimize the risk of serious side effects. Most side effects associated with CAR T-cell therapy can be managed with supportive care and medication.

## Introduction

Surgery, chemotherapy, and radiation therapy are the traditional treatments for cancer. Immunology is the branch of science that studies all aspects of the body's immune system. Advances in this field have led to a greater understanding of the ways in which the body's own defenses can be harnessed to treat blood cancers. Cancer researchers study the immune system and how it helps to destroy cancer cells. Chimeric antigen receptor (CAR) T-cell therapy is called "immunotherapy" because it uses a patient's own T cells (lymphocytes that are part of the immune system) to recognize and attack cancer cells.

This booklet provides a brief overview of the immune system and immunotherapy as well as information on how CAR T-cell therapy works, its side effects and its role in the treatment of some blood cancers.

## The Natural Immune System and Immunotherapy

The immune system is the body's defense against infection and cancer. It is a network of cells and organs that defend the body from foreign substances called "antigens." Antigens are substances such as chemicals, bacteria and viruses. Antigens in the body stimulate the immune system to make antibodies that target the toxic material enabling immune system cells to identify and kill infected cells. This is the body's "immune response" to antigens.

Lymphocytes are a type of white blood cell. These cells form part of the body's complex immune system. These cells respond to foreign organisms and help fight cancer. Lymphocytes are found primarily in the lymph nodes and the spleen, in other lymphatic organs including the bone marrow and the thymus, and in the lymphatic channels. Some lymphocyte cells enter the bloodstream. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. B lymphocytes make the antibodies that recognize and target antigens. B lymphocytes are found in the bone marrow and other parts of the lymphatic system. T lymphocytes mature in the thymus and have several functions, including helping B lymphocytes make antibodies against invasive organisms and killing infected cells in the body. Natural killer cells can also attack cancer cells and eliminate viruses.

B-cell lymphomas and leukemias begin when normal B cells mutate (change) and become cancerous. These cancerous B cells multiply uncontrollably. B cells can also develop into plasma cells. When normal plasma cells mutate, they can become cancerous. That is how myeloma begins.

Immunotherapy improves the body's ability to detect and attack cancer cells. It is an active area of clinical research and there are proven immunotherapy treatments for people with certain types of cancer. Many immunotherapies are either approved for use

## Chimeric Antigen Receptor (CAR) T-Cell Therapy

or are under study in clinical trials to determine their effectiveness in treating various types of cancer. In addition to CAR T-cell therapy, other types of immunotherapies include monoclonal antibody therapy, radioimmunotherapy, antibody drug conjugates and therapeutic cancer vaccines.

Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) for the free LLS booklet *Immunotherapy* for more information about immunotherapy treatments.

### Chimeric Antigen Receptor (CAR) T-Cell Therapy

Autologous CAR T-cell therapy involves engineering a patient's own T cells to recognize and attack cancer cells. "Autologous" means the use of an individual's own cells or tissues in this therapy. In CAR T-cell therapy, white blood cells are taken from a patient's blood in a procedure called "apheresis" or "leukapheresis" and sent to a laboratory or manufacturing facility. There, the T cells are separated and then modified so they have artificial receptors on their surface. The receptors direct the engineered T cell to find and attack the cancer cells. These artificial receptors are called "chimeric antigen receptors." The number of engineered CAR T cells is multiplied in the laboratory or manufacturing facility. When there are enough of these cells, they are frozen and sent to the patient's hospital or treatment center. When the patient is ready for treatment, the CAR T cells are thawed and given back to the patient through an intravenous (IV) infusion.

The most frequently targeted antigen in CAR T-cell immunotherapy for leukemia and lymphoma is called "cluster of differentiation 19 (CD19)." The CD19 antigen is present on the surface of nearly all cancerous B cells. It is also present on healthy (non-cancerous) B cells, but not on other cell types. Because the human body can tolerate prolonged periods of B-cell loss (depletion), CD19 is considered an ideal target antigen for CAR T-cell immunotherapy (see *B-Cell Aplasia* on page 6). Trials of treatment using CAR T cells that target other antigens expressed on various blood-related cancers are also under way (see **Table 1** on page 4).

### The Chimeric Antigen Receptor (CAR) T-Cell Process

**T cells are collected from a patient.** Using a procedure called "apheresis," blood is temporarily removed from the patient's vein and put through an apheresis machine

which separates the blood into its four components: red blood cells, white blood cells, platelets and plasma. White blood cells are collected and the T cells (a type of white blood cell) are removed. The remaining blood is infused back into the patient's body. See **Figure 1** on page 3.

**T cells that have been engineered in a laboratory can recognize proteins (or antigens) on the surface of tumor cells.** The patient's T cells are sent to a laboratory or a drug manufacturing facility for genetic engineering. Deoxyribonucleic acid (DNA) is introduced into the cells to produce CARs on the surfaces of the cells. Chimeric antigen receptors are artificial receptors that allow the T cells to recognize antigens on targeted (cancer) cells.

