CAR-T Cell Therapy: Process and Clinical Considerations Summary Guide

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CAR-T=chimeric antigen receptor-T cell.

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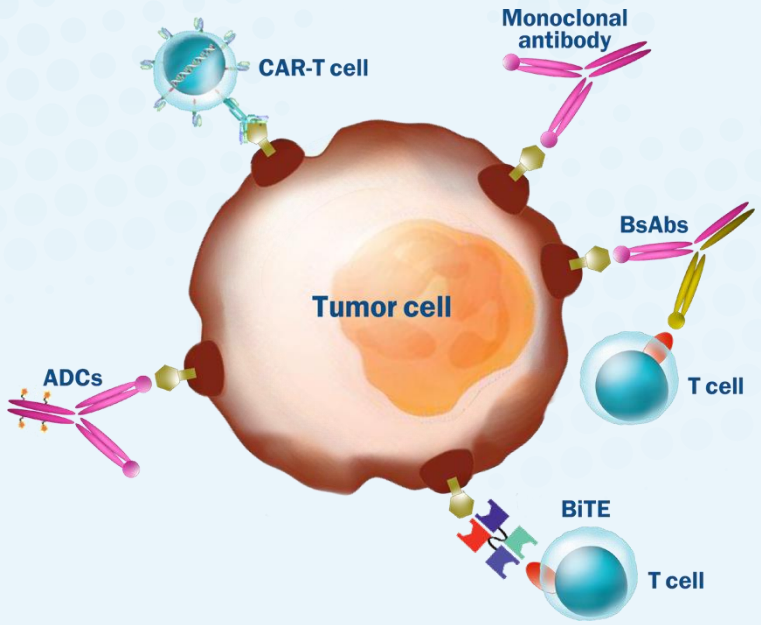
Select Immunotherapy Strategies

Select Immunotherapy Strategies: Understanding Chimeric Antigen Receptor-T Cell (CAR-T) Bispecific Antibodies (BsAbs), and Antibody Drug Conjugate (ADCs)

Over the past few decades, immunotherapies have been developed to help the immune system recognize and attack cancer cells more effectively. Some immunotherapies include, CAR-T cell therapy, BsAbs, and ADCs.[1]

Immunotherapy targeted to antigens on tumor cells[2]



Immunotherapy mechanisms and differences

CAR-T[3]

CAR-T cell therapy involves genetically modifying a patient's own T cells to express a specialized receptor (CAR) that recognizes a specific antigen on cancer cells, enabling the T cells to identify and eliminate them.

BsAbs[4,5]

BsAbs have 2 distinct binding domains. One binds to tumor-associated antigens and the other attaches to a T cell. This allows the T cell to attack the tumor cell directly.

BiTEs are a subset of BsAbs.

ADCs[6,7]

ADCs consist of a mAb linked to a cytotoxic drug. Once the antibody binds to its target antigen on the tumor cell, it delivers the cytotoxic drug that is released and typically, through DNA damage, leads to cell death.

BiTE=bispecific T-cell engager; CAR=chimeric antigen receptor; DNA=deoxyribonucleic acid; mAb=monoclonal antibody.

References: 1. Lancman G et al. Bispecific antibodies in multiple myeloma: present and future. *Blood Cancer Discov.* 2021;2(5):423-433. doi:10.1158/2643-3230.BCD-21-0028 **2.** Rodríguez-Lobato LG et al. Why immunotherapy fails in multiple myeloma. *Hemato.* 2021; 2(1):1-42. https://doi.org/10.3390/hemato2010001 **3.** Shah NN et al. Multi targeted CAR-T cell therapies for B-cell malignancies. *Front Oncol.* 2019;9:146. doi:10.3389/fonc.2019.00146 **4.** Research C for DEA. Bispecific antibodies: an area of research and clinical applications. U.S. Food And Drug Administration. Published February 14, 2024. https://www.fda.gov/drugs/spotlight-cderscience/bispecific-antibodies-area-research-and-clinical-applications **5.** Verkleij CPM et al. T-cell redirecting bispecific antibodies targeting BCMA for the treatment of multiple myeloma. *Oncotarget.* 2020;11(45):4076-4081. doi:10.18632/oncotarget.27792 **6.** D'Agostino M et al. Monoclonal antibodies to treat multiple myeloma: a dream come true. *Int J Mol Sci.* 2020;21(21):8192. doi:10.3390/ijms21218192 **7.** Swan D et al. The evolving status of immunotherapies in multiple myeloma: the future role of bispecific antibodies. *Br J Haematol.* 2022;196(3):488-506. doi:10.1111/bjh.17805

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The CAR-T Patient Care Team

The referring oncology practice and CAR-T Treatment Center share an important partnership.

