

**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. These genetically modified T cells will express a specific receptor (the chimeric antigen receptor) that allows them to identify and attack cells that have the target antigen. In the laboratory, the number of these engineered T cells is multiplied and the modified cells are eventually returned to the patient and re-infused into the bloodstream.
- **Tisagenlecleucel (Kymriah™)** is approved by the United States Food and Drug Administration (FDA) for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is either refractory or in either a second or a later relapse. It is also approved for 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.
- **Axicabtagene ciloleucel (Yescarta®)** is FDA approved for the treatment of adult patients with either 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.

Axicabtagene ciloleucel is also approved for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

- **Brexucabtagene Autoleucel (Tecartus™)** is FDA approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) and for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- **Idecabtagene vicleucel (Abecma®)** is FDA approved 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.
- Serious side effects are associated with CAR T-cell therapy, some of which can be life threatening. Diligent 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 have been the foundation of cancer treatment. Advances in the field of immunology (a branch of science that studies all aspects of the immune system) have led to a greater understanding of the ways in which the body's own defenses can be used for treatment of blood cancers. Cancer researchers are studying how the immune system can help destroy cancer cells. Chimeric antigen receptor (CAR) T-cell therapy immunotherapy 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 and information on how CAR T-cell therapy may work, its possible side effects and its role in the treatment of blood cancer.

### The Natural Immune System and Immunotherapy

The immune system is the body's defense against infection and cancer. It is a network of organs along with cells that defend the body from foreign substances called "antigens." Antigens stimulate the activation of the immune system to target foreign material and kill infected cells.

Lymphocytes are part of this complex immune system. These cells respond to foreign organisms and help to fight cancer. Most lymphocytes are found in the lymph nodes, the spleen, a few other lymphatic organs (eg, the bone marrow and the thymus) and the lymphatic channels, but some 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 marrow and other parts of the lymphatic system. T lymphocytes mature in the thymus. They have several functions, including helping B lymphocytes to make antibodies against invasive microbes, and directly killing invading or infected cells in the body. Natural killer cells 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 many people with certain types of cancer. Immunotherapies that are either approved for use or are under study in clinical trials to determine their effectiveness in treating various types of cancer include monoclonal antibody therapy, radioimmunotherapy, therapeutic cancer vaccines and CAR T-cell therapy.

**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 T-cell therapy involves engineering patients' own T cells to recognize and attack cancer cells. White blood cells are taken from a patient in a procedure called "apheresis" and sent to a laboratory or manufacturing facility. There, the T cells

are separated and then modified so that they express an artificial receptor on their surface—one that directs the engineered T cell to find and attack the cancer cell. These 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. There, the CAR T cells are thawed and given back to the patient via an intravenous 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 expressed on the surface of nearly all healthy and cancerous B cells, including lymphoma and leukemia B cells. The CD19 antigen is expressed only on B cells and not on other cells; further, patients can tolerate prolonged periods of B-cell depletion (see *B-cell Aplasia* on page 6), so CD19 is considered an ideal target antigen for CAR T-cell immunotherapy. Trials of CAR T cells that target other antigens expressed on various hematologic 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.** T cells are collected via apheresis, a procedure during which blood is withdrawn from the body and one or more blood components (such as plasma, platelets or white blood cells) are removed. The remaining blood is then infused back into the body.

**T cells engineered in a laboratory are able to recognize proteins on the surface of tumor cells.** In the CAR T-cell process, the 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 surface of the cells. Chimeric antigen receptors are proteins that allow the T cells to recognize an antigen on targeted 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.

## 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 (lymphodepletion). This process makes space for the CAR T cells before patients receive the infusion. Once they are infused into the patient's bloodstream, the CAR T cells will multiply in number. These are "attacker" cells that will recognize, and attack cells that have the targeted antigen on their surfaces.

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

The CAR T cells may eradicate all of the cancer cells and they may remain in the body months after the infusion has been completed. The therapy has resulted in long-term remissions for some types of blood cancer.

There are three approved treatments for CAR T-cell therapy.

**Tisagenlecleucel (Kymriah™)** is approved by the United States Food and Drug Administration (FDA) 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. It is also approved for 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 not indicated for treatment of patients with primary central nervous system lymphoma. Tisagenlecleucel is a CD19-directed genetically modified autologous T-cell immunotherapy.