**These engineered T cells are known as "chimeric antigen receptor (CAR) T cells."**

**The number of engineered CAR T cells is then multiplied.** The number of the patient's genetically modified T cells is "expanded" by multiplying them in the laboratory. When there are enough of them, the CAR T cells are frozen and sent to the hospital or center where the patient is being treated. The method used to collect cells and complete this "manufacturing process" ranges from 3 to 4 weeks.

**At the hospital or treatment center, the CAR T cells are thawed and then infused into the patient.** Many patients are given a brief course of one or more chemotherapy agents to reduce the number of normal T cells in the body (this is called "lymphodepletion"). This process is important because it "makes space" for the CAR T cells in the patient receiving the infusion. Then the genetically modified CAR T cells are infused into the patient's bloodstream via an intravenous (IV) infusion or through an existing central line. The process usually takes less than 30 minutes. In the body, the CAR T cells seek out cancer cells that express the antigen they have been trained to target. These "attacker" cells recognize and destroy cells that have the target antigen on their surfaces. When they encounter the antigen, the CAR T cells become activated, attack and kill the tumor cells. Then these T cells increase their numbers by making copies of themselves.

**The CAR T cells may help guard against recurrence.**

The CAR T cells may not only eradicate all the cancer cells in the body, but they may remain in the body for months after the infusion has been completed. This therapy has resulted in long-term remissions for some patients with certain types of blood cancer.

There are **six** approved CAR T-cell therapies. The Package Insert and/or the Full Prescribing Information for each medication is available on the internet:

# Chimeric Antigen Receptor (CAR) T-Cell Therapy

**Tisagenlecleucel (Kymriah®)** has been approved by the US Food and Drug Administration (FDA) since 2017 for the treatment of:

- Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (B-ALL) that is either refractory or in a second or later relapse
- Adult patients with relapsed or refractory large B-cell lymphoma—after two or more lines of systemic therapy—including: diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL)
- Adult patients with relapsed or refractory FL after two or more lines of systemic therapy

Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy.

Tisagenlecleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

**Axicabtagene ciloleucel (Yescarta®)** has been FDA-approved since 2017 for the treatment of:

- 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 large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL)
- Adult patients with relapsed or refractory FL after two or more lines of systemic therapy

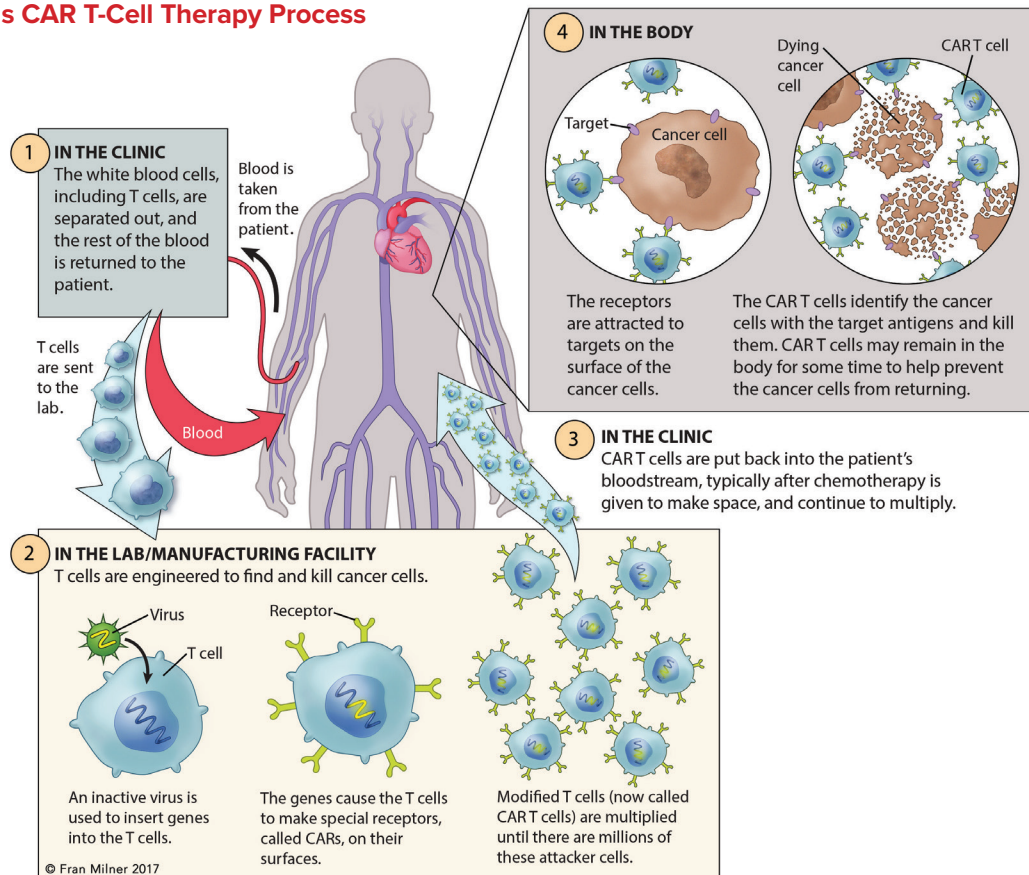
Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T-cell immunotherapy. Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

