CAR-T Therapy: Process and Clinical Considerations Summary Guide

CAR-T=chimeric antigen receptor-T cell.

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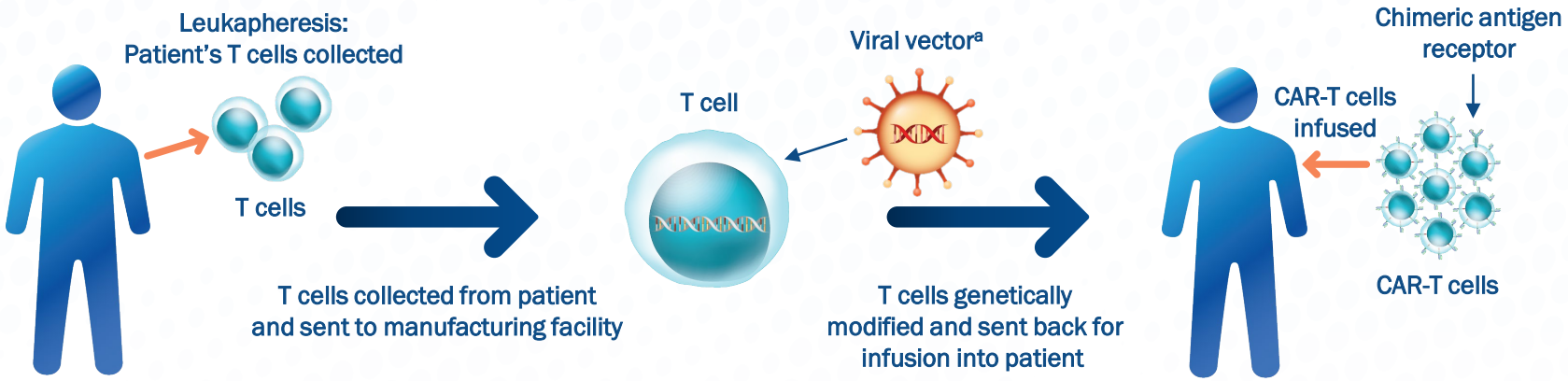
Table of Contents

What is CAR-T?

CAR-T cells are T cells that have been collected from the patient, genetically modified to find a target expressed on the surface of tumor cells, and returned to the patient in a single infusion.

CAR-T Therapy: Immune Response and Tumor Cell Targeting[1,2]



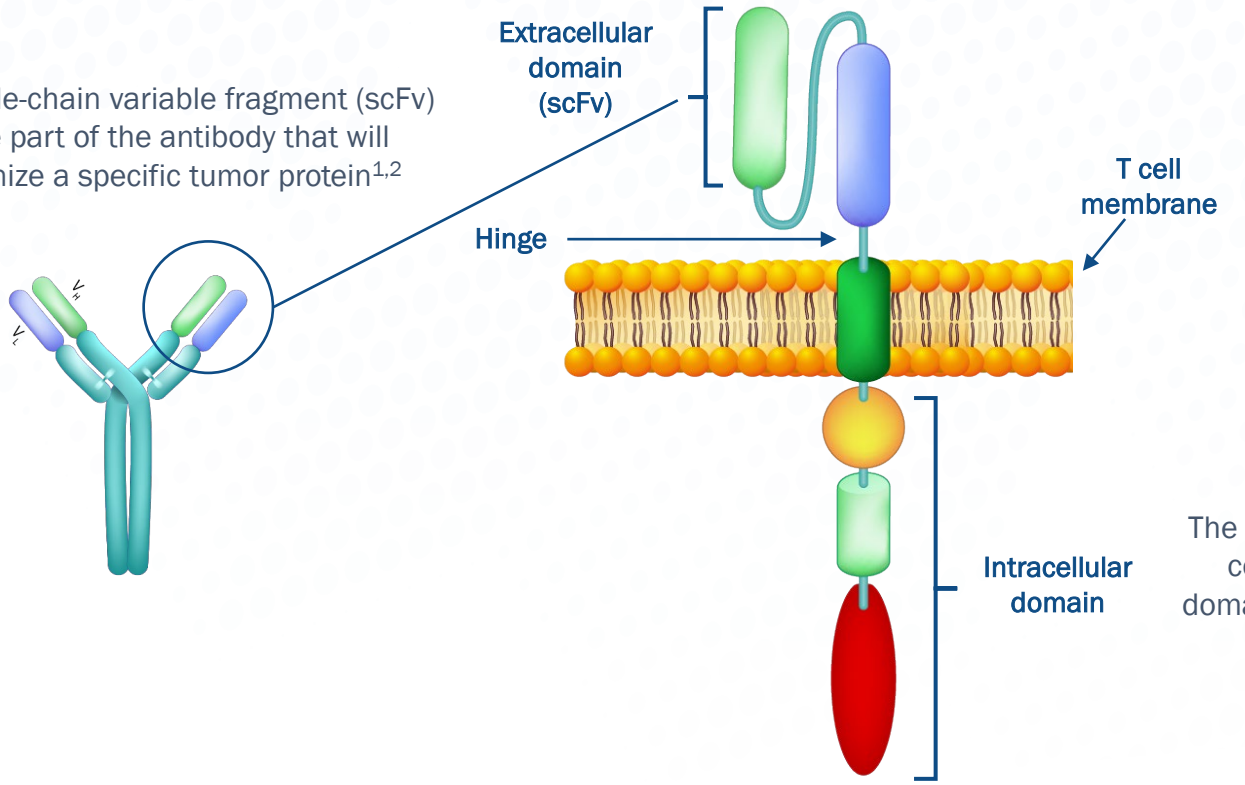
- CAR-T therapy uses the immune system (T cells) to find and attack targets that are expressed on the surface of tumor cells by modifying isolated T cells collected from the patient to express CARs[1,3]
- The specificity of antibodies and the activation of T cells are a combined process in CAR-T therapy[1,3]

