

Facts About Chimeric Antigen Receptor (CAR) T-Cell Therapy

Introduction

Autologous chimeric antigen receptor (CAR) T-cell therapy for the treatment of hematologic malignancies has generated intense interest from patients, families and healthcare providers. Clinical trials are underway for multiple B-cell malignancies, including B-cell acute lymphoblastic leukemia (B-ALL), Hodgkin lymphoma and non-Hodgkin lymphoma (NHL, including mantle cell lymphoma [MCL], follicular lymphoma [FL] and marginal zone lymphoma [MZL]), chronic lymphocytic leukemia (CLL), acute myeloid leukemia (AML) and multiple myeloma (MM).

The first 2 autologous CAR T-cell therapies, tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®), were approved by the US Food and Drug Administration in 2017. In July of 2020, the FDA approved brexucabtagene autoleucel (Tecartus™). The movement of these and other products currently in development into clinical practice will require sufficient understanding by all parties of the technology and medical management surrounding the use of these personalized, “living” biologics in patients with cancer. This publication will explain the rationale behind CAR T-cell therapy, describe approved therapies, summarize efficacy results to date, detail significant risks that have emerged, provide practical medical management information, and highlight some unique challenges involved in the anticipated integration of this therapy into clinical practice.

Highlights

- CAR T-cell therapy equips a patient’s T cells with the ability to detect and destroy malignant cells by combining the specificity of a monoclonal antibody with the cytotoxic and memory capabilities of endogenous T cells.
- CAR T-cell therapy involves isolating a patient’s T cells and then transfecting them with the CAR gene, expanding the cells, and re-infusing them into the patient.
- Tisagenlecleucel (Kymriah®) is approved for the treatment of patients up to 25 years of age with B-ALL (refractory or in second or later relapse). It is also approved for adult patients with relapsed or refractory (r/r) large B-cell lymphoma after 2 or more lines of systemic therapy.
- Axicabtagene ciloleucel (Yescarta®) is approved for the treatment of adults with r/r large B-cell lymphoma after 2 or more lines of systemic therapy.
- Brexucabtagene autoleucel (Tecartus™) is approved for the treatment of adults with r/r MCL.
- CARs used in the 3 approved products and in the most advanced clinical trials are directed against CD19, which is expressed on the surface of the vast majority of B cells, including B-cell malignancies.
- The time from T-cell harvest to infusion of CAR T cells varies from a few days to weeks.
- CAR T cells generally reach peak levels in the patient between 1 and 2 weeks after infusion.
- The degree of expansion and persistence of CAR T cells is one indicator of efficacy.
- Clinical trial data have demonstrated high efficacy for r/r B-cell acute lymphoblastic leukemia, and lasting remissions have been reported.
- Clinical trial data have demonstrated encouraging results for r/r chronic lymphocytic leukemia and non-Hodgkin lymphoma, with durable remissions reported.
- CAR T-cell therapy is associated with serious side effects, including cytokine release syndrome, neurotoxicity, macrophage activating syndrome and B-cell aplasia. Patient deaths have been reported.
- Additional CAR targets are under investigation for the treatment of other hematologic malignancies, as well as solid tumors.
- Studies are underway to evaluate the safety and efficacy of CAR T cells, and to streamline the manufacturing process.

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What is a chimeric antigen receptor (CAR)?

Manufacturing a targeted T cell

CAR T-cell therapy essentially leverages the natural ability of the human immune system to detect and destroy cancer cells. In order to effectively eliminate cancer cells, cytotoxic T cells must first recognize them as dangerous. The T cells must then be activated, proliferate, and effectively kill the target cell.

CARs are genetically engineered cell surface receptors designed to equip a patient's own T cells with the ability to recognize and bind to antigens (cell surface proteins) found on tumor cells.

CARs consist of an extracellular domain capable of binding tightly to a tumor antigen, fused to a signaling domain partly derived from the T-cell receptor (TCR) (**Figure 1**).