**Brexucabtagene autoleucel (Tecartus®)** has been FDA-approved since 2020 for the treatment of adult patients with:

- Relapsed or refractory mantle cell lymphoma (MCL)
- Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Tecartus is a CD19-directed genetically modified autologous T-cell immunotherapy.

**Figure 1. Autologous CAR T-Cell Therapy Process**



# Chimeric Antigen Receptor (CAR) T-Cell Therapy

**Lisocabtagene maraleucel (Breyanzi®)** has been FDA-approved since 2021 for the treatment of adult patients with large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma (FL) grade 3B, who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- Relapsed or refractory disease after two or more lines of systemic therapy

Lisocabtagene maraleucel is a CD19-directed genetically modified autologous T-cell immunotherapy.

Lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

**Idecabtagene vicleucel (Abecma®)** has been FDA-approved since 2021 for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

Idecabtagene vicleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy.

**Ciltacabtagene autoleucel (Carvykti™)** has been FDA-approved since 2022 for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Ciltacabtagene autoleucel is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy.

**Table 1** in the next column lists some of the CAR T-cell therapy antigen targets that are approved for use by the FDA or that are under study in clinical trials for hematologic malignancies and their potential off-tumor targets.

**Table 1. Select Antigens Being Targeted in CAR T-Cell Trials for Hematologic Malignancies and Potential Off-Tumor Targets**

Antigen	Hematologic Malignancy	Potential Normal Tissue Impacted
<b>CD5</b>	T-ALL, T-cell lymphoma	Normal T cells
<b>CD7</b>	T-ALL, T-cell lymphoma	Normal T cells
<b>CD19</b>	ALL, CLL, NHL	Normal B cells
<b>CD20</b>	ALL, CLL, NHL	Normal B cells
<b>CD22</b>	B cell leukemias; B-cell lymphomas	Normal B cells
<b>Igκ</b>	CLL, NHL, myeloma	Normal B cells
<b>ROR1</b>	CLL, NHL	Pancreas parathyroid, adipose (fat) tissue
<b>CD30</b>	NHL, HL	Resting CD8 T cells
<b>CD33</b>	AML	Multipotent myeloid precursors, unipotent colony-forming cells, and maturing granulocytes and monocytes
<b>CLL-1</b>	AML	Peripheral blood leukocytes and in the spleen
<b>CD138</b>	Myeloma	Precursor and plasma B cells, epithelia
<b>CD123</b>	AML	Bone marrow myeloid progenitors, B cells, mast cells, monocytes, macrophages, endothelial cells
<b>BCMA</b>	Myeloma	B cells

**Abbreviations:** ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BCMA, B-cell maturation antigen (also known as "tumor necrosis factor receptor"); CAR, chimeric antigen receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; CLL-1, C-type lectin-like molecule-1; HL, Hodgkin lymphoma; Igκ, immunoglobulin kappa light chain; NHL, non-Hodgkin lymphoma; T-ALL, T-cell acute lymphoblastic leukemia.

**Clinical Trials.** Chimeric antigen receptor T-cell therapy has shown varying degrees of efficacy in the treatment of leukemia, lymphoma and myeloma in clinical trials. Even though CAR T-cell therapy is FDA-approved for treatment of some cancers, the use of this treatment is still being researched in clinical trials to determine if other diseases may respond to CAR T-cell therapy and to improve outcomes. Trial protocols vary. Depending on the clinical trial, care may be provided in either a hospital setting or an outpatient treatment center staffed by healthcare professionals who have experience administering cellular immunotherapy. Patients may have to stay at the treatment facility, or they may need to plan to stay nearby before, during or following treatment. Some trial protocols require patients to confirm the availability of a caregiver before they can enroll in the trial. If there is concern about finding a caregiver, the healthcare team can help identify appropriate caregivers from their support system.

### Possible Side Effects of Chimeric Antigen Receptor (CAR) T-Cell Therapy

While many patients have reported only mild to moderate side effects with CAR T-cell therapy, this treatment is sometimes associated with significantly serious side effects. It is important to speak with your doctor about potential side effects before starting any treatment.