CARs=chimeric antigen receptors; CAR-T=chimeric antigen receptor-T cell.
[a]Some manufacturing methods use alternatives to viral vectors for modifying T cells.
References: 1. Majzner RG, Mackall CL. *Nat Med*. 2019;25(9):1341-1355. **2.** Wang X, Rivière I. *Mol Ther Oncolytics*. 2016;3:16015. **3.** June CH, Sadelain M. *N Engl J Med*. 2018;379(1):64-73.

What is CAR-T?

Chimeric[a] Antigen Receptors (CARs): Combining Antibody and T Cell Domains[1-3]

The single-chain variable fragment (scFv) is the part of the antibody that will recognize a specific tumor protein[1,2]



T cells collected from patients are genetically modified to express the CAR[2]

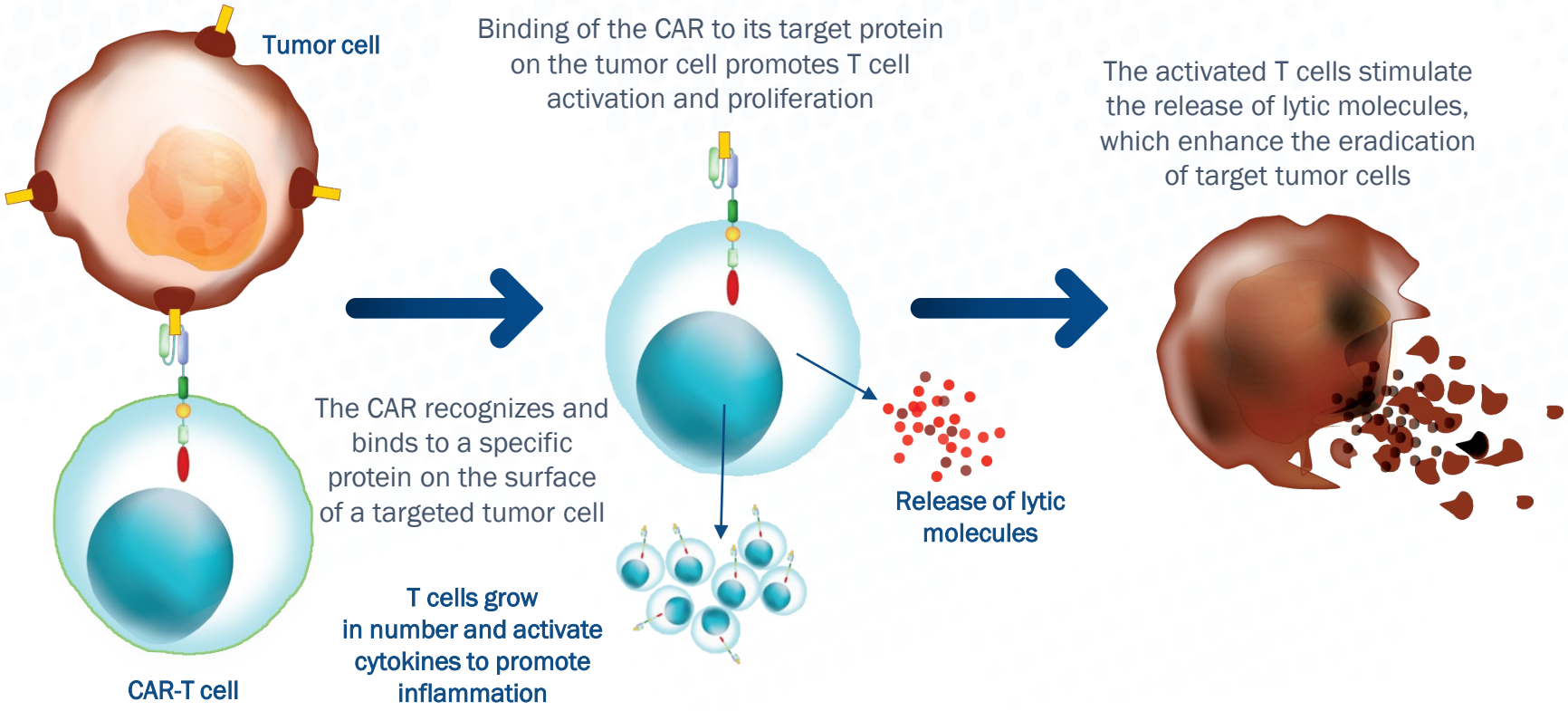
The intracellular domain includes costimulatory and signaling domains that help the T cells grow and fully activate[1]