Referring oncology practice

Educating patients about CAR-T treatment

Educating patients on and coordinating referrals to a CAR-T Treatment Center

Screening patients for potential CAR-T eligibility

Long-term monitoring of patients after CAR-T treatment

CAR-T Treatment Center

Educating patients about CAR-T treatment

Coordinating intake of patients for consultations and treatment

Managing treatment logistics

Determining bridging therapy options with input from referring practice

CAR-T administration

Monitoring patients after CAR-T treatment

Coordinating return of patients to referring oncology team

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CAR-T=chimeric antigen receptor-T cell.

Introduction to CAR-T

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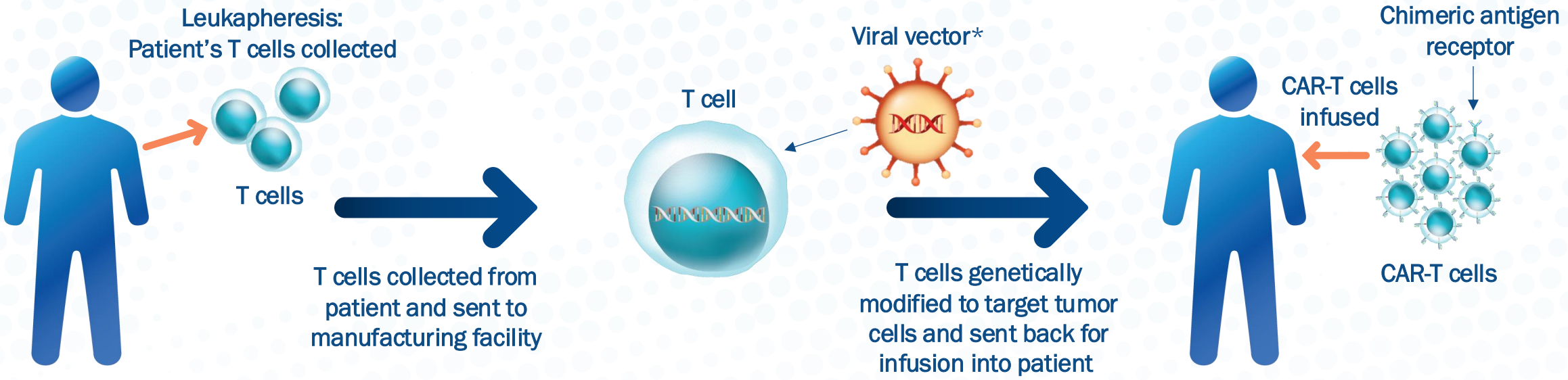
CAR-T Cell Therapy: A Personalized Immunotherapy for Tumor Cell Targeting[1,2]



- CAR-T cell therapy uses the immune system 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 cell therapy[1,3]