Figure 1. Chimeric antigen receptors (CARs)

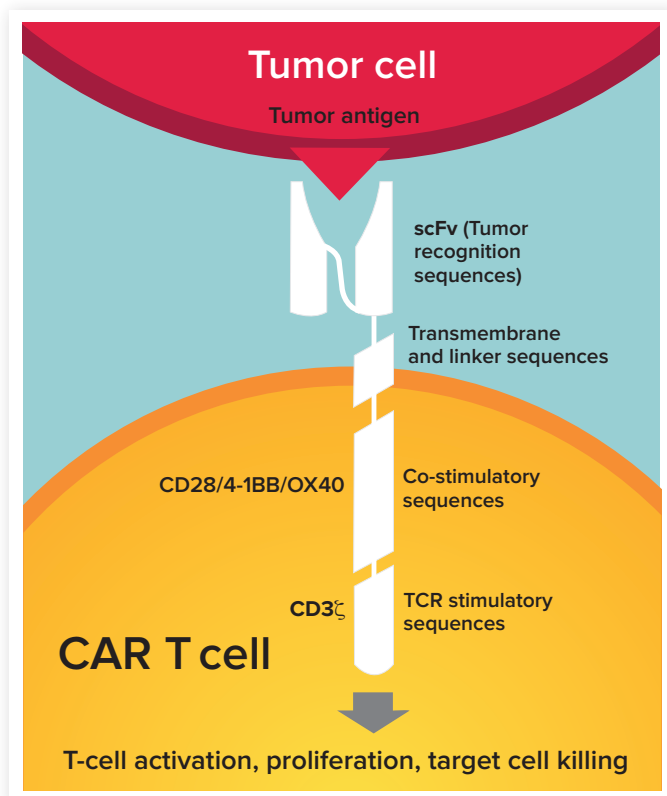


Figure 1. The structure of a CAR

The extracellular, tumor-antigen recognition domain (scFv) consists of a fragment of a monoclonal antibody specific for the desired target. The intracellular signaling domain consists of a portion of the endogenous T-cell receptor (TCR) signaling domain (CD3 ζ) and a co-stimulatory domain (CD28, 4-1BB, and OX40 have all been used as co-stimulatory domains in CARs in clinical trials). Binding of tumor target antigen results in T-cell activation, proliferation, and target cell elimination.

The CAR is activated when the extracellular domain binds to a tumor antigen, resulting in the activation of the T-cell cytotoxic response and tumor cell destruction.

The CAR extracellular domain consists of a fragment of a tumor-specific monoclonal antibody (a single-chain variable fragment, or scFv). The scFv used in the 3 approved products and in the most advanced clinical trials for B-cell malignancies is one directed against the cell surface protein CD19, which is expressed on the surface of the vast majority of B-cell malignancies, in addition to normal B cells. Other potential CAR tumor target antigens are under active investigation.

The intracellular portion of the CAR consists of the signaling portion of the receptor, which when activated by tumor antigen binding to the scFv causes T-cell activation, proliferation and cytokine secretion to eliminate the tumor cell. Full activation of endogenous T cells requires 2 signals, and CARs are designed to replicate both. For CAR T cells, the first signal is provided by the intracellular signaling portion of the T-cell receptor (TCR) (the CD3 zeta [ζ] subunit, **Figure 1**). The second signal is provided by a “co-stimulatory” domain consisting of CD28, 4-1BB, or OX40. The external antibody portion of the CAR is anchored to the membrane by linker and transmembrane sequences.

The chimeric CAR molecule thus combines the specificity of a monoclonal antibody with the cytotoxic and memory capabilities of endogenous T cells.

Autologous CAR T-cell therapy involves genetically transferring the CAR gene directly into a patient's own T cells, which have been collected by leukapheresis. The CAR equips the T cells to recognize and destroy cancer cells when infused back into the patient.

CARs differ in design, the vector used for gene transfer, and manufacturing processes. CAR designs may differ in the scFv region, intracellular co-stimulatory domains, and linker and transmembrane sequences (**See Figure 1**).

How does CAR T-cell therapy work?