**Axicabtagene Ciloleucel (Yescarta®)** is FDA approved 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. This is also approved for adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma. Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T cell immunotherapy.

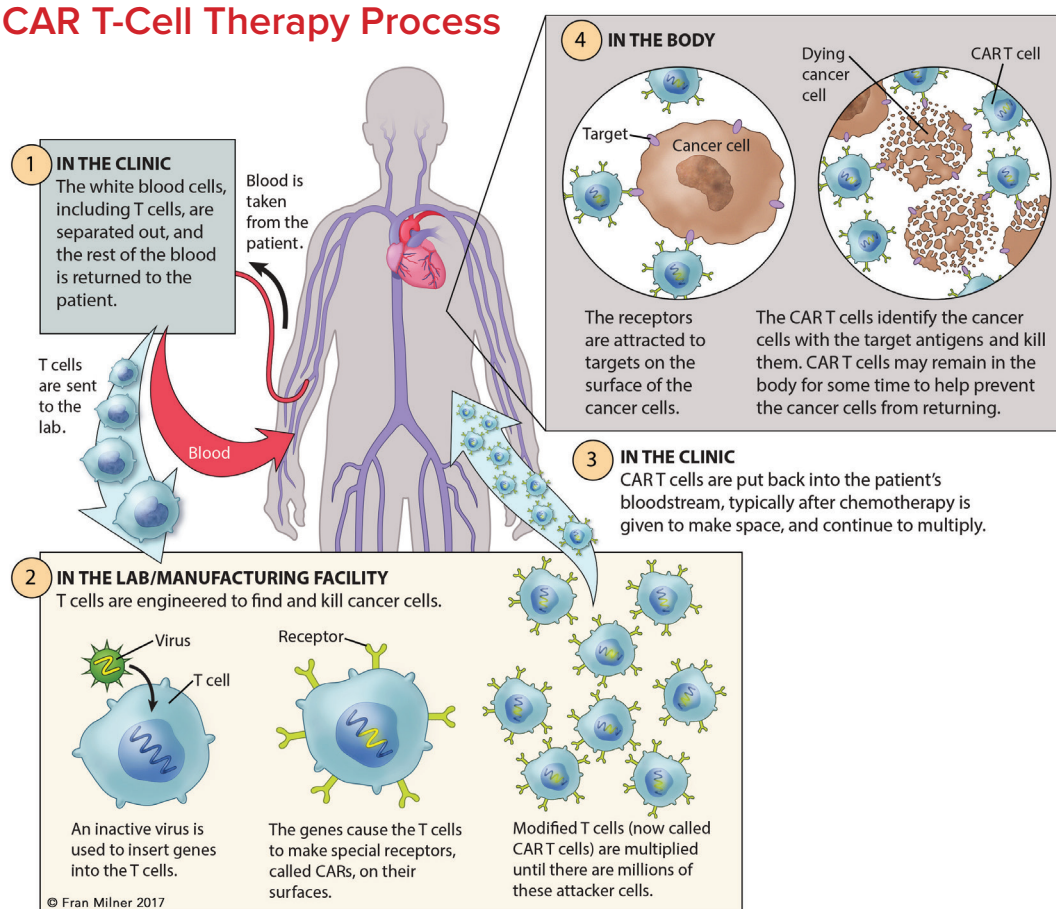
**Brexucabtagene Autoleucel (Tecartus™)** is FDA approved for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) and for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Tecartus is a CD19-directed genetically modified autologous T cell immunotherapy.

**Table 1. Chimeric antigen receptor target antigens for hematologic malignancies and potential off-tumor targets**

Antigen	Hematologic Malignancy	Potential Normal Tissue Impacted
<b>CD19</b>	ALL, CLL, NHL, HL	Normal B cells
<b>CD20</b>	CLL, NHL	Normal B cells
<b>CD22</b>	ALL, NHL	Normal B cells
<b>Id<math>\kappa</math></b>	CLL, NHL, myeloma	Normal B cells
<b>ROR1</b>	CLL, NHL	Pancreas, parathyroid, adipose cells
<b>CD30</b>	NHL, HL	Resting CD8 T cells
<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>NKG2D-L</b>	AML, myeloma	Gastrointestinal lining, endothelial cells
<b>BCMA</b>	Myeloma	B cells
<b>Lewis-Y carbohydrate antigen (CD174)</b>	AML, myeloma	Early myeloid progenitor cells

**Key.** 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; HL, Hodgkin lymphoma; Ig $\kappa$ , immunoglobulin kappa light chain; NHL, non-Hodgkin lymphoma; NKG2D-L, natural killer group 2D-ligands; ROR 1, receptor tyrosine kinase-like orphan receptor 1.