Most side effects resulting from CAR T-cell therapy will either resolve on their own or can be managed with appropriate treatment. Some of the most common potential side effects of CAR T-cell therapy include cytokine release syndrome (CRS); neurologic toxicities (immune effector cell-associated neurotoxicity syndrome [ICANS]); tumor lysis syndrome; anaphylaxis; and (in cases of cluster of differentiation 19 (CD19)-targeting CAR), B-cell aplasia. All treatment centers certified to infuse CAR T cells employ evidence-based strategies to minimize or counteract these side effects. Each of these side effects is discussed in detail in the following sections.

**Cytokine Release Syndrome.** This potentially serious side effect is frequently associated with CAR T-cell therapy. Cytokines (chemical messengers that help the T cells carry out their functions) are produced when the CAR T cells multiply and kill cancer cells. When the CAR T cells encounter their antigen targets, they are rapidly activated. At this point, numerous inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF $\alpha$ ) and interferon gamma (IFN $\gamma$ ), are released. The large amounts of cytokines produced and then released by the activated immune system cause a collection of mild to potentially life-threatening signs and symptoms known as “cytokine release syndrome (CRS).”

Common signs and symptoms of CRS can include:

- Fever
- Fatigue
- Headache
- Low blood pressure (hypotension)
- Hypoxia (lack of oxygen reaching the tissue)
- Tachycardia (abnormally rapid heart rate)
- Chills

More serious signs and symptoms of CRS include:

- Capillary leak (fluid and proteins leaking out of tiny blood vessels and flowing into surrounding tissues, resulting in dangerously low blood pressure and difficulty breathing)
- Cardiac arrest (the heart stopping)
- Cardiac arrhythmia (abnormal heartbeat)

- Cardiac failure (heart failure)
- Encephalopathy (damage or disease that alters brain function or structure)
- Hemophagocytic lymphohistiocytosis (life-threatening immune system condition when T and natural killer (NK) cells become overactive causing too much inflammation)/macrophage activation syndrome (HLH/MAS) (an uncontrolled immune system working overtime, leading to inflammation)
- Renal insufficiency (poor kidney function)
- Poor lung oxygenation
- Multiple organ failure

Healthcare workers caring for patients receiving CAR T cells have been trained to recognize and treat signs and symptoms of CRS.

A patient with severe CRS may require intensive care treatment. Although most signs and symptoms are reversible, the potential life-threatening risk of this side effect of CAR T-cell therapy should not be underestimated. Deaths have been reported both in CAR T-cell therapy trials, and after infusion of FDA-approved CAR T cells.

Depending on the severity of CRS, patients may require only supportive care with fever-reducing medication and intravenous (IV) fluids at the guidance of the doctor. Or they may require rapid intervention with immunosuppressive anti-cytokine-directed therapy and/or corticosteroids. Researchers discovered that patients with the most severe reactions expressed high levels of IL-6 (and other cytokines), secreted by T cells and other immune cells that are activated in response to inflammation. The challenge for researchers has been to find an appropriate therapy that eases the symptoms of uncontrolled inflammation without diminishing the antitumor effectiveness of the engineered T cells. Recent research has shown that the effects of CRS can be lessened by the infusion of the monoclonal antibody **tocilizumab (Actemra®)**, which blocks the IL-6 receptor and reduces inflammation without compromising the effectiveness of FDA-approved CAR T cells. Tocilizumab is approved by the FDA for the treatment of adults and pediatric patients 2 years of age and older who have either CAR T-cell-induced severe or life-threatening CRS.

If signs and/or symptoms of severe CRS either do not improve with tocilizumab, or if they are getting worse, corticosteroids are typically used to reverse CRS. It is not known whether high doses of corticosteroids affect the ability of CAR T cells to completely destroy the cancer cells, but patients who have received corticosteroids

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have achieved long-lasting remissions. When CRS is life-threatening, corticosteroids may be the only way to stop symptoms from getting worse.

Other methods that aim to reduce the risk of developing severe CRS are being explored in clinical trials. They include:

- Using multiple low-dose CAR T-cell therapy infusions (instead of one single higher-dose infusion)
- Treating patients earlier in the course of their disease
- Decreasing the burden of disease prior to CAR T-cell infusion through “bridging” therapies such as chemotherapy, targeted therapy or radiation therapy

Depending on the patient and the CAR T cells, CRS may occur within 1 to 21 days of CAR T-cell infusion. The duration of CRS is variable and depends on a number of factors including the type of intervention used to manage it.

**Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).** The connection between CRS and neurologic adverse events is not completely understood. The frequency, severity and nature of neurological toxicity is different among CAR T-cell products. This could be due to either differences in the products, the relatively small number of patients studied, or to both of these. The effects of ICANS have been observed in patients undergoing CAR T-cell treatment of acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), B-cell non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). Common signs and symptoms of ICANS include language impairment (aphasia), confusion, delirium, involuntary muscle twitching, hallucinations or unresponsiveness. Seizures have also been reported. The underlying cause of ICANS is unclear. It is not known whether the presence of CAR T cells in the central nervous system is related to either the occurrence or the severity of neurotoxicity. The cause of neurotoxicity is the subject of intense investigation by researchers.