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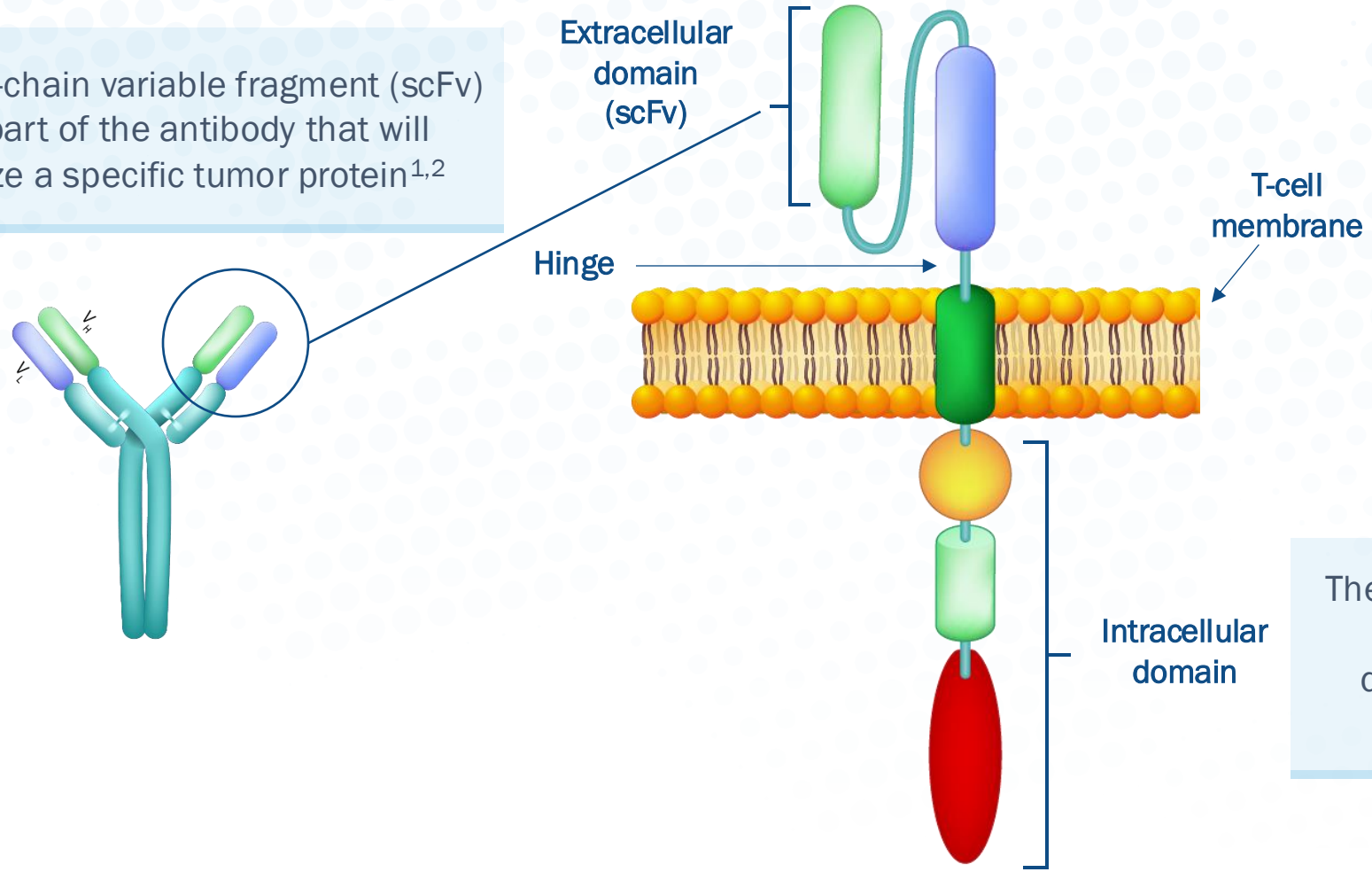
CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor-T cell.
*Some manufacturing methods use alternatives to viral vectors for modifying T cells.

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.

Chimeric* 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]



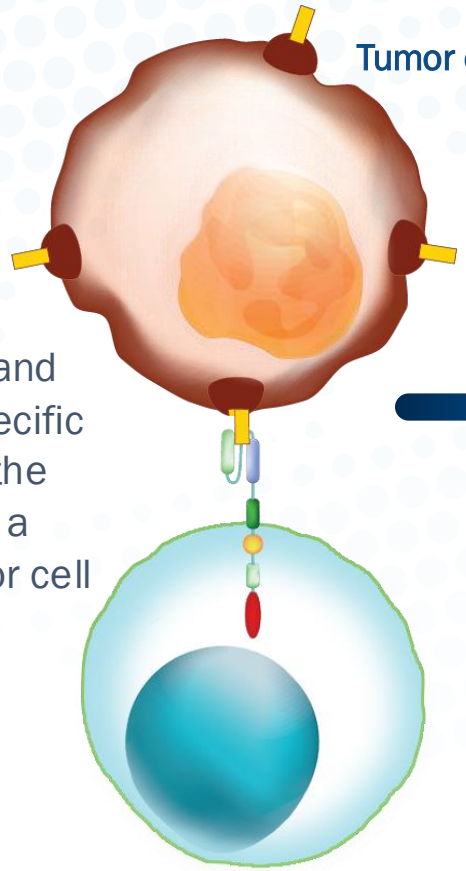
T cells collected from patients are genetically modified to express the CAR[2]

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

*Composed of parts from different origins.