## Autologous CAR T-Cell Therapy Process



**Idecabtagene vicleucel (Abecma®)** is FDA approved 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.

**Table 1** on page 3 lists some of the CAR T-cell therapy antigen targets, currently approved for use by the FDA or under study in clinical trials for hematologic malignancies, and their potential off-tumor targets.

**Clinical Trials.** Even though CAR T-cell therapy is FDA approved, this treatment continues to be available in clinical trials. Trial protocols vary. Depending on the clinical trial, care may be provided in either a hospital setting or an intensive 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 close by 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

Chimeric antigen receptor T-cell therapy has shown varying degrees of effectiveness in the treatment of leukemia, lymphoma and myeloma in clinical trials. While many patients have reported only mild to moderate side effects, this treatment is sometimes associated with significant 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 (as well as the strategies employed to minimize or counteract these effects) include cytokine release syndrome (CRS); macrophage activation syndrome (MAS); neurologic toxicities [immune effector cell-associated neurotoxicity syndrome (ICANS)]; tumor lysis syndrome; anaphylaxis; on-target, off-tumor toxicity and B-cell aplasia.

**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 (including interleukin-6 [IL-6], tumor necrosis factor-alpha [TNF $\alpha$ ] and interferon gamma [IFN $\gamma$ ]) are released. The large amounts of cytokines that are 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.”

The signs and symptoms of CRS can be mild and flulike and include

- Fever
- Fatigue
- Headache
- Chills.

More serious signs and symptoms of CRS include

- Low blood pressure (hypotension)
- Tachycardia (abnormally rapid heart rate)
- Capillary leakage (fluid and proteins leaking out of tiny blood vessels and flowing into surrounding tissues, resulting in dangerously low blood pressure)
- Cardiac arrest
- Cardiac arrhythmias
- Cardiac failure
- Hemophagocytic lymphohistiocytosis (life-threatening immune system activation)/macrophage activation syndrome (life-threatening activation of macrophages) (HLH/MAS)
- Hypoxia (lack of oxygen reaching the tissue)
- Renal insufficiency (poor function of the kidneys)
- Poor lung oxygenation
- Multiple organ failure.

Severe CRS requires 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 in CAR T-cell therapy trials.

Depending on its severity, CRS can be self-limited (requiring only supportive care with fever-reducing medication and intravenous (IV) fluids) at the guidance of the doctor or it may require rapid intervention with immunosuppressive anticytokine-directed therapy and/or corticosteroids. Researchers have discovered that patients with the most severe reactions expressed high levels of IL-6, and other cytokines, secreted by T cells and other bystander immune cells 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. Fortunately, 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 T cells. Tocilizumab is approved by the FDA for the treatment of adults and pediatric patients 2 years of age and older with CAR T-cell-induced severe or life-threatening CRS.

If severe CRS signs and symptoms either do not improve with tocilizumab, or if they are getting worse, corticosteroids are 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, these drugs may be the only way to stop worsening symptoms. Your doctor may also prescribe **siltuximab (Sylvant®)**, another monoclonal antibody that blocks IL-6, as a treatment for CRS.

Other methods aiming 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 a single high-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 it depends on the type of intervention used to manage it.



**Macrophage Activation Syndrome (MAS).** This side effect is closely associated with severe CRS. The syndrome is a condition caused by the excessive activation and multiplication of T cells and macrophages. It is generally seen in patients with chronic autoimmune and rheumatic diseases. Fortunately, research has shown that MAS (like CRS) can be lessened by the infusion of the monoclonal antibody **tocilizumab (Actemra®)**. Corticosteroids and anticytokine therapy can be considered as treatment options if MAS is severe and the symptoms persist or are getting worse.

**Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).** The connection between CRS, MAS and neurologic adverse events is not completely understood. The frequency, severity and nature of neurological toxicity seem to be different between CAR T-cell products. This could be due to differences in the product or due to the small number of patients studied or both. These 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) and multiple myeloma. Common signs and symptoms include language impairment (aphasia), confusion, delirium, involuntary muscle twitching, hallucinations, or unresponsiveness. Seizures have also been reported. The underlying cause of ICANS is unclear and it is not known whether the presence of CAR T cells in the central nervous system is related to the occurrence or severity of neurotoxicity. The cause of neurotoxicity is the subject of intense investigation by researchers.

Neurotoxicity has been reversible in most cases and the symptoms have resolved over several days without intervention or apparent long-term effects. However, there can be life-threatening adverse neurological events and there have been fatalities resulting from neurologic complications of CAR T-cell therapy, notably cerebral edema (swelling in the brain). Although ICANS is sometimes associated with the presence of CRS, the symptoms usually are neither prevented nor mitigated by IL-6 blocking medication. Some symptoms of neurologic toxicity have been treated with anti-epileptic medication and/or corticosteroids. Some patients may receive prophylactic (preventative) medications, such as levetiracetam (Keppra®, Keppra® XR, Spritam®). More study is needed to understand the mechanism of action, associated risk factors and best management of this potential side effect.

**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 can be delayed and may occur 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 breakdown of cancer cells. The complication is managed by standard supportive therapy, including hydration and the use of 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 itself. Signs and symptoms associated with anaphylaxis include hives, facial swelling, low blood pressure and respiratory distress. There have been a few reports of acute anaphylaxis. Thorough monitoring and immediate treatment of this life-threatening side effect are critical for patients receiving CAR T-cell therapy.

**On-Target, Off-Tumor Toxicity.** An important factor in the safe and successful use of CAR T cells is choosing the proper tumor-associated antigen to target. The ideal antigen for CAR T cells has the following key characteristics:

- Expression on all tumor cells
- Expression on the tumor cell surface
- Defining role in tumor cell survival
- Lack of expression on healthy tissues.

Unfortunately, it is rare to find such an ideal target. Many tumor antigens are also expressed on healthy cells in tissues. Damage to such noncancerous normal tissue by CAR T cells may pose life-threatening risks, especially when cells in essential tissues such as the heart, lung or liver express the target antigen. B-cell aplasia following CD19-targeted CAR T-cell therapy is an example of on-target, off-tumor toxicity.

**B-Cell Aplasia.** Chimeric antigen receptor T-cell therapy targeting antigens found on the surface of B cells not only destroy cancerous B cells but also normal B cells. Therefore, B-cell aplasia (low numbers 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 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 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 study is needed to assess the late effects of B-cell aplasia.

**Infection.** Twenty to forty percent of patients may have prolonged cytopenias (low numbers of white blood cells, red blood cells and platelets) in addition to B-cell aplasia which can result in serious bacterial or viral 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 will be maintained on prophylactic therapy (treatment designed to prevent a disease from occurring) for 1 to 2 years, depending on blood cell count recovery.

### 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 CAR T-cell therapy patients with blood cancers. With the United States Food and Drug Administration (FDA) approval of **tisagenlecleucel (Kymriah™)**, **axicabtagene ciloleucel (Yescarta™)**, **idecabtagene vicleucel (Abecma®)** and **brexucabtagene autoleucel (Tecartus™)**, CAR T-cell therapy represents an option for B-cell acute lymphoblastic leukemia (B-ALL), diffuse large B-cell lymphoma, follicular lymphoma, myeloma and mantle cell lymphoma patients whose disease has relapsed.

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 test result. Talk to the healthcare team about any concerns and questions.

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. Relapses may be due to the tumor cells losing the

expression of the cluster of differentiation 19 (CD19) antigen, the limited persistence of CAR T cells, or inhibition of CAR T-cell activity.

Studies of CAR T-cell therapy in other blood cancers, including chronic lymphocytic leukemia (CLL), as well as multiple myeloma, also show potential. Research is also under way exploring the application of CAR T-cell therapy in the treatment of solid tumors.

Most patients participating in CAR T-cell trials have only been followed for a relatively short time; however, data providing information about early responses to therapy is fast emerging. Researchers will be able to predict the duration of these responses after trial participants have been followed over the long term. 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.