CAR T-cell therapies require a high degree of coordination between the primary oncology team and the manufacturing facility in which the CAR T cells are generated. The primary oncology team begins by determining a patient's eligibility for CAR T-cell therapy and provides continuing care throughout the entire process, from prescreening to long-term follow-up. While specific protocols vary for each product and clinical trial, CAR T-cell therapy generally involves the following steps:

1. Patients are evaluated to determine if CAR T-cell therapy is safe and appropriate. The patient's cells are then collected by leukapheresis.

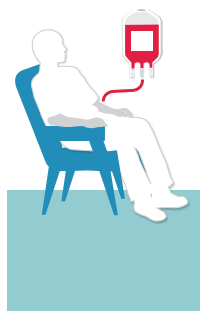


In general, patients eligible for CAR T-cell therapy must:

- Have tumors that are positive for the CAR target (CD19, for example).
- Have an adequate number of T cells for collection. The threshold for a patient's required absolute lymphocyte count varies by protocol.
- Not have an active, uncontrolled infection.
- Have adequate performance status and organ function.
- Not have certain relevant comorbidities, such as certain cardiovascular, neurologic, or immune disorders.

It is important to note that prescreening tests and precise criteria for eligibility vary by treatment regimen or protocol, malignancy and CAR T-cell product.

2. T cells are harvested from the patient by leukapheresis.

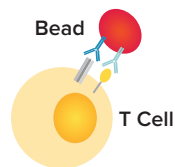


The patient's treatment regimen is frequently altered to increase the likelihood that a sufficient number of functional T cells can be collected. This may include the avoidance of:

- Corticosteroids within a certain time frame prior to leukapheresis.
- Salvage chemotherapy within a certain time frame prior to leukapheresis.

Depending on the product or clinical trial, the collected cells may be frozen and shipped to a Good Manufacturing Practice (GMP) facility for further processing. CAR T-cell manufacturing facilities are highly specialized, requiring complex infrastructure and highly skilled, knowledgeable staff. There, lymphocytes are enriched, and cell subsets (such as CD4+ and CD8+ T cells) may be selected.

3. T cells are activated.

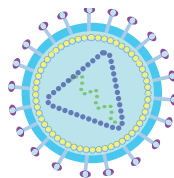


The isolated T cells are placed in culture and are activated, typically by exposing them to antibody coated beads.

The capacity of T cells to grow *in vitro* varies from patient to patient.

A significant number of patients have been excluded from selected clinical trials due to inadequate *in vitro* T cell expansion capacity. The development of "off-the-shelf" (allogeneic) CAR T cells, described below, is an area of active investigation as a means to broaden CAR T-cell therapy.

4. The CAR gene is introduced into activated T cells *in vitro*.



Means of introducing the CAR gene into T cells include the use of several viral vectors, which results in permanent genome modification and persistent CAR expression. These vectors have

been shown to have low oncogenic potential and limited immunogenicity. Other expression systems, including plasmid-based and transient expression systems, are currently in development.

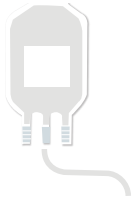
5. The CAR T cells are expanded *in vitro*.



In order to generate sufficient numbers of CAR T cells for therapy, the cells are expanded using a variety of culture systems.

Following expansion, the cells are washed and concentrated, and samples are removed for quality testing. Finally, the CAR T cells may be frozen for shipment to the infusion site.

6. Meanwhile, the patient undergoes “preconditioning” chemotherapy.

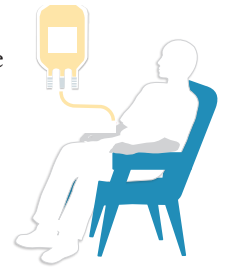


In the days prior to infusion of CAR T cells, the patient undergoes chemotherapy to deplete endogenous lymphocytes, which allows for the engraftment and expansion of CAR T cells. Lymphodepletion “makes room” for the CAR T cells and reduces immunosuppressive cells that may threaten

CAR T-cell expansion. Lymphodepletion also releases endogenous intracellular inflammatory cytokines, which promote CAR T-cell activity once the cells are infused. Preconditioning regimens vary by protocol and by individual patient.