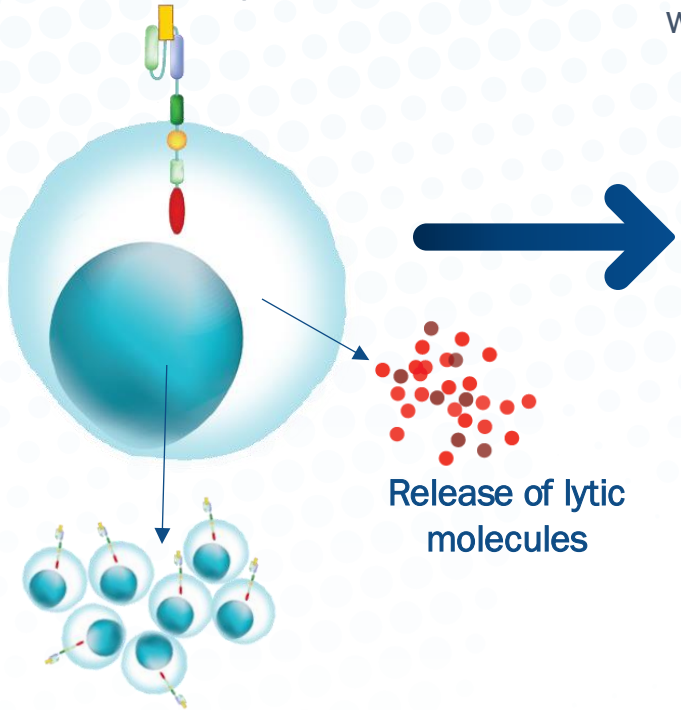
References: 1. June CH, Sadelain M. *N Engl J Med*. 2018;379(1);64-73. **2.** Majzner RG, Mackall CL. *Nat Med*. 2019;25(9):1341-1355. **3.** Dwivedi A et al. *Front Immunol*. 2019;9:3180.

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



The CAR recognizes and binds to a specific protein on the surface of a targeted tumor cell

Binding of the CAR to its target protein on the tumor cell promotes T-cell activation and proliferation



The activated T cells stimulate the release of lytic molecules, which enhance the eradication of targeted tumor cells

CAR-T cells can persist in the body for weeks or months, searching for and eradicating tumor cells

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.

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Summary: What Is CAR-T?

How does CAR-T cell therapy work?[1-7]

- CAR-T cells are T cells that have been collected from a patient, genetically modified to find a target expressed on the surface of tumor cells, and returned to the patient in a single infusion
- CARs include an extracellular domain that recognizes specific targets on malignant cells and an intracellular domain that activates T cells to expand and eliminate targeted tumor cells

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

References: 1. June CH, Sadelain M. *N Engl J Med*. 2018;379(1):64-73. **2.** Zhao L, Cao YJ. *Front Immunol*. 2019;10:2250. **3.** Neeson P et al. *Gene Ther*. 2010;17(9):1105-1116. **4.** Darcy PK et al. *J Immunol*. 2000;164(7):3705-3712. **5.** Majzner RG, Mackall CL. *Nat Med*. 2019;25(9):1341-1355. **6.** Benmebarek M-R et al. *Int J Mol Sci*. 2019;20(6):1283. **7.** Seif M et al. *Front Immunol*. 2019;10:2711.

CAR-T Treatment Process

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CAR-T=chimeric antigen receptor-T cell.

What Type of Patient Is Generally Eligible for CAR-T Cell Therapy?[1-4]

- Has disease that is controllable while they wait for CAR-T cell therapy to be ready
- Meets trial criteria or use is consistent with product labeling
- Is in general good health with good ECOG performance status
- Has a support system for patient journey
- Has been diagnosed with one of the hematologic cancers for which CAR-T is currently a treatment option

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. **4.** CAR T cells: Engineering immune cells to treat cancer. *Cancer.gov*. Published March 10, 2022. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

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Logistical Considerations[1-3]

What is the distance to the closest CAR-T Treatment Center?

Can the patient and their care partner travel or remain close to the CAR-T Treatment Center for an extended period of time (~4 weeks)?

Timing may depend on patient and on CAR-T Treatment Center.

Does the patient need any resources to assist them with access to treatment?

Many CAR-T manufacturers have robust patient support programs that address lodging, travel support, and other resources.

Where can the patient receive leukapheresis and bridging therapy if necessary?