[a]Composed of parts from different origins.

References: 1. June CH, Sadelain M. *N Engl J Med*. 2018;379(1);64-73. **2.** Majzner RG, Mackall CL. *Nat Med*. 2019;25(9):1341-1355. **3.** Dwivedi A, et al. *Front Immunol.* 2019;9:3180.

What is CAR-T?

CAR-T Cell Activation: Tumor Recognition and Cell Death[1-6]



CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor-T cell.

References: 1. Zhao L, Cao YJ. *Front Immunol*. 2019;10:2250. **2.** Neeson P, et al. *Gene Ther*. 2010;17(9):1105-1116. **3.** Darcy PK, et al. *J Immunol*. 2000;164(7):3705-3712. **4.** June CH, Sadelain M. *N Engl J Med*. 2018;379(1):64-73. **5.** Benmebarek M-R, et al. *Int J Mol Sci*. 2019;20(6):1283. **6.** Fan M, et al. *J Hematol Oncol*. 2017;10(1):151.

The CAR-T Treatment Process

The CAR-T Treatment Process[1,2]

The patient's journey begins at consultation and referral to the Certified Treatment Center.[a] Continued communication and collaboration supports treatment success. Some patients may undergo bridging therapy between apheresis and infusion.[b1]

1. LEUKAPHERESIS
2. MANUFACTURING
3. LYMPHODEPLETION
4. INFUSION OF CAR-T CELLS
5. MONITORING AND LONG-TERM FOLLOW-UP

CAR-T=chimeric antigen receptor-T cell.
[a]Different CAR-T centers may offer different CAR-T products.[1]
[b]Patients may receive additional therapy for disease control before their CAR-T treatment at the discretion of the treating physician at either the Certified Treatment Center or referring oncology center.[1,2]
References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40.

The CAR-T Treatment Process

What Type of Patient Is Generally Eligible for CAR-T Therapy?

- Disease not likely to rapidly progress[1,2]
- Meets trial criteria or use is consistent with product labeling[1,2]
- In general good health with good performance status (ECOG 0-1)[3]
- Has a support system for patient journey[2]

CAR-T=chimeric antigen receptor-T cell; ECOG=Eastern Cooperative Oncology Group.

References: 1. Dave H, et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. **3.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34.

The CAR-T Treatment Process

1. Leukapheresis

T cells are collected during leukapheresis[1]

The quality and quantity of T cells collected through leukapheresis impact the target number of T cells in the manufactured product[1-3]

To ensure the quality of cells collected and reduce the likelihood of complications, certain medications should be stopped prior to leukapheresis[a1]

Timeline for stopping medications prior to leukapheresis[ab1]

[b]These timelines may vary depending on the product/CAR-T therapy.

