

**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 change the genetic makeup of cells. Genetically modified T cells express the chimeric antigen receptor (CAR), which allows them to identify and attack cancer cells. In the laboratory, the number of these engineered CAR T cells is multiplied and the modified cells 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 FDA-approved: tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®), brexucabtagene autoleucel (Tecartus®), lisocabtagene maraleucel (Breyanzi®), idecabtagene vicleucel (Abecma®) and ciltacabtagene autoleucel (Carvykti™). For prescribing information, please see page 3.
- Serious side effects are associated 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 that the body's own defenses can be harnessed to treat blood cancers. Cancer researchers continue to study how the immune system can help destroy cancer cells. Chimeric antigen receptor (CAR) T-cell therapy is called "immunotherapy" because it uses a patient's own T cells 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 that cause the body to create an immune response against it. Antigens that get in the body stimulate the immune system to target their toxic material and kill any cells they have infected.

Lymphocytes are a type of white blood cell that 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 arise when normal B cells mutate (change) and become cancerous. These cancerous B cells then multiply and crowd out normal B cells.

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 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

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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 Facts* and for more information about immunotherapy treatments.

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

Autologous chimeric antigen receptor (CAR) T-cell therapy involves engineering a patient's own T cells to recognize and attack cancer cells. "Autologous" means using an individual's own cells or tissues. In CAR T-cell therapy, white blood cells are taken from a patient 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 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 cells. Because the human body can tolerate prolonged periods of B-cell loss (called "depletion"), CD19 is considered an ideal target antigen for CAR T-cell immunotherapy (see B-cell aplasia on page 6). Trials of CAR T cells that target other antigens expressed on various blood-related cancers are also under way (see Table 1 on page 3).

### 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, which are found within the white blood cells, are removed. The remaining blood is infused back into the patient's body.

#### **T cells 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 chimeric antigen receptors (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 or 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 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 through an existing central line or IV, a process that 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. As the CAR T cells attack tumor cells, they become activated and multiply.

#### **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:

**Tisagenlecleucel (Kymriah®)** is approved by the U.S. 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

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

- 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

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®)** is FDA-approved since 2017 for the treatment of adult patients with:

- Relapsed or refractory large B-cell lymphoma—after two or more lines of systemic therapy—including DLBCL NOS, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
- Relapsed or refractory follicular lymphoma (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®)** is 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.

**Lisocabtagene maraleucel (Breyanzi®)** is FDA-approved since 2021 for the treatment of 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) NOS (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

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

**Idecabtagene vicleucel (Abecma®)** is 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™)** is 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.

