Bristol Myers Squibb®

CAR T Cell Therapy Overview for Non-CAR T Hematology Practitioners

CAR T Academy: CAR T Cell Therapy Overview for Non-CAR T Hematology Practitioners

01: INTRODUCTION TO CAR T CELL THERAPY

02: PATIENT JOURNEY AND CLINICAL CONSIDERATIONS