Neurotoxicity is reversible in most cases, and signs and/or symptoms usually resolve over several days without intervention or apparent long-term effects. However, neurologic complications of CAR T-cell therapy can be life-threatening. Harmful neurological events have been reported, notably, cerebral edema (swelling in the brain), and fatalities have occurred. Some symptoms of neurologic toxicity can be treated with anti-epileptic medication and/or corticosteroids. Some patients may receive prophylactic (preventative, before CAR T-cell therapy) anti-epileptic medications, such as **levetiracetam (Keppra®, Keppra® XR, and Spritam®)**. More study

is needed to understand the mechanism of action, associated risk factors and best management of the ICANS side effect.

Signs and symptoms of ICANS can sometimes be subtle. As a result, patients are frequently asked to complete a series of assessments during their treatment to ensure that they do not have neurologic toxicities. This assessment may include asking patients to write a sentence, to report the date, or perform other simple tasks to demonstrate that they do not have any developing neurologic symptoms.

**Tumor Lysis Syndrome (TLS).** This syndrome is another known side effect of CAR T-cell therapy. It is a group of metabolic complications that can occur due to the breakdown of dying cells—usually at the onset of toxic cancer treatments. However, the onset of TLS may be delayed, occurring one month or more after CAR T-cell therapy. Tumor lysis syndrome can cause damage to organs, such as the kidney, and it can be a life-threatening complication of any treatment that causes the breakdown of cancer cells. Tumor lysis syndrome is managed by standard supportive therapy, including hydration (water and fluids) and the medications **allopurinol (Zyloprim®, Alopurin®)** and **rasburicase (Elitek®)** to manage increased levels of uric acid.

**Anaphylaxis (Life-Threatening Allergic Reaction).** There is potential for a patient receiving CAR T-cell therapy to have an overwhelming immune response (an anaphylactic reaction) to the CAR (chimeric antigen receptor) itself. Signs and symptoms associated with anaphylaxis include hives, facial swelling, low blood pressure and respiratory distress. There have been reports of acute anaphylaxis. Immediate treatment and thorough monitoring of this life-threatening side effect are critical for patients receiving CAR T-cell therapy.

**B-Cell Aplasia.** Chimeric antigen receptor T-cell therapy that targets antigens found on the surface of B cells destroys not only cancerous B cells but also normal B cells. Therefore, B-cell aplasia (a low number of healthy B cells or absent B cells) is an expected result of successful CD19-specific CAR T-cell treatment, and it has served as a useful indicator of ongoing CAR T-cell activity. This adverse effect, however, also results in the body’s reduced ability to make the antibodies that protect against infection. Intravenous or subcutaneous immunoglobulin replacement therapy may be given to prevent infection, especially in patients who experience recurrent or severe infections. B-cell depletion (loss of B cells) has been reported in nearly all patients treated

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with CD19-targeted CAR T cells. Depending on the CAR T-cell configuration, B-cell aplasia can last from months to years. Long-term follow-up analysis is needed to assess the late effects of B-cell aplasia.

**Infection.** In addition to low numbers of healthy B cells (aplasia), a number of patients (20% to 40%) who receive CAR T-cell therapy may have prolonged cytopenias. A low number of the white blood cells, red blood cells or platelets is called a “cytopenia.” A cytopenia can result in serious bacterial, viral or fungal infections. In addition, opportunistic infections (infections that occur due to a unique opportunity, such as a weakened immune system) can occur. As a precautionary measure, following CAR T-cell therapy, depending on the patient’s blood cell count recovery, most patients will be maintained on prophylactic therapy (treatment designed to prevent an infection from occurring).

### Immunizations

Since CAR T-cell therapy is a relatively new treatment, there is still much that needs to be learned about the use of vaccines. Experts believe that vaccination after CAR T-cell therapy is an important part of the long-term follow-up plan for patients. Doctors who have begun to study vaccination divide patients into two categories: CAR T-cell patients who have had a previous stem cell transplant and CAR-T cell patients who have not had a previous stem cell transplant. Patients need to speak to the doctor and follow the doctor’s recommended vaccination schedule. Coronavirus disease 2019 (COVID-19) and flu vaccines are also recommended. For more information, patients should consult with their doctors.

### Pediatric and Adolescent Chimeric Antigen Receptor (CAR) T-Cell Therapy

**Tisagenlecleucel (Kymriah®)** is approved by the FDA for treatment of pediatric and adolescent patients with B-cell precursor acute lymphoblastic leukemia (B-ALL), based on this drug’s remarkable success in early clinical trials.