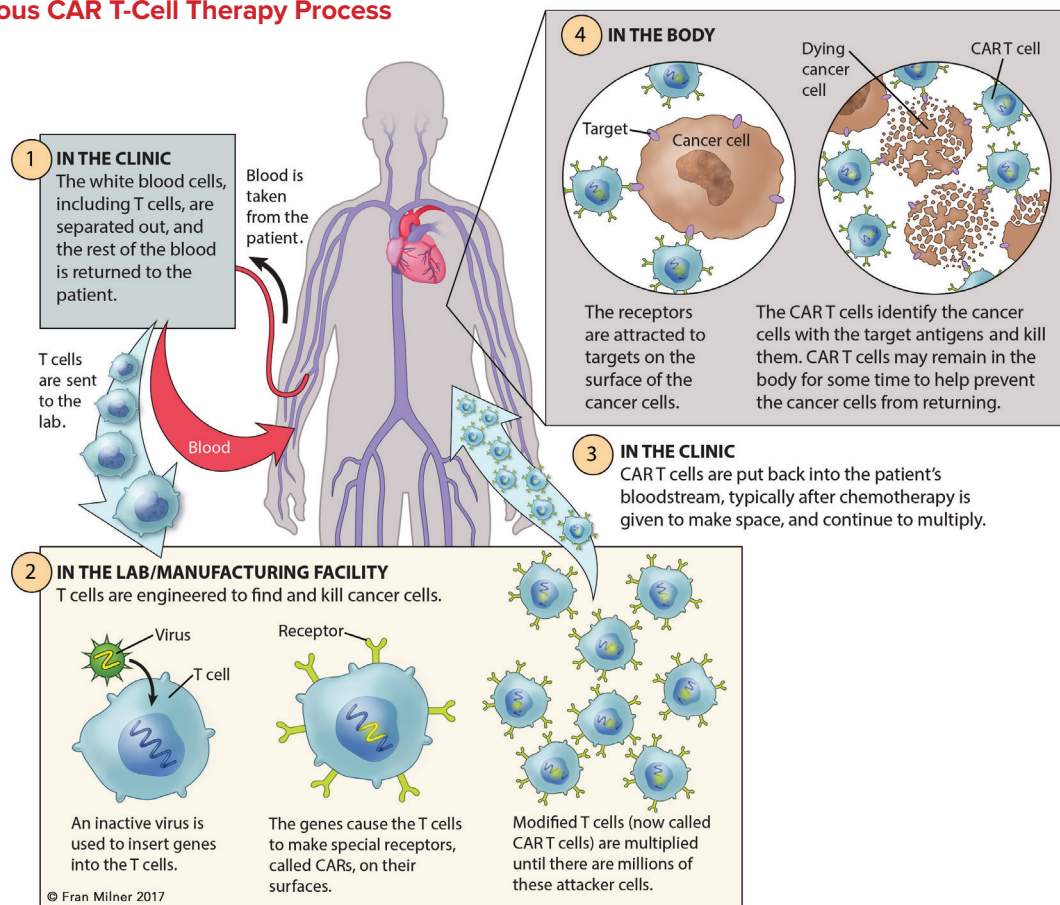
Table 1 below lists some of the CAR T-cell therapy antigen targets currently approved for use by the FDA or that are under study in clinical trials for hematologic malignancies and their potential off-tumor targets.

**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>Id<sub>κ</sub></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; Igk, immunoglobulin kappa light chain; NHL, non-Hodgkin lymphoma; NKG2D-L, natural killer group 2D-ligands; ROR 1, receptor tyrosine kinase-like orphan receptor 1; T-ALL, T-cell acute lymphoblastic leukemia.

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



**Clinical Trials.** Chimeric antigen receptor T-cell therapy has shown varying degrees of effectiveness 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, this treatment continues to be used in clinical trials to determine if other diseases may respond to CAR T-cell therapy. Trial protocols vary. Depending on the clinical trial, care may be provided in either a hospital setting or an outpatient treatment center with 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.

## 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 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 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 sections below.

**Cytokine Release Syndrome (CRS).** 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,



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

including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF ) and interferon gamma (IFN ), 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” or 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 leak out of tiny blood vessels and flow 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 NK cells become overactive causing too much inflammation)/ macrophage activation syndrome (immune system is uncontrolled and works overtime, leading to too much inflammation) (HLH/MAS)
- Renal insufficiency (poor function of the kidneys)
- 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.

Severe cytokine release syndrome (CRS) may require intensive care treatment. Although most symptoms are reversible, the potential life-threatening risk 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 its severity, 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 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 T cells. Tocilizumab is approved by the FDA for the treatment of adults and pediatric patients 2 years of age and older who have CAR T-cell-induced severe or life-threatening CRS.

If signs and 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 have achieved long-lasting remissions. When CRS is life-threatening, corticosteroids may be the only way to stop symptoms from getting worse. Your doctor may also prescribe **siltuximab (Sylvant®)**, another monoclonal antibody that blocks IL-6 or other anti-cytokine therapies, as a treatment for CRS.

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.

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

The frequency, severity and nature of neurological toxicity is different among CAR T-cell products. This could be due to differences in the products, the relatively small number of patients studied, or both. ICANS side effects have been observed in the 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 symptoms usually resolve over several days without intervention or apparent long-term side effects. However, neurologic complications of CAR T-cell therapy can be life-threatening. Harmful neurological events have been reported (notably cerebral edema, ie, swelling in the brain), and fatalities have occurred. Although ICANS is sometimes associated with the presence of CRS, the symptoms usually are neither prevented nor mitigated by IL-6 blocking medication because IL-6 does not cross the blood-brain barrier. 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.