CAR-T=chimeric antigen receptor-T cell.
[a]Depending on product prescribing information and treating physician recommendation.
References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** Dave H, et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **3.** Perica K, at al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141.

The CAR-T Treatment Process

Bridging[a1,2]

After leukapheresis, when the patient's fresh or cryopreserved T cells are sent to the manufacturing facility for genetic modification, bridging therapy may be appropriate for certain clinical objectives

Disease control

Reducing tumor burden

Maintaining performance status

Bridging therapies may vary among patients, and patients are monitored for any adverse reactions

Continued communication across the multidisciplinary team is important to manage disease state during bridging therapy, and prior to lymphodepletion and CAR-T infusion

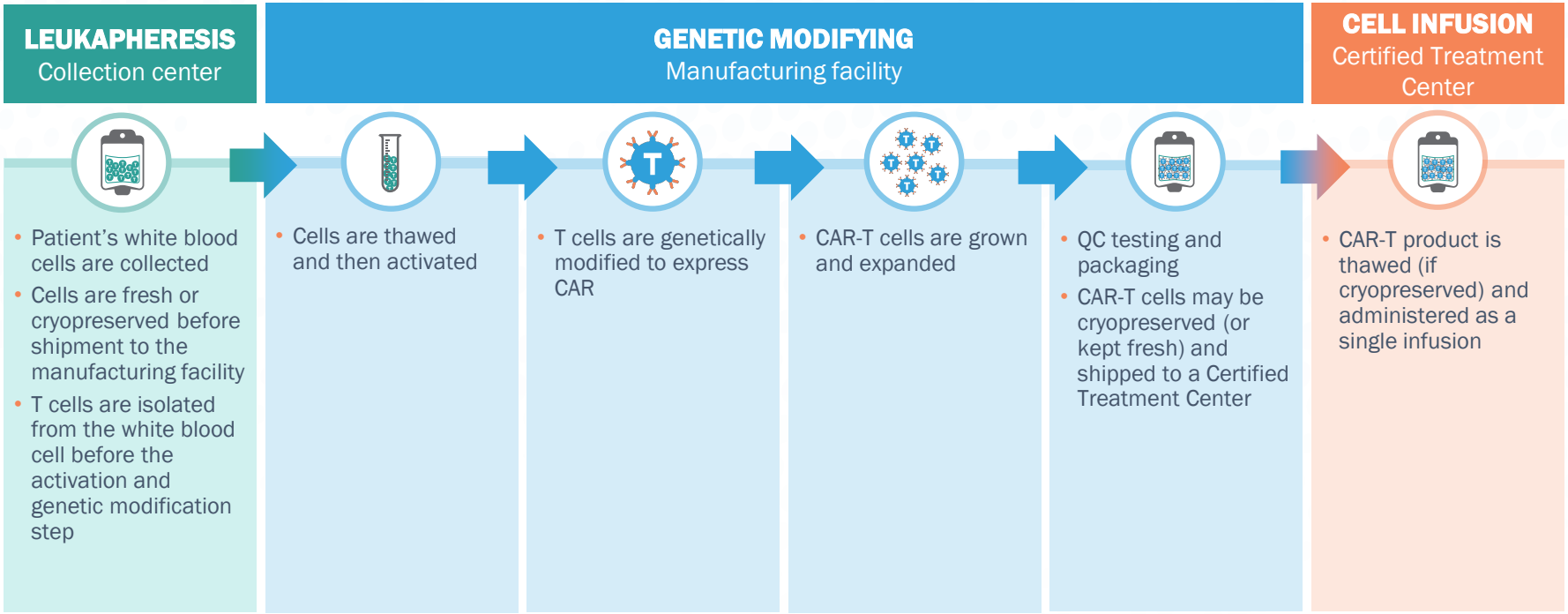
Some patients may undergo bridging therapy between apheresis and infusion[1]

CAR-T=chimeric antigen receptor-T cell.
[a]Patients may receive additional therapy for disease control before their CAR-T treatment at the discretion of the treating physician at either the Certified Treatment Center or referring oncology center.
References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40.

The CAR-T Treatment Process

2. Manufacturing

The manufacturing phase is a multistep process[1-3]



CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor-T cell; QC=quality control.

References: 1. Dave H, et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **2.** Vormittag P, et al. *Curr Opin Biotechnol*. 2018;53:164-181. **3.** Panch SR, et al. *Mol Ther*. 2019;27(7):1275-1285.