Some of the strategies being studied in trials to improve specificity and minimize toxic side effects associated with CAR T-cell therapy include

- **Allogeneic CAR T-Cell Therapy.** Clinical trials are beginning to explore the potential of allogeneic CAR T-cell therapy, which uses T cells from healthy donors instead of using a patient's own T cells. In allogeneic CAR T-cell therapy, donor T cells are isolated in a manufacturing facility, engineered to express CARs to recognize and destroy cancer cells, and modified using gene editing to reduce the risk of an autoimmune response when given to a patient who is not the cell donor. As a result, allogeneic therapies may be able to address some of the current limitations of autologous CAR T-cell therapy, such as speed, reliability, access and cost.
- **MB-102 T-cell therapy.** This is a CD123-directed CAR T-cell therapy that has been granted orphan drug designation by the FDA for the treatment of patients with acute myeloid leukemia (AML). This is the second orphan drug designation for MB-102, the first being for the treatment of patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN). A clinical trial for patients with AML, BPDCN, and high-risk myelodysplastic syndrome is available.
- **Standardization of Each Patient's Dosage of T cells.** Chimeric antigen receptor T-cell therapies generally begin with a mixture of various types of T cells, some

with very different functions. By creating a better defined “T-cell cocktail,” researchers expect to have better control of dosage and toxicity.

- **Suicide Switches.** If the immune response becomes excessive and toxicity is spiraling out of control, doctors can administer a drug that activates a switch in the CAR T cell, triggering the CAR T cells to self-destruct. Other CARs are designed to only be active in the presence of a drug, so they could be turned on and off, depending on toxicities.
- **Multiple Protein Targets.** Finding proteins on cancer cells that are absent from healthy tissues is a great challenge for researchers. Proteins that are only associated with cancer cells could serve as targets for CAR T cells. By focusing on multiple proteins expressed by cancer cells, therapy could provide a more precise way to mark malignant cells for destruction. Alternatively, a CAR could target multiple different targets independently to avoid resistance developing by the loss of one or another antigen.
- **Combining CAR T Cells with Other Immunotherapies.** In some studies, CAR T cells have been administered along with other immunotherapy agents, such as the anti-PD-1 monoclonal antibody **pembrolizumab (Keytruda®)** or the anti-PD-L1 antibody **atezolizumab (Tecentriq®)**, in order to enhance the therapeutic effect and/or persistence of CAR T-cell therapy.
- **Alternative Delivery Routes.** CAR T-cell therapy is administered intravenously (IV). Some trials, aiming to minimize off-tumor toxicity, have been exploring the use of alternative routes for the delivery of the T cells, such as intratumorally (directly into the tumor), intracerebrally (within the brain) and other localized injections.
- **Prophylactic Measures.** Studies are exploring ways to reduce the incidence of severe cytokine release syndrome (CRS) and neurologic toxicities. For example, studies are under way that are combining CAR T-cell therapy with preventative measures, such as administration of corticosteroids and anti-interleukin 1 (a protein in the body that causes joint damage) therapy such as **anakinra (Kineret®)**, before the onset of toxicities.

Studies are also looking at other ways to improve CAR T-cell therapy by enhancing CAR T-cell production, identifying additional targets and receptors, identifying patient risk factors for developing adverse effects and decreasing the side effects of CAR T-cell therapy.

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.

### Enrolling in a Clinical Trial

Clinical trials test new drugs and treatments, many of which are supported by LLS research programs, before they are approved by the United States Food and Drug Administration (FDA) as standard treatments. Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments.

Patient participation in clinical trials is important in the development of new and more effective treatments and may provide patients with additional treatment options. Patients interested in participating in a clinical trial involving chimeric antigen receptor (CAR) T-cell therapy are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them.

When you and your doctor discuss CAR T-cell therapy as a potential treatment option for you, it may be helpful to have

- A list of questions to ask concerning risks versus benefits of such a trial (visit [www.LLS.org/WhatToAsk](http://www.LLS.org/WhatToAsk) for printable question guides)
- A family member, friend, or another advocate accompany you—both for support and to take notes.

For more information about clinical trials, call our LLS Information Specialists at (800) 955-4572. They can provide information and conduct individualized clinical-trial searches for patients, family members and healthcare professionals. When appropriate, Information Specialists refer patients for personalized clinical-trial navigation by trained nurses, a service which is available through the Clinical Trial Support Center. Visit [www.LLS.org/CTSC](http://www.LLS.org/CTSC) for more information.