7. The CAR T cells are infused back into the patient.

The cells, which are typically delivered to the infusion site and kept in a frozen state until just before the infusion, are thawed and infused into the patient. In some studies, cells are given by fresh infusion. Depending on the product or clinical trial, cells may be infused in the inpatient setting, or in the outpatient setting with careful monitoring.



The dose of CAR T cells varies by protocol; finding the optimal cell doses, number of doses, and infusion timing that will provide maximal efficacy with minimal toxicity are areas of active investigation.

CAR T cells generally reach peak levels between 1 and 2 weeks after infusion. The degree of expansion and persistence of CAR T cells may be indicators of CAR T-cell efficacy. The capacity for CAR T cells to develop into memory cells has been demonstrated – instances of sustained persistence of CD19-directed CAR T cells out several years have been reported.

Figure 2. CAR T cell manufacturing process

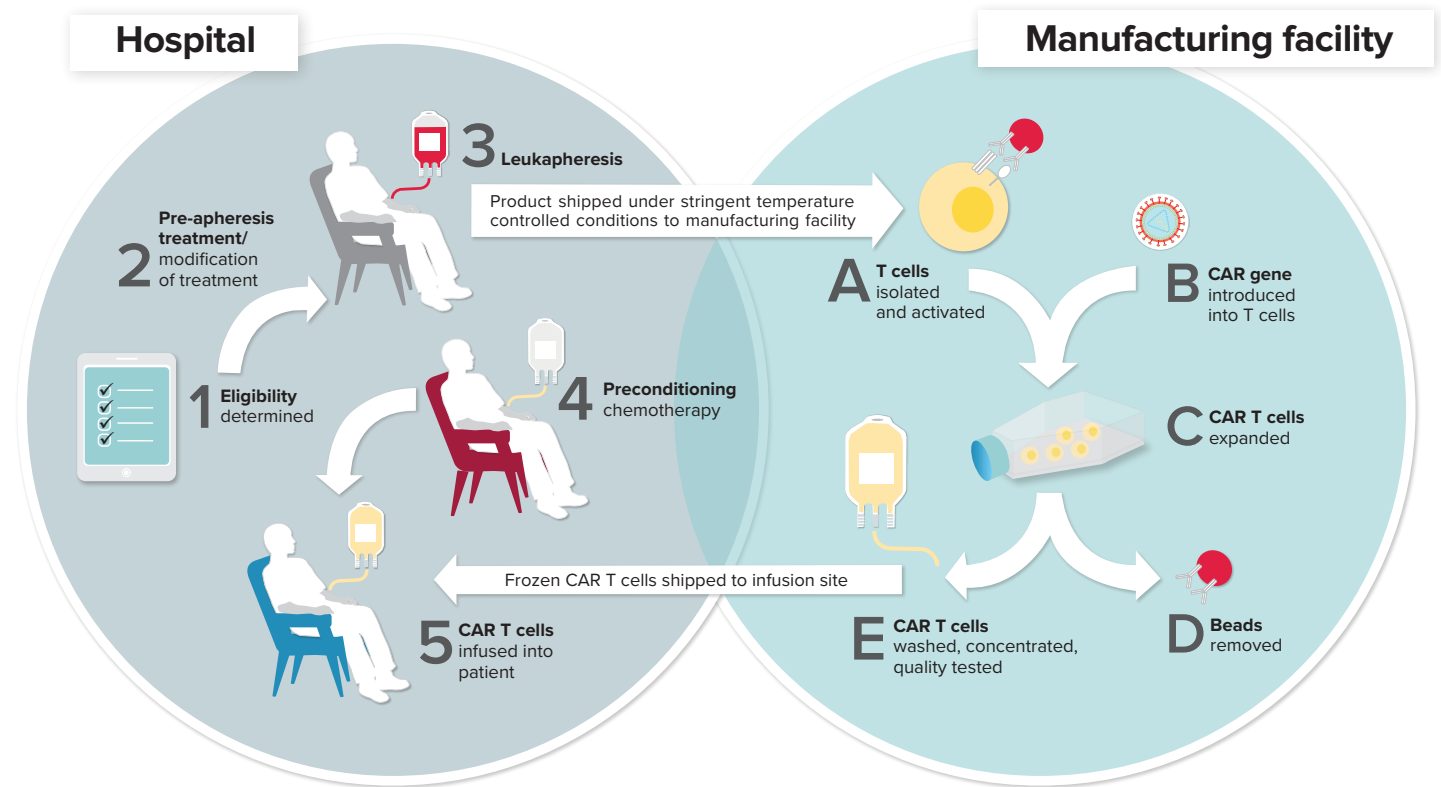


Figure 2. The time from endogenous T-cell collection to CAR T-cell infusion varies, but typically takes several weeks. The entire process, from prescreening to CAR T-cell infusion, is summarized.

Clinical trial results

Efficacy

The most advanced clinical trials, including those completed for approved therapies, have evaluated CD19-directed CAR T-cell therapy for the treatment of relapsed and refractory B-cell acute lymphoblastic leukemia (r/r B-ALL). While various studies differed in patient selection criteria, CAR design, method of gene transfer, cell culture techniques, preconditioning regimens, and the timing and dose of cell infusions, high efficacy has been observed at multiple centers. While clinical trial data are continually being updated, complete response (CR) rates have ranged from 70% to 90%, and lasting remissions have been reported. In the phase 2 pivotal trial for tisagenlecleucel, the overall remission rate (ORR, defined as CR/CRi within 3 months) for patients with r/r B-ALL was 82% (n = 50). All infused patients with a best overall response of CR/CRi were minimal residual disease (MRD) negative; 95% of these patients were negative by day 28.

Relapse occurs, and may in some cases be related to tumor cells losing expression of CD19 (CD19 “escape variants”) or limited persistence of CAR T cells. Relapse data are continually being updated as patients proceed further out from treatment.