ICANS symptoms 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. TLS 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.** CAR 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 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. Cytopenias are low numbers of white blood cells, red blood cells or platelets. 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 result, most patients are maintained on prophylactic therapy (treatment designed to prevent an infection from occurring) following CAR T-cell therapy; this will depend on each patient's blood cell count recovery.

**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. COVID-19 and flu vaccines are also recommended. For more information, patients should consult with their doctors.

### Pediatric and Adolescent CAR T-Cell Therapy

The FDA has approved **tisagenlecleucel (Kymriah®)** for treatment of pediatric and adolescent patients with B-ALL, based on this drug's remarkable success in early clinical trials. However, compared to adult patients, the process of enrolling pediatric and young adult patients in clinical trials is often much slower than it is for adults, due to the need to demonstrate safety and tolerability in adults before this population can be studied.

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 with your healthcare team how treatment of children with CAR T-cell therapy may differ from that of adults.

### Follow-Up Care

Some patients will receive their 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 lab work, supportive care and possibly imaging tests (such as X-rays, CAT scans, MRIs, etc). A patient's local hematologist/oncologist should continue cancer checkups. Patients are also advised to keep their caregivers included in these appointments since they have been with the patient throughout the CAR-T cell treatment process and caregivers may be the first to notice any changes or side effects the patient may have.

Most patients participating in CAR T-cell trials have been followed only 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 trial participants have been

followed over longer terms. Patients who have had CAR-T cell treatment face similar long-term and late effects as those of other cancer patients. Fertility and endocrine late effects are also especially important to follow up on.

It is important for more pediatric 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 B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma (DLBCL), large B-cell lymphoma, follicular lymphoma (FL), myeloma, and mantle cell lymphoma (MCL) 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.

Studies of CAR T-cell therapy in other blood cancers, including chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML), T-cell malignancies and Hodgkin lymphoma (HL) also show potential. Research is also under way exploring the application of CAR T-cell therapy, and other cellular immunotherapies, in the treatment of solid tumors and brain tumors.

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.

### 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 Food and Drug Administration (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 cancer clinical trials are searching for a 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
  - o A new drug
  - o An approved therapy for a different diagnosis
  - o A new drug combination
  - o 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 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 a clinical trial would be appropriate 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.

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. 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).



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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 chapters throughout the United States and in Canada. To find the chapter nearest to you, visit our website at [www.LLS.org/ChapterFind](http://www.LLS.org/ChapterFind) or contact:

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Rye Brook, NY 10573

Contact an Information Specialist at (800) 955-4572  
Email: [infocenter@LLS.org](mailto:infocenter@LLS.org)

LLS offers free information and services for patients and families touched by blood cancers. The following entries list various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team.

**Consult with an Information Specialist.** Information Specialists are highly trained oncology social workers, nurses and health educators. They offer up-to-date

disease, treatment and support information. Language services (interpreting and translation) are available. Please contact our Information Specialists or visit our website for more information:

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

**Clinical Trials Support Center (CTSC).** Research is ongoing to develop new treatment options for patients. LLS offers help for patients and caregivers in understanding, identifying and accessing clinical trials. 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. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**One-on-One Nutrition Consultations.** Access free one-on-one nutrition consultations provided by a registered dietitian who has experience in oncology nutrition. Dietitians assist callers with information about healthy eating strategies, side effect management and survivorship nutrition. They also provide additional nutrition resources. Please visit [www.LLS.org/nutrition](http://www.LLS.org/nutrition) to schedule a consultation or for more information.

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

**LLS Health Manager™ App.** This free mobile app helps you manage your health by tracking side effects, medication, food and hydration, questions for your doctor, and more. Export the information you've tracked in a calendar format and share it with your doctor. You can also set up reminders to take medications, hydrate, and eat. Visit [www.LLS.org/HealthManager](http://www.LLS.org/HealthManager) to download for free.