Disease distribution in this population and treatment regimens prior to CAR T-cell therapy will be different from that for adults. These factors may be important to consider when assessing potential differences in response rates and the toxicity profile. It is important to discuss such issues with members of your healthcare team to learn how treatment of children with CAR T-cell therapy may differ from the treatment of adults.

For pediatric and young adult patients who qualify for a CAR T-cell therapy clinical trial, the process of enrolling

in a trial is often much slower than it is for adults. This is due to the need to demonstrate the drug’s safety and tolerability in adults before its use can be studied in younger patients.

### Financial Concerns

CAR T-cell therapy is expensive and may not be fully covered by health insurance. In addition to the cost of the treatment, patients may have significant expenses for collection of cells, the prep regimen, time off work, transportation and lodging costs, the need for a caregiver and for that caregiver to take time off, meals and childcare. If patients are undergoing CAR-T as part of a clinical trial, there may be additional financial resources available. It is important for patients and caregivers to speak with their healthcare team for referrals to organizations to be sure they can cover these costs.

### Follow-Up Care

Some patients will receive their chimeric antigen receptor (CAR) T-cell therapy in a different center from the place where they received their cancer treatment. If this is the case, it is important for patients to have their CAR-T cell oncologist connect with, and stay in touch with, their primary hematologist/oncologist, to continue proper management of care. Follow-up appointments for CAR T-cell therapy will include laboratory work, supportive care and possibly imaging tests (such as x-rays, computerized tomography (CT) and magnetic resonance imaging (MRI) scans, etc). A patient’s local hematologist/oncologist should continue cancer checkups. Patients are advised to have their caregivers accompany them to these appointments since these are the people who have been with them throughout the CAR-T cell treatment process and they may be the first to notice any changes or side effects the patient may be experiencing.

Most patients receiving CAR T-cell treatment have been followed for a relatively short time; however, data providing information about responses to therapy (including duration of response) is fast emerging. Researchers will be able to better predict the duration of these responses after patients have been followed over longer terms. Patients who have had CAR-T cell treatment face long-term and late effects that are similar to those of other cancer patients. It is especially important to follow up on potential fertility and endocrine late effects.

It is important for more pediatric, young adult and adult patients to be enrolled in clinical trials. Larger study samples, evaluated over more extended periods, will

help researchers further understand the impact of this type of therapy, ways to reduce its toxicity and improve the management of adverse side effects.

### Results, Limitations and the Future of Chimeric Antigen Receptor (CAR) T-Cell Therapy

Chimeric antigen receptor T-cell clinical trials have generated impressive results in the early outcomes of patients with blood cancers. With the FDA approval of **tisagenlecleucel (Kymriah®)**, **axicabtagene ciloleucel (Yescarta®)**, **idecabtagene vicleucel (Abecma®)**, **brexucabtagene autoleucel (Tecartus®)**, **lisocabtagene maraleucel (Breyanzi®)**, and **ciltacabtagene autoleucel (Carvykti™)**, CAR T-cell therapy represents a potential to treat certain leukemias, lymphomas and myeloma in patients whose disease has relapsed or is refractory to treatment.

In some studies, up to 90 percent of children and adults with B-ALL whose disease had either relapsed multiple times or failed to respond to standard therapies, achieved remission after receiving CAR T-cell therapy.

Patients treated with tisagenlecleucel and who need to receive additional treatment after CAR T-cell therapy will be screened for HIV (human immunodeficiency virus). These patients may show a false-positive HIV test result due to the virus used to generate the CAR T cells. Patients are advised to talk with their healthcare team about concerns and ask questions.

CAR T-cell therapy is being studied for use in other blood cancers, including chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), T-cell malignancies and Hodgkin lymphoma (HL).

Despite its current limitations, CAR T-cell therapy has demonstrated that it has the potential to mark a new era in cancer treatment and personalized immunotherapy.

Patients and caregivers can work with **Clinical Trial Nurse Navigators** who will help find clinical trials and personally assist them throughout the entire clinical trial process. **Please call an LLS Information Specialist at (800) 955-4572 or visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information about clinical trials and the Clinical Trial Support Center at LLS.**

### Clinical Trials for Blood Cancers

Every new drug or treatment regimen goes through a series of studies called “clinical trials” before it becomes

part of standard therapy. A clinical trial for new cancer drugs and treatments is a carefully controlled research study that aims to improve the care and treatment of cancer patients. In the United States, the FDA requires all new drugs and other treatments to be tested in clinical trials before they are made available to the public. At any given time, there are thousands of cancer clinical trials available as doctors and researchers are always seeking new and better treatments for patients.