Encouraging clinical responses have also been reported in trials of CD19-directed CAR T cells for the treatment of r/r chronic lymphocytic leukemia (r/r CLL) and r/r non-Hodgkin lymphoma (r/r B-NHL). While encouraging, response rates for CAR T-cell therapy for the treatment of r/r CLL and r/r B-NHL have not approached those seen in B-ALL.

In the phase 2 trial for tisagenlecleucel in adult r/r diffuse large B-cell lymphoma (DLBCL), the overall response rate was 52% and the CR rate was 40%.

In the phase 1/2 pivotal trial for axicabtagene ciloleucel in patients with refractory large B-cell lymphoma, the overall response rate was 83% and the CR rate was 58%. Clinical trials are underway in FL, MCL and MZL.

In the phase 2 trial for brexucabtagene autoleucel in patients with r/r MCL, the complete remission rate was 62% and the objective response rate was 87%.*

Clinical trials that target the B-cell maturation antigen (BCMA) are underway for treatment of multiple myeloma.

While many patients with B-ALL that have undergone successful CAR T-cell therapy proceed to allogeneic hematopoietic stem cell transplant (HSCT), other patients have not. Precisely how CAR T-cell therapy will fit into current treatment paradigms – and whether it will best serve as a replacement for transplant or a bridge to transplant – are still open questions.

Relapses may not respond to a second infusion of the same CAR T cells. This may be due to multiple factors:

1. The relapse may be due to escape variants, in which the malignancy no longer expresses the target antigen.
2. The CARs may be immunogenic, such that the patient’s immune system eliminates a second infusion of CAR T cells due to an immune response.

Approaches to treating relapse due to escape variants, including using CAR T cells directed against a second target, are under investigation.

CD19 has proven to be an effective CAR target for many B-cell malignancies and is the basis for the 3 approved therapies. Other CARs in clinical trials target additional markers found on a wide variety of hematologic malignancies. “Ideal” target antigens for CAR T-cell therapy would be restricted to tumor cells. However, most CAR T-cell targets are also expressed on normal cells. The tissue distribution of the marker must be taken into consideration in order to avoid the destruction of non-malignant or essential cells.

Identification of additional tumor markers that can be leveraged for CAR T-cell therapy across a wide range of hematologic malignancies is an area of active investigation.