**LLS Coloring for Kids™.** This free coloring app allows children (and adults) to express their creativity and offers activities to help them learn about blood cancer and its treatment. The app includes blank canvases, general coloring pages, and pages from LLS coloring books. This app can be used anywhere and may help pass the time in waiting rooms or during treatment. Visit [www.LLS.org/ColoringApp](http://www.LLS.org/ColoringApp) to learn more and download.

**Financial Assistance.** LLS offers financial support including insurance premium and medication co-pay assistance, as well as travel and other needs, to eligible individuals with blood cancer. 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

### Información en Español (LLS information in Spanish).

Please visit [www.LLS.org/espanol](http://www.LLS.org/espanol) 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.

**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 to reach out and share information. Please visit [www.LLS.org/chat](http://www.LLS.org/chat) for more information.

**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.

**LLS Chapters.** LLS offers 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 chapter, please:

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

**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. Please visit [www.LLS.org/ResourceDirectory](http://www.LLS.org/ResourceDirectory) for more information.

**Advocacy.** The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please:

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

**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 VA at (800) 749-8387
- Visit: [www.publichealth.va.gov/exposures/AgentOrange](http://www.publichealth.va.gov/exposures/AgentOrange)

**World Trade Center (WTC) Survivors.** People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help 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, lived, worked or were in school in the 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

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

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.

### References

Bakker ABH, van den Oudenrijn S, Bakker AQ, et al. C-type lectin-like molecule-1: a novel myeloid cell surface marker associated with acute myeloid leukemia. *Cancer Research*. 2004;65:8443-8450.

Brodsky AN. The promise of CAR T cell therapy in 2019 and beyond. Cancer Research Institute [website]. <https://www.cancerresearch.org/blog/september-2019/promise-car-t-cell-therapy-2019-beyond>. Accessed October 15, 2021.

Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. *Blood Reviews*. 2019;34:45-55. doi:10.1016/j.blre.2018.11.002

Gill S, Maus MV, Porter DL. Chimeric antigen receptor T cell therapy: 25 years in the making. *Blood Reviews*. 2016;30:157-167.

Hauser JR, Hong H, Babady NE, Papanicolaou GA, Tang Y-W. False-positive results for human immunodeficiency virus type 1 nucleic acid amplification testing in chimeric antigen receptor T cell therapy. *Journal of Clinical Microbiology*. 2019;58(1):e01420-19. doi:10.1128/JCM.01420-19

Laetsch TW, Myers GD, Baruchel A, et al. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. *Lancet Oncology*. 2019;20(12):1710-1718. doi:10.1016/S1470-2045(19)30493-0

Laszlo GS, Estey EH, Walter RB. The past and future of CD33 as a therapeutic target in acute myeloid leukemia. *Blood Reviews*. 2014;28:143-153. <https://www.sciencedirect.com/science/article/abs/pii/S0268960X14000320?via%3Dihub>

National Cancer Institute. CAR T cells: engineering patient's immune cells to treat their cancers. <https://www.cancer.gov/about-cancer/treatment/research/car-t-cells>. Updated: July 30, 2019. Accessed October 20, 2021.

Neelapu SS. Managing the toxicities of CAR T-cell therapy. *Hematological Oncology*. 2019;37(S1):48-52. doi: 10.1002/hon.2595

Shi H, Sun M, Wang Z. Chimeric antigen receptor for adoptive immunotherapy of cancer: latest research and future prospects. *Molecular Cancer*. 2014;13:219. [www.molecular-cancer.com/content/13/1/219](http://www.molecular-cancer.com/content/13/1/219). Accessed October 14, 2021.

The Leukemia & Lymphoma Society. *Immunotherapy Facts*. <https://www.lls.org/booklet/immunotherapy>. Revised December 2019. Accessed October 19, 2021.

Yanez L, Sanchez-Escamilla M, Perales MA. Car T cell toxicity: current management and future directions. *HemaSphere*. 2019;3(2):e186. doi: 10.1097/HS9.0000000000000186

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