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CAR-T=chimeric antigen receptor-T cell.

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[1,2]

The patient's journey begins with the referring HCP identifying if a patient might benefit from CAR-T. Eligible patients are then referred to a CAR-T Treatment Center,* where they are re-evaluated for eligibility. Continued communication between the referring and treating teams supports treatment success.

1 **LEUKAPHERESIS**

2 **BRIDGING THERAPY**

Some patients may undergo bridging therapy between leukapheresis and infusion.†

3 **MANUFACTURING**

4 **LYMPHODEPLETION**

5 **INFUSION OF CAR-T CELLS**

6 **MONITORING AND LONG-TERM FOLLOW-UP**

CAR-T=chimeric antigen receptor-T cell; HCP=healthcare provider.

*Different CAR-T centers may offer different CAR-T products.[1]

†Patients may receive additional therapy for disease control before their CAR-T treatment at the discretion of the treating physician at either the CAR-T 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.

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The CAR-T Treatment Process

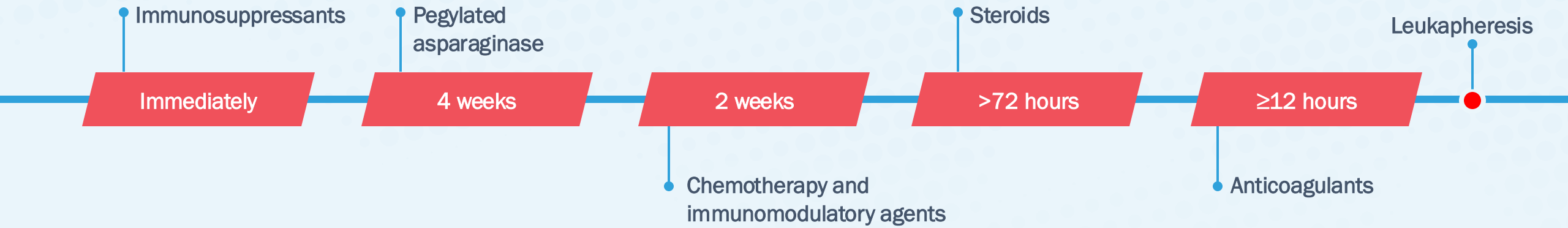
1 Leukapheresis[1-3]

T cells are collected during leukapheresis

The quality and quantity of T cells collected through leukapheresis impact the target number of T cells in the manufactured product

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

Timeline for stopping medications prior to leukapheresis*



These timelines may vary depending on the product/CAR-T cell therapy.

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CAR-T=chimeric antigen receptor-T cell.

*Depending on product Prescribing Information and treating physician recommendation.

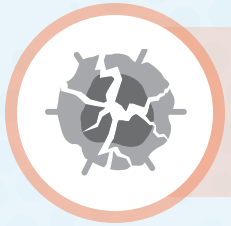
References: 1. Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** Dave H et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **3.** Perica K at al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141.

The CAR-T Treatment Process

2 Bridging[1,2]*

After leukapheresis and concurrent with manufacturing, bridging therapy may be appropriate for some patients.

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 cell infusion

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CAR-T=chimeric antigen receptor-T cell.

*Patients may receive additional therapy for disease control before their CART treatment at the discretion of the treating physician at either the CAR-T 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

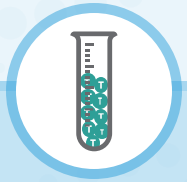
3 Manufacturing

The manufacturing phase is a multistep process that can take between 3 and 6 weeks, but can vary per patient and product.[1-6]

LEUKAPHERESIS
Collection center

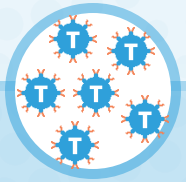
- Patient's white blood cells are collected
- Cells are fresh or cryopreserved before shipment to the manufacturing facility
- T cells are isolated from the white blood cells before the activation and genetic modification step

GENETIC MODIFYING
Manufacturing facility



- Cells are thawed (if frozen) and then activated

- T cells are genetically modified to express the CAR



- CAR-T cells are grown and expanded

- QC testing and packaging
- CAR-T cells may be cryopreserved (or kept fresh) and shipped to a CAR-T Treatment Center

LYMPHODEPLETING CHEMOTHERAPY

CELL INFUSION
CAR-T Treatment Center

- CAR-T product is thawed (if cryopreserved) and administered as a single infusion

Some patients may undergo bridging therapy between leukapheresis and infusion.*

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

*Patients may receive additional therapy for disease control before their CART treatment at the discretion of the treating physician at either the CAR-T Treatment Center or referring oncology center.[5,6]

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. **4.** Professional CCM. CAR T-Cell Therapy. Cleveland Clinic. Published December 19, 2024. https://my.clevelandclinic.org/health/treatments/17726-car-t-cell-therapy **5.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **6.** Beaupierre A et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40.