The CAR-T Treatment Process

3. Lymphodepletion[1-6]

Lymphodepletion before CAR-T cell therapy:

- Reduces regulatory T cells and myeloid-derived suppressor cells, making the environment more hospitable to CAR-T cells
- Suppresses host immune system and decreases immunogenicity
- Increases persistence of infused CAR-T cells

The patient may be prepared for CAR-T therapy over the course of 3 to 4 days with lymphodepleting chemotherapy, which **typically** includes the following agents:

CYCLOPHOSPHAMIDE[a]	FLUDARABINE[a]
IV daily	IV daily

Dosing and regimen may vary according to the patient's cancer and renal function, as well as the CAR-T therapy prescribed.

CAR-T=chimeric antigen receptor-T cell.
[a]Lymphodepleting agents other than cyclophosphamide or fludarabine may be used.
References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **3.** Cyclophosphamide. Prescribing Information. Baxter Healthcare Corporation; 2013. Accessed March 20, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf **4.** Fludara® (fludarabine phosphate). Prescribing Information. Bayer HealthCare Pharmaceuticals Inc.; 2008. **5.** Neelapu SS. *Blood*. 2019;133(17):1799-1800. **6.** Wagner DL, et al. *Nat Rev Clin Oncol*. 2021;18(6):379-393.

The CAR-T Treatment Process

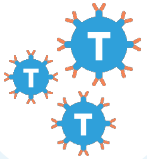
4. Infusion of CAR-T Cells

The process may vary depending on the manufacturer[1,2]

- Medications may be administered preinfusion per protocols[3,4]

CAR-T cells are usually cryopreserved and must be used shortly after thawing[3]

- Fresh cells may be an option from some manufacturers[5]



The CAR-T cell population generally continues to expand after infusion[1]

- Adverse reactions can occur immediately after infusion or can be delayed[2,6]

CAR-T=chimeric antigen receptor-T cell.

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. **3.** Dave H, et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **4.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40. **5.** Panch SR, et al. *Mol Ther*. 2019;27(7):1275-1285. **6.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316.

The CAR-T Treatment Process

5. Monitoring[a]

Patient at or near Certified Treatment Center → Patient under the care of referring oncologist

CAR-T infusion	MONITORING *~4 weeks after infusion*	LONG-TERM MONITORING *~4+ weeks after infusion*
	• Immediate post-infusion care is necessary to identify adverse reactions[1,2] • Reevaluation may occur at 30 days after infusion[1,3]	• Patients should be monitored for disease progression or relapse[3] • Monitor for toxicities that may present over the long term[1,3] • Patient monitoring requires continued collaboration between the Certified Treatment Center and the referring oncologist[3] • Patients will be required to return to the Certified Treatment Center at regular intervals for the first few years[1,3]

[a]Timing may vary among patients.
CAR-T=chimeric antigen receptor-T cell.

References: 1. Dave H, et al. *Curr Hematol Malig Rep.* 2019;14(6):561-569. **2.** Neelapu SS. *Hematol Oncol.* 2019;37(suppl 1):48-52. **3.** Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23(2):27-34.

Common Adverse Reactions in CAR-T

The serious adverse reactions discussed in the following slides are only those most commonly reported for CAR-Ts and are not indicative of any specific treatment.

Cytokine Release Syndrome (CRS)[a]

- Activation and proliferation of T cells initiates a cytokine cascade from lymphocytes and other immune cells[1-3]
- Toxicity is characterized by high levels of serum cytokines and inflammatory markers, and consensus toxicity grading criteria were introduced in 2019 to improve standardization in toxicity assessments[1-3]
- Symptoms can appear within hours to 14 days following infusion[2]

SIGNS AND SYMPTOMS[1,2,4]

Including but not limited to:

- Fever
- Chills
- Hypotension
- Hypoxia
- Elevated liver enzymes
- Rigors

MANAGEMENT CONSIDERATIONS[3]

Including but not limited to:

- Supportive care
- Tocilizumab
- Steroids
- Vasopressors
- Oxygen

CAR-T=chimeric antigen receptor-T cell.