**Visit [www.LLS.org/booklets](http://www.LLS.org/booklets) to see the free LLS booklet *Understanding Clinical Trials for Blood Cancers*.**

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



## Acknowledgment

The Leukemia & Lymphoma Society appreciates the review of this material by

### Loretta J. Nastoupil, MD

Associate Professor  
Director, Lymphoma Outcomes Database  
Section Chief, New Drug Development  
Department of Lymphoma/Myeloma, Division of Cancer Medicine  
The University of Texas MD Anderson Cancer Center  
Houston, TX

## 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:

The Leukemia & Lymphoma Society  
3 International Drive, Suite 200  
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 master's level 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: [infocenter@LLS.org](mailto:infocenter@LLS.org)
- Live chat: [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)
- Visit: [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. When appropriate, 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.

**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.

**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)

**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.

**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.

**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)

**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). Enter “depression” in the search box

**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)

## 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.

## References

- Brodsky AN. The promise of CAR T cell therapy in 2019 and beyond. *Cancer Research Institute*. <https://www.cancerresearch.org/blog/september-2019/promise-car-t-cell-therapy-2019-beyond> Accessed August 28, 2020.
- Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. *Blood Review*. 2019;34:45-55. doi:10.1016/j.blre.2018.11.002
- Curran KJ, Brentjens RJ. Chimeric antigen receptor T cells for cancer immunotherapy. *Journal of Clinical Oncology*. 2015;33(15):1703-1706.
- Gill S, Maus MV, Porter DL, et al. Chimeric antigen receptor T-cell therapy: 25 years in the making. *Blood Reviews*. 2016;30:157-167.
- Gross G, Eshar Z. Therapeutic potential of T cell chimeric antigen receptors (CARs) in cancer treatment: counteracting off-tumor toxicities for safe CAR T cell therapy. *Annual Review of Pharmacology and Toxicology*. 2016;56:59-83.
- Hauser JR, Hong H, Babady NE, et al. 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
- Juno Therapeutics. Chimeric Antigen Receptor Technology. <https://www.junotherapeutics.com/thescience/car-technology>. Accessed August 27, 2020.
- 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. *The Lancet*. 2019 20(12):1710-1718. [https://doi.org/10.1016/S1470-2045\(19\)30493-0](https://doi.org/10.1016/S1470-2045(19)30493-0)
- Maus MV, Levine B. Chimeric antigen receptor T-cell therapy for the community oncologist. *The Oncologist*. 2016;21:608-617.
- National Cancer Institute. CAR T cells: engineering patient's immune cells to treat their cancers. [www.cancer.gov/about-cancer/treatment/research/car-t-cells](http://www.cancer.gov/about-cancer/treatment/research/car-t-cells). Updated: July 30, 2019. Accessed August 27, 2020.
- Neelapu SS. Managing the toxicities of CAR T-cell therapy. *Hematological Oncology*. 2019;37(S1):48-52.
- Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nature Reviews Clinical Oncology*. 2018;15(1):47-62.
- 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 September 4, 2020.
- The Leukemia & Lymphoma Society. *Immunotherapy Facts*. <https://www.lls.org/resource-center/download-or-order-free-publications?language=English&category=Treatment&sortby=alpha&el-view=card-view> Revised December 2019. Accessed August 27, 2020.
- US Food and Drug Administration. FDA approval brings first gene therapy to the United States [news release]. August 30, 2017. <https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states> Accessed August 27, 2020.
- US Food and Drug Administration. FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma [news release]. October 18, 2017. <https://www.fda.gov/news-events/press-announcements/fda-approves-car-t-cell-therapy-treat-adults-certain-types-large-b-cell-lymphoma> Accessed August 28, 2020.
- Yanez L, Sanchez-Escamilla M, Perales MA. Car t cell toxicity: current management and future directions. *HemaSphere*. 2019;3(2):1-10.

This publication is designed to provide accurate and authoritative information in regard to the subject matter covered. It is distributed as a public service by The Leukemia & Lymphoma Society (LLS), with the understanding that LLS is not engaged in rendering medical or other professional services.