Many clinical trials are searching for a cancer cure. This means devising safer, more effective treatments that destroy cancer cells and keep them from coming back. Other clinical trials look for new ways to improve existing treatments and to improve the quality of life for patients. There are trials for patients at every stage of treatment as well as for those whose disease is in remission. Researchers design cancer clinical trials to study new ways to:

- Treat cancer using
  - A new drug
  - An approved therapy for a different diagnosis
  - A new drug combination
  - A new way of delivering a drug (pill, intravenously [IV], etc)
- Manage cancer symptoms and alleviate the side effects of treatment
- Find and diagnose cancer
- Prevent cancer from returning
- Manage long-term side effects

Participation in a carefully conducted clinical trial may be the best available treatment option for some patients and should be considered each time treatment is discussed with the doctor. Patient participation in past clinical trials has resulted in the therapies we have today. Patients interested in participating in a clinical trial are encouraged to talk with their hematologist-oncologists about whether enrolling in a clinical trial would be an appropriate option for them.

When you and your hematologist-oncologist discuss a clinical trial as a potential treatment option, it may be helpful to:

- Have a list of questions to ask concerning the risks versus the benefits of such a trial (visit [www.LLS.org/WhatToAsk](http://www.LLS.org/WhatToAsk) for lists of suggested questions).
- Ask a family member, friend, or another advocate to accompany you to your doctor visit—both for support and to take notes.



# Chimeric Antigen Receptor (CAR) T-Cell Therapy

Patients and caregivers can work with an LLS **Clinical Trial Nurse Navigator** who will help find clinical trials and assist them throughout the entire clinical-trial process. Our Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers and clinical trials. Your Clinical Trial Nurse Navigator will:

- Speak with you to understand your goals and help you decide if a trial might be right for you
- Help you to understand the clinical-trial process, including your rights and obligations as a patient
- Ask you for details about your diagnosis, your past treatments and responses, your current physical condition, your medical history and your genetic profile, any of which might impact your eligibility for certain clinical trials
- Help you understand how your financial situation, insurance coverage, support network and ability and willingness to travel far distances might impact your choice of clinical trials
- Guide and advocate for you in your efforts to enroll in a clinical trial, including connecting you with trial sites
- Help you address and overcome obstacles to enrollment
- Be available for support throughout your experience in the clinical-trial process

**Please call an LLS Information Specialist at (800) 955-4572 or visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information about clinical trials and the Clinical Trial Support Center at LLS.**

**Also, visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to view *Understanding Clinical Trials for Blood Cancers*.**

**Feedback.** To give suggestions about this booklet, visit [www.LLS.org/PublicationFeedback](http://www.LLS.org/PublicationFeedback).

## Acknowledgements

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## We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has regions throughout the United States and in Canada. To find the region nearest

to you, visit our website at [www.LLS.org/LocalPrograms](http://www.LLS.org/LocalPrograms) or contact an Information Specialist at (800) 955-4572.

LLS offers free information and services for patients and families affected by blood cancers. This section lists various resources you may find helpful.

### For Help and Information

**Consult with an Information Specialist.** Information Specialists can assist you through cancer treatment, financial and social challenges and give accurate, up-to-date disease, treatment and support information. Our Information Specialists are highly trained oncology social workers and nurses. Language services are available. For more information, please:

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. ET)
- Email and Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)

**Clinical Trials (Research Studies).** Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. Pediatric and adult patients and caregivers can work with our Clinical Trial Nurse Navigators who will help find clinical trials and provide personalized support throughout the entire clinical trial process. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**Nutrition Consultations.** Schedule a free one-on-one nutrition consultation with one of our registered dietitians who have expertise in oncology nutrition. Consultations are available to patients and caregivers of all cancer types. Dietitians can assist with information about healthy eating strategies, side effect management and more. Please visit [www.LLS.org/nutrition](http://www.LLS.org/nutrition) for more information.

**Free Information Booklets.** LLS offers free education and support booklets for patients, caregivers and healthcare professionals that can either be read online or ordered. Please visit [www.LLS.org/booklets](http://www.LLS.org/booklets) for more information.

**Telephone/Web Education Programs.** LLS offers free telephone/Web and video education programs for patients, caregivers and healthcare professionals. Please visit [www.LLS.org/programs](http://www.LLS.org/programs) for more information.

**Financial Assistance.** LLS offers financial support to eligible individuals with blood cancer for insurance premiums, co-pays, and non-medical expenses like travel, food, utilities, housing, etc. For more information, please:

- Call: (877) 557-2672
- Visit: [www.LLS.org/finances](http://www.LLS.org/finances)

## Chimeric Antigen Receptor (CAR) T-Cell Therapy

**Resources for Families.** Blood cancer occurs in a small number of children. Families face new challenges, and the child, parents and siblings may all need support. LLS has many materials for families including a caregiver workbook, children's book series, an emotion flipbook, dry erase calendar, coloring books and a coloring app, a school reentry program, and other resources. For more information, please

- Call: (800) 955-4572
- Visit: [www.LLS.org/FamilyWorkbook](http://www.LLS.org/FamilyWorkbook)

**Podcast.** *The Bloodline with LLS* is here to remind you that after a diagnosis comes hope. Listen in as patients, caregivers, advocates, doctors and other healthcare professionals discuss diagnosis, treatment options, quality-of-life concerns, treatment side effects, doctor-patient communication and other important survivorship topics. Visit [www.LLS.org/TheBloodline](http://www.LLS.org/TheBloodline) for more information and to subscribe to access exclusive content, submit ideas and topics, and connect with other listeners.