Safety

While CAR T-cell therapy has shown tremendous promise, data from clinical trials and the use of commercial products reveal a similar pattern of serious toxicities. Consideration of CAR T-cell therapy should take into account the potential for circulating CAR T cells to persist for years. The American Society for Transplantation and Cellular Therapy (ASTCT) has published consensus guidelines for grading the severity of the 2 toxicities most commonly seen in patients who have received CAR T-cell therapy: cytokine release syndrome (CRS) and neurotoxicity. Toxicity prevention and management are primary focuses of current investigation.

*Brexucabtagene autoleucel was granted accelerated approval by the FDA for r/r MCL. Continued approval may depend on verification of response rates and description of clinical benefit in a confirmatory trial.

Cytokine release syndrome (CRS)

CRS is a systemic inflammatory response due to high circulating levels of inflammatory cytokines, resulting from CAR T-cell expansion and activation in response to tumor antigen binding. Some degree of CRS has been observed in most CD19-directed CAR T-cell clinical trials, ranging from mild flu-like symptoms (malaise, fatigue, myalgia, nausea, anorexia) to high fever, tachycardia, hypotension, hypoxia and organ failure requiring vasopressors, ventilatory support and supportive care in the ICU.

CRS typically occurs within the first 1 to 3 weeks after cell infusion. CRS severity appears to correlate with disease burden in B-ALL. CRS grading systems and treatment algorithms have been established as part of each treatment protocol and may be center-specific.

Severe CRS can be mitigated by the use of anti-IL-6 receptor monoclonal antibody (eg, tocilizumab) and corticosteroids; however, higher dose corticosteroids have the disadvantage of potentially dampening the anti-tumor response. Tocilizumab is frequently used as a front-line treatment for severe CRS, though assessment of its effect on CAR T-cell proliferation and activity is ongoing. The reported incidence of CRS of any severity following CD19-targeted CAR T-cell therapy varies among clinical trials. In the majority of cases, CRS is reversible, and depending on management strategies, typically resolves in patients by 2 to 3 weeks. However, patient deaths have occurred as a result of severe CRS following CAR T-cell therapy.

All 3 approved products are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), and all have specific instructions in their prescribing information for managing CRS and neurotoxicity.

Neurotoxicity

Neurotoxicity has often been observed in clinical trials with CD19-directed CAR T-cell therapy. The incidence of neurotoxicity (of any severity) reported in different clinical trials has varied. Symptoms include confusion, delirium, dysphasia, global encephalopathy and seizures. Symptoms of neurotoxicity may not occur at the same time as CRS and may not be controlled by IL-6 receptor blocking with tocilizumab. Effective management strategies are under active investigation. Treatment approaches include corticosteroids and supportive care, which may include anti-epileptic medication.

Patients experiencing neurotoxicity may require ICU support, depending on the severity of symptoms. Patients with mild symptoms can sometimes be observed without receiving steroids. A neurologist is often consulted. The mechanism of neurotoxicity is unknown, though CAR T cells have been found in the spinal fluid of affected patients. While reversible in the majority of cases, cerebral edema associated with neurotoxicity is a rare but potentially fatal complication of CAR T-cell therapy, and deaths have occurred as a result.

Macrophage activation syndrome (MAS)/ hemophagocytic lymphohistiocytosis (HLH)

MAS typically occurs concurrently with CRS, with many clinical manifestations overlapping. Laboratory findings associated with the activation of macrophages include high levels of ferritin, C-reactive protein (CRP) and d-dimer. Transaminitis and elevated triglycerides have been observed, with hypofibrinogenemia and bleeding occurring in a small number of patients. IL-6 receptor blocking therapy with tocilizumab and corticosteroids has been effective in some cases of MAS and CRS. In some cases of HLH, etoposide chemotherapy can be used.

B-cell aplasia (“on-target, off-tumor” toxicity)

Normal B cells and B-cell precursors express CD19, and B-cell aplasia that can last for months or years is an expected consequence of successful CD19-directed CAR T-cell therapy. Patients may receive immunoglobulin replacement therapy and appropriate antimicrobial prophylaxis.