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The CAR-T Treatment Process

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

CYCLOPHOSPHAMIDE* IV daily

FLUDARABINE* IV daily

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

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

*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. **4.** Fludara®. Prescribing Information. Bayer HealthCare Pharmaceuticals Inc.. **5.** Neelapu SS. *Blood*. 2019;133(17):1799-1800. **6.** Wagner DL et al. *Nat Rev Clin Oncol*. 2021;18(6):379-393.

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The CAR-T Treatment Process

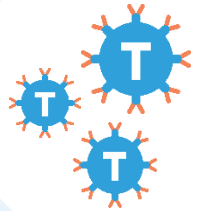
5 Infusion of CAR-T Cells[1-6]

The process may vary depending on the manufacturer

- Medications may be administered preinfusion per protocols

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

- Fresh cells may be an option from some manufacturers



The CAR-T cell population will expand after infusion

- Adverse reactions can occur immediately after infusion or can be delayed

Some CAR-T cell therapies are available through a restricted program under the Risk Evaluation and Mitigation Strategy (REMS).[1]

Patients can receive their CAR-T cell infusion in the inpatient or outpatient setting, dependent upon the product and the CTC's discretion.

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CAR-T=chimeric antigen receptor-T cell; CTC=CAR-T Treatment Center.

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

6 Monitoring[1-3]*

Patient at or near CAR-T Treatment Center

Patient under the care of referring oncologist

CAR-T cell infusion

MONITORING
~4 weeks after infusion

- Immediate post-infusion care is necessary to identify adverse reactions (primarily CRS and ICANS)
- Reevaluation may occur at 30 days after infusion; patient will transition back to referring oncologist when medically appropriate

LONG-TERM MONITORING
~4+ weeks after infusion

- Patients should be monitored for disease progression or relapse
- Monitor for toxicities that may present over the long-term and manage as medically appropriate
- Patient monitoring requires continued collaboration between the CAR-T Treatment Center and the referring oncologist
- Patients may be required to return to the CAR-T Treatment Center at regular intervals for the first few years

CAR-T=chimeric antigen receptor-T cell; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome.
*Timing may vary among patients.

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.

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The CAR-T Treatment Process

Transition of Care Considerations[1,2]

After approximately 4 weeks of close monitoring following CAR-T cell therapy infusion and any adverse events have returned to Grade 1 or less, the CAR-T Treatment Center will notify the patient's referring physician about their CAR-T cell therapy experience and recovery. **Patient care is then transitioned from the CAR-T Treatment Center to the referring physician.**[1]

TRANSFERRING CARE

The healthcare team at the CAR-T Treatment Center may relay the following to the referring physician upon transition of care[2]:

- A copy of the patient wallet card
- A copy of the CAR-T cell therapy Prescribing Information and Medication Guide
- An accurate medication list
- **Hospital records** (eg, pre–CAR-T cell therapy workup results, notes made during inpatient CAR-T cell therapy, the latest staging information, notes from the last ambulatory visit, discharge summary inclusive of any adverse events experienced after CAR-T cell therapy)
- Information on specific laboratory orders and how often they should be drawn
- Recommendations and guidelines for possible blood product administration, if required
- Outline of approximate dates when patient will follow up with CAR-T Treatment Center

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

References: 1. Beaupierre A et al. *J Adv Pract Oncol*. 2019;10(suppl3):29-40. **2.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34.

The CAR-T Treatment Process (cont'd)

COMMUNICATION[2]

Ongoing close communication with the referring physician is essential for a smooth transition of care.

- The healthcare team at the CAR-T Treatment Center should communicate with the referring physician's team about the toxicities associated with CAR-T cell therapy, steroid use, and long-term effects of treatment (ie, B-cell aplasia and hypogammaglobulinemia)
- A point of contact should be provided to the referring physician (explain when and how to contact the oncologist who treated the patient with CAR-T cell therapy)

PATIENT/CARE PARTNER KNOWLEDGE[2]

The patient needs to understand that they will be followed over time **by their primary oncologist more often and by the CAR-T Treatment Center team less often.**

Hand off procedures for transitioning patients from the treating provider to the referring provider ensure seamless continuity of care and include a clearly defined follow-up plan.