### Free Mobile Apps.

- LLS Coloring For Kids™ — Allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. Visit [www.LLS.org/ColoringApp](http://www.LLS.org/ColoringApp) to download for free.
- LLS Health Manager™ — Helps you track side effects, medication, food and hydration, questions for your doctor, and more. Visit [www.LLS.org/HealthManager](http://www.LLS.org/HealthManager) to download for free.

**Suggested Reading.** LLS provides a list of selected books recommended for patients, caregivers, children and teens. Visit [www.LLS.org/SuggestedReading](http://www.LLS.org/SuggestedReading) to find out more.

### Connecting with Patients, Caregivers and Community Resources

**LLS Community.** The one-stop virtual meeting place for talking with other patients and receiving the latest blood cancer resources and information. Share your experiences with other patients and caregivers and get personalized support from trained LLS staff. Visit [www.LLS.org/community](http://www.LLS.org/community) to join.

**Weekly Online Chats.** Moderated online chats can provide support and help cancer patients and caregivers reach out and share information. Please visit [www.LLS.org/chat](http://www.LLS.org/chat) for more information.

**Local Programs.** LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection® Program* (a peer-to-peer support program), local support groups and other great resources. For more information about these programs or to contact your region, please:

- Call: (800) 955-4572
- Visit: [www.LLS.org/LocalPrograms](http://www.LLS.org/LocalPrograms)

**Advocacy and Public Policy.** Working closely with dedicated volunteer advocates, LLS's Office of Public Policy elevates the voices of patients to state and federal elected officials, the White House, governors and even courts. Together, we advocate for safe and effective treatments. We pursue policies that would make care more accessible to all patients. And, most of all, we advocate for the hope for a cure. Want to join our work? Visit [www.LLS.org/advocacy](http://www.LLS.org/advocacy) for more information.

**Other Helpful Organizations.** LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, patient care and other needs. For more information, please visit [www.LLS.org/ResourceDirectory](http://www.LLS.org/ResourceDirectory) to view the directory.

### Additional Help for Specific Populations

**Información en Español (LLS information in Spanish).** Please visit [www.LLS.org/espanol](http://www.LLS.org/espanol) for more information.

**Language Services.** Let members of your healthcare team know if you need translation or interpreting services because English is not your native language, or if you need other assistance, such as a sign language interpreter. Often these services are free.

**Information for Veterans.** Veterans who were exposed to Agent Orange while serving in Vietnam may be able to get help from the United States Department of Veterans Affairs. For more information, please

- Call: the Veterans Affairs (800) 749-8387
- Visit: [www.publichealth.va.gov/exposures/AgentOrange](http://www.publichealth.va.gov/exposures/AgentOrange)

**Information for Firefighters.** Firefighters are at an increased risk of developing cancer. There are steps that firefighters can take to reduce the risk. Please visit [www.LLS.org/FireFighters](http://www.LLS.org/FireFighters) for resources and information.

**World Trade Center Health Program.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be able to get help

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from the World Trade Center (WTC) Health Program.

People eligible for help include:

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area and those who lived, worked or were in school in that area
- Responders to the Pentagon and the Shanksville, PA, crashes

For more information, please

- Call: WTC Health Program at (888) 982-4748
- Visit: [www.cdc.gov/wtc/faq.html](http://www.cdc.gov/wtc/faq.html)

**People Suffering from Depression.** Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time, for example, if you feel depressed every day for a 2-week period. For more information, please:

- Call: The National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at [www.nimh.nih.gov](http://www.nimh.nih.gov) and enter “depression” in the search box

## Resources

### The National Cancer Institute (NCI)

[www.cancer.gov](http://www.cancer.gov)

(800) 422-6237

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including CAR T-cell therapy.

### The National Comprehensive Cancer Network® (NCCN)

[www.nccn.org](http://www.nccn.org)

The National Comprehensive Cancer Network®, a not-for-profit alliance of 26 of the world’s leading cancer centers devoted to patient care, research, and education, is dedicated to improving the quality, effectiveness, and efficiency of cancer care so that patients can have the best quality of life. Through the leadership and expertise of clinical professionals at NCCN Member Institutions, NCCN develops practice guidelines that are appropriate for use by patients, clinicians and other healthcare decision-makers.

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Information Specialist: **800.955.4572**

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