A summary of the toxicities associated with CD19-directed CAR T-cell therapy, in addition to timing and management strategies, is shown in **Table 1**.

Table 1. Toxicities associated with CD19-directed CAR T-cell therapy*

	Signs and Symptoms	Timing	Management
Cytokine release syndrome (CRS)	Fever, myalgia, hypotension, hypoxia, potential organ failure	Usually within 1-3 weeks postinfusion	<ul style="list-style-type: none"> • Tocilizumab • Corticosteroids • Severe CRS may require vasopressors, ventilatory support and supportive care in the ICU
Neurotoxicity	Confusion, delirium, hallucinations, encephalopathy, aphasia, facial paresis, mutism, myoclonus, tremors, somnolence, seizures	May not be concurrent with CRS	<ul style="list-style-type: none"> • Corticosteroids • Supportive care, which may include anti-epileptic medication
Macrophage activation syndrome (MAS)	High levels of ferritin, CRP, d-dimer; hypofibrinogenemia associated with bleeding, transaminitis and elevated triglycerides	Concurrently or shortly after CRS	<ul style="list-style-type: none"> • Tocilizumab • Corticosteroids • Etoposide (in some cases of hemophagocytic lymphohistiocytosis [HLH])
B-cell aplasia	Hypogammaglobulinemia	Within first few weeks postinfusion, may last indefinitely	<ul style="list-style-type: none"> • Immunoglobulin replacement therapy • Prophylactic antibiotics in some cases

CRP = C-reactive protein

*Specific instructions for managing toxicities associated with tisagenlecleucel (Kymriah®), axicabtagene ciloleucel (Yescarta®), and brexucabtagene autoleucel (Tecartus™) are provided in the prescribing information.

The future

Strategies to maximize outcomes of CAR T-cell therapies, minimize toxicities, broaden targets beyond CD19, and target solid tumors are all areas of active investigation. In addition, standards establishing how CAR T-cell therapy might best fit within current treatment paradigms have not yet been determined.

Improving CAR T-cell safety

Efforts to manage the risk of serious toxicity include:

1. Developing methods to predict individual patient risk of CRS and neurotoxicity so that the dose and timing of CAR T-cell infusion can be adjusted accordingly (“risk-adapted dosing”).
2. Modulation of CAR T-cell activity and persistence, including:
 - **Development of CARs** that are activated only in the presence of small molecule drugs that can be administered according to patient tolerability (known as “switchable” or “multi-chain” CARs).
 - **“Suicide” systems**, allowing for the destruction of CAR T cells should life-threatening toxicity occur. Numerous methods are in development, including co-expressing pro-apoptotic genes under the control of inducible promoters along with the CAR gene.
 - **Transient expression systems** that provide CAR expression only for approximately 7 days. Repeated CAR T-cell infusions would theoretically be required for effective disease control.
3. Improving the specificity of CARs. Efforts have included the development of:
 - **“Affinity-tuned” CARs**, designed with a lower affinity for the target antigen, theoretically narrowing CAR targeting only to tumor cells that greatly overexpress the antigen.
 - **“Tandem” CARs**, in which the 2 CAR cytoplasmic signaling domains are separated onto 2 different CAR molecules having different tumor target specificities. CAR T-cell activation results only in the presence of both target antigens, increasing specificity.

Improving CAR T-cell efficacy

Numerous efforts to improve the efficacy and persistence of CAR T cells are underway and include:

1. Combining CAR T cells with other therapies, including PD-1 blocking antibodies or kinase inhibitors.
2. Development of “armored CARs” that co-express pro-inflammatory cytokines such as IL-12 or IL-15 to allow for increased CAR T-cell proliferation and persistence in the face of tumor-mediated immunosuppression.
3. Co-expression of 2 CARs that target different antigens (CD19 and CD22, for example) with the goal of reducing remissions due to escape variants.