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CAR-T=chimeric antigen receptor-T cell.

References: 1. Beaupierre A et al. *J Adv Pract Oncol*. 2019;10(suppl3):29-40. **2.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34.

CAR-T Safety

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

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CAR-T=chimeric antigen receptor-T cell.

Adverse Reactions: Cytokine Release Syndrome (CRS)[1-4]

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

SIGNS AND SYMPTOMS

Including, but not limited to:

- Fever
- Chills
- Hypotension
- Hypoxia
- Elevated liver enzymes
- Rigors
- May be associated with Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS)
- Multi-system organ dysfunction

MANAGEMENT CONSIDERATIONS

Including, but not limited to:

- Supportive care
- Tocilizumab
- Steroids
- Vasopressors
- Oxygen

CRS, neurologic toxicities, and T-cell malignancies are currently in the Boxed Warnings for approved CAR-T products. Other adverse events are in the Warnings and Precautions for each CAR-T product.[1-4]

CAR-T=chimeric antigen receptor-T cell.

References: 1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **2.** Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: mechanisms, manifestations and management. *Blood Rev*. 2019;34:45-55. **3.** Neelapu SS. Managing the toxicities of CAR T-cell therapy. *Hematol Oncol*. 2019;37(suppl1):48-52. **4.** Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. *J Immunother Cancer*. 2018;6(1):56.

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ASTCT Consensus Grading of Cytokine Release Syndrome (CRS)[1]

CRS PARAMETER*	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fever†‡	Temperature ≥38 °C	Temperature ≥38 °C	Temperature ≥38 °C	Temperature ≥38 °C
		With		
Hypotension†	None	Not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or§		
Hypoxia†	None	Requiring low-flow nasal cannula‖ or blow-by	Requiring high-flow nasal cannula,‖ facemask, non-rebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CAR-T=chimeric antigen receptor-T cell; CPAP=continuous positive airway pressure; CTCAE=Common Terminology Criteria for Adverse Events.

*Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

†Not attributable to any other cause.

‡In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity.

§CRS grade is determined by the more severe event.

‖Low-flow nasal cannula is ≤6 L/min and high-flow nasal cannula is >6 L/min.

Reference: 1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

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Adverse Reactions: Neurotoxicity, Including Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)[1-6]*

- 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
- Symptoms may appear simultaneously with CRS, after CRS has resolved, or in patients who did not experience CRS

SIGNS AND SYMPTOMS

Including but not limited to:

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

MANAGEMENT CONSIDERATIONS

Including but not limited to:

- Supportive care
- Non-sedating seizure prophylaxis
- Corticosteroids
- Brain imaging and neurological testing
- Lumbar puncture

LONG-TERM MONITORING

All patients receiving CAR-T cell therapy should be monitored lifelong for secondary malignancies.

Monitor for their underlying disease and symptoms of the long-term side effects of that disease, plus effects of CAR-T including CRS.

CRS=cytokine release syndrome.

*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]

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.** Dave H et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569.

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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*

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**

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CAR-T=chimeric antigen receptor-T cell; ICANS=immune effector cell-associated neurotoxicity syndrome.
*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.

ASTCT Consensus Grading of Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS) for Adults[1]

NEUROTOXICITY DOMAIN	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ICE Score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; or stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

ASTCT=American Society for Transplantation and Cellular Therapy; CTCAE=Common Terminology Criteria for Adverse Events; EEG=electroencephalogram; ICE=immune effector cell-associated encephalopathy; ICP=intracranial pressure.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause.

*A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable.

†Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

‡Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

§Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Reference: 1. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant*. 2019;25(4):625-638.

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Adverse Reactions Monitoring the First 4 Weeks After Infusion[1,2]

Both the patient and their care partner should be educated on identifying signs and symptoms of potential side effects after CAR-T infusion and how and to whom to report them.

Care partners provide key support for patients, as they are often the first people to notice subtle changes in a patient's status.

For at least 4 weeks after infusion, side effects should be reported to the CAR-T Treatment Center. Early signs and symptoms may include:

- Fever
- Low blood pressure
- Difficulty breathing
- Tremors
- Confusion

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CAR-T=chimeric antigen receptor-T cell.