[a]CRS and neurological toxicities are currently the 2 Boxed Warnings for approved CAR-T products. Other adverse events are in the Warnings and Precautions in the full Prescribing Information for each CAR-T product.[5-10]

References: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **2.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55. **3.** Neelapu SS. *Hematol Oncol*. 2019;37(S1):48-52. **4.** Shimabukuro-Vornhagen A, et al. *J Immunother Cancer*. 2018;6(1):56. **5.** Kymriah® (tisagenlecleucel). Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **6.** Tecartus® (brexucabtagene autoleucel). Prescribing Information. Kite Pharma, Inc; 2021. **7.** Yescarta® (axicabtagene ciloleucel). Prescribing Information. Kite Pharma, Inc; 2022. **8.** Breyanzi® (lisocabtagene maraleucel). Prescribing Information. Summit, NJ: Bristol-Myers Squibb Company; 2022. **9.** CARVYKTI® (ciltacabtagene autoleucel) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **10.** Abecma® (idecabtagene vicleucel). Prescribing Information. Bristol-Myers Squibb Company; 2021.

Common Adverse Reactions in CAR-T

Neurologic Toxicity and Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)[a] [b]

- Characterized by a pathologic response following any immunotherapy involving the central nervous system and resulting in the activation or engagement of endogenous or infused T cells and/or other immune cells[1]
- Symptoms may appear simultaneously with CRS, after CRS has resolved, or in patients who did not experience CRS[2-5]

SIGNS AND SYMPTOMS[1,3]

Including but not limited to:

- Aphasia
- Altered levels of consciousness
- Agitation
- Delirium
- Cognitive impairment
- Motor weakness

MANAGEMENT CONSIDERATIONS[1,3]

Including but not limited to:

- Supportive care
- Seizure prophylaxis or medication
- Corticosteroids
- Brain imaging and neurological testing

- FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of CAR-T therapies outweigh the risks of CRS and neurological toxicities

Other Adverse Reactions

Other common adverse reactions associated with CAR-T therapy may vary between products and include, but are not limited to[6-11]:

- Increased risk of infection and weakened immune system due to cytopenia
- Abnormalities in/of electrolytes
- Allergic reactions

CAR-T=chimeric antigen receptor-T cell; CRS=cytokine release syndrome.

[a]ICANS is a neurologic toxicity seen with immune therapy that involves the activation of endogenous or infused immune effector cells such as T cells.[1]

[b]CRS and neurological toxicities are currently the 2 Boxed Warnings for approved CAR-T products. Other adverse events are in the Warnings and Precautions in the full Prescribing Information for each CAR-T product.[5-10]

References: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **2.** Siegler EL, Kenderian SS. *Front Immunol*. 2020;11:1973. **3.** Neelapu SS. *Hematol Oncol*. 2019;37(suppl 1):48-52. **4.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55. **5.** Borrega JG, et al. *Hemasphere*. 2019;3(2):e191. **6.** Kymriah® (tisagenlecleucel). Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2022. **7.** Tecartus® (brexucabtagene autoleucel). Prescribing Information. Kite Pharma, Inc; 2021. **8.** Yescarta® (axicabtagene ciloleucel). Prescribing Information. Kite Pharma, Inc; 2022. **9.** Breyanzi® (lisocabtagene maraleucel). Prescribing Information. Summit, NJ: Bristol-Myers Squibb Company; 2022. **10.** CARVYKTI® (ciltacabtagene autoleucel) [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **11.** Abecma® (idecabtagene vicleucel). Prescribing Information. Bristol-Myers Squibb Company; 2021.

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Common Adverse Reactions in CAR-T

Immune Effector Cell–Associated Encephalopathy (ICE) Score[1]

The ICE score is a consensus tool developed to provide objective grading of encephalopathy symptoms across CAR-T treatments

It is an essential tool in grading ICANS

SCORE	ICANS GRADE
10	No impairment
7-9	Grade 1
3-6	Grade 2
0-2	Grade 3
0	Grade 4[a]

Orientation	Orientation to year, month, city, hospital: **4 points**
Naming	Ability to name 3 objects (eg, point to clock, pen, button): **3 points**
Following commands	Ability to follow simple commands (eg, “Show me 2 fingers”): **1 point**
Writing	Ability to write a standard sentence (eg, “Our national bird is the bald eagle”): **1 point**
Attention	Ability to count backwards from 100 by 10: **1 point**

CAR-T=chimeric antigen receptor-T cell; ICANS=immune effector cell-associated neurotoxicity syndrome.
[a]Due to the patient being unarousable and unable to perform assessment.
Reference: 1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

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