Improving and streamlining the manufacturing process

Efforts to streamline and standardize the manufacture of CAR T cells in a cost-effective and time-efficient manner are underway. These include the development of “universal” or “off-the-shelf” CARs, which lack endogenous T-cell markers, allowing for allogeneic CAR T-cell therapy. This would streamline production while broadening CAR T-cell therapy to those patients who lack sufficient numbers of endogenous T cells for processing.

One “off the shelf” approach is the use of CAR-armed natural killer (NK) cells, which can target tumors without antigen presentation or HLA matching. Anti-CD19 CAR-NK cells have been used with some success in early clinical trials targeting lymphoid tumors.

While CAR T-cell therapy holds great promise, emerging data from clinical trials and post-marketing surveillance of approved therapies will continue to inform its appropriate place in the clinical management of hematologic malignancies.

Frequently asked questions

1. Which patients are considered good candidates for CAR T-cell therapy?

Patients receiving Yescarta®, Kymriah® or Tecartus™ should be deemed by their physician to have adequate organ function and performance status to tolerate the therapy.

Currently, patients enrolled in CAR T-cell clinical trials are those with advanced relapsed or refractory malignancy. The suitability of CAR T-cell therapy as a first line treatment in hematologic malignancies has not been studied. While protocols vary for each trial, in general, patients eligible for CAR T-cell therapy must:

- Have tumors that are positive for the CAR target (CD19, for example)
- Have an adequate number of T cells for collection. The threshold for a patient's required absolute lymphocyte count varies among clinical trials.
- Not have an active, uncontrolled infection, including hepatitis B, hepatitis C, or HIV.
- Have adequate performance status and organ function.
- Not have certain relevant comorbidities, such as certain cardiovascular, neurologic, or immune disorders. These may vary among clinical trials.

2. Where does the infusion of CAR T cells take place?

Depending on the protocol, cells may be infused in the inpatient setting, or with careful monitoring in the outpatient setting.

3. Does successful CAR T-cell therapy eliminate the need for transplant?

The standard of care for patients who achieve complete remission with conventional treatment for B-ALL is to proceed with allogeneic HSCT; however, whether this is warranted in all cases after successful CAR T-cell therapy is an open question – proceeding to transplant is not standard of care for NHL post-CAR T-cell therapy.

4. How do we help connect patients to the appropriate clinical trials?

Information Specialists at The Leukemia & Lymphoma Society engage patients in conversations about the role of clinical trials in their treatment, help them develop a list of questions to ask their doctor about participating in a clinical trial, provide personalized clinical trial navigation when appropriate, and assist in trying to overcome the obstacles to enrollment. Contact: 800.955.4572.

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Website: www.LLS.org

Email: infocenter@LLS.org

LLS offers free information and services for patients and families touched by blood cancers as well as for healthcare professionals. The resources listed below are available to you and your patients.

Consult with an Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (M-F, 9 a.m. to 9 p.m. ET)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/informationsspecialists

Clinical Trials Support Center. Clinical trials for new treatments are ongoing. Patients and healthcare professionals can learn about clinical trials and how to access them. When appropriate, personalized clinical trial navigation by trained nurses is also available. For more information, please

- Call: (800) 955-4572 to speak with our LLS Information Specialists who can help conduct clinical trial searches
- Visit: www.LLS.org/CTSC

Free Information Booklets. LLS offers free education and support publications that can either be read online or downloaded. Free print versions can be ordered. For more information, please visit: www.LLS.org/booklets.

- **CAR T-Cell Therapy Facts** for patients. www.LLS.org/booklets and select treatment.

LLS Webpage on CAR T-Cell Therapy.

www.LLS.org/CART

Información en Español. (LLS information in Spanish.) For more information, please visit: www.LLS.org/espanol.

Web, Telephone, Podcast and In-person Education programs for:

- Healthcare Professionals: www.LLS.org/CE
- Patients and caregivers: www.LLS.org/programs and www.LLS.org/educationvideos

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and healthcare professionals. It is a place to ask questions, get informed, share your experience, and connect with others. To join visit: www.LLS.org/community

LLS Regions. 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), in-person 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/chapterfind

Additional Resource

The National Cancer Institute (NCI)

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 NCI also provides a clinical trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where healthcare professionals and patients can look for clinical trials.