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(suppl3):29-40.

Adverse Reactions Monitoring Beyond 4 Weeks and Long Term[1-6]

Some side effects may persist or appear 4 weeks or more after CAR-T cell infusion, such as:	
Guillain-Barré Syndrome	Secondary malignancies
Immune mediated myelitis	Parkinsonism
Cranial nerve palsies	Peripheral neuropathy
Cytokine release syndrome	Prolonged and/or recurrent cytopenias
Increased early mortality	Serious infections including febrile neutropenia
Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome	Neurologic toxicity, including immune effector cell–associated neurotoxicity syndrome

Neurologic events may present in the 8 weeks following infusion and beyond. The patient should refrain from driving or engaging in hazardous activities for at least 8 weeks at the doctor's discretion, or if a new symptom appears.

Patients are typically being monitored by their local hematologist/oncologist at this point in the CAR-T journey.

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CAR-T=chimeric antigen receptor-T cell.

References: 1. Abecma®. Prescribing Information. Celgene Corporation. **2.** Yescarta®. Prescribing Information. Kite Pharma, Inc. **3.** CARVYKTI®. Prescribing Information. Janssen Biotech, Inc. **4.** Kymriah®. Prescribing Information. Novartis Pharmaceuticals Corporation. **5.** Breyanzi®. Prescribing Information. Juno Therapeutics, Inc. **6.** Tecartus®. Prescribing Information. Kite Pharma, Inc.

Patient Support System[1]

The patient should have access to a support system to provide assistance as needed through the CAR-T process

A care partner will be a valuable source of encouragement, emotional support, and daily assistance

Coach your patient's care partner on identifying signs and symptoms of side effects when they happen, and how to report them to healthcare professionals on the multidisciplinary team

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CAR-T=chimeric antigen receptor-T cell.

Reference: 1. Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34.

Role of the Care Partner[1]

BEFORE TREATMENT

- Management of medications
- Household and general care (eg, cooking, cleaning, maintenance)
- Additional point of contact for the referring healthcare team

DURING TREATMENT

- Transportation to/from the CAR-T Treatment Center or other appointments
- Management of medications
- Additional point of contact for the treating healthcare team

AFTER TREATMENT

- **Help monitor the patient for signs and symptoms of side effects, especially during the first 28 days**
- Remain with the patient for extended periods of time in their home or outpatient facility
- Management of medications
- Household and general care (eg, cooking, cleaning, maintenance)
- Additional point of contact for transition back to referring healthcare team

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Reference: 1. Beaupierre A et al. *Clin J Oncol Nurs.* 2019;23(2):27-34.

CAR-T Cell Therapy Summary[1-7]

OVERVIEW OF CAR-T CELL THERAPIES

- Uses T cells that have been genetically modified to express a CAR that specifically targets and attacks tumor cells
- Requires coordination between a referring oncologist and a CAR-T Treatment Center

CAR-T TREATMENT PROCESS AND ELIGIBILITY

- Assess the patient and discuss eligibility consistent with product labeling
- Treatment decision is made by the physician at the CAR-T Treatment Center in consultation with the referring oncologist and the patient
- Educate the patient on the need for a care partner and the care partner's role in long-term monitoring

LONG-TERM SUPPORT

- Healthcare teams at both the CAR-T Treatment Center and the referring oncology center will continue to communicate regarding patients' disease status and safety

CAR-T SAFETY

- Serious toxicities can occur after CAR-T treatment. Monitor for symptoms of side effects indicating CRS or ICANS
- Adverse reactions can occur soon after treatment or beyond 4 weeks. Patients should be monitored lifelong for secondary malignancies associated with CAR-T treatment

CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor-T cell; CRS=cytokine release syndrome; ICANS=Immune Effector Cell-Associated Neurotoxicity Syndrome.

References: 1. Jacoby E et al. *Immunol Rev*. 2019;290(1):39-59. **2.** Vormittag P et al. *Curr Opin Biotechnol*. 2018;53:164-181. **3.** Zhao L, Cao YJ. *Front Immunol*. 2019;10:2250. **4.** Beaupierre A et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **5.** Dave H et al. *Curr Hematol Malig Rep*. 2019;14(6):561-569. **6.** Perica K et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. **7.** Beaupierre A et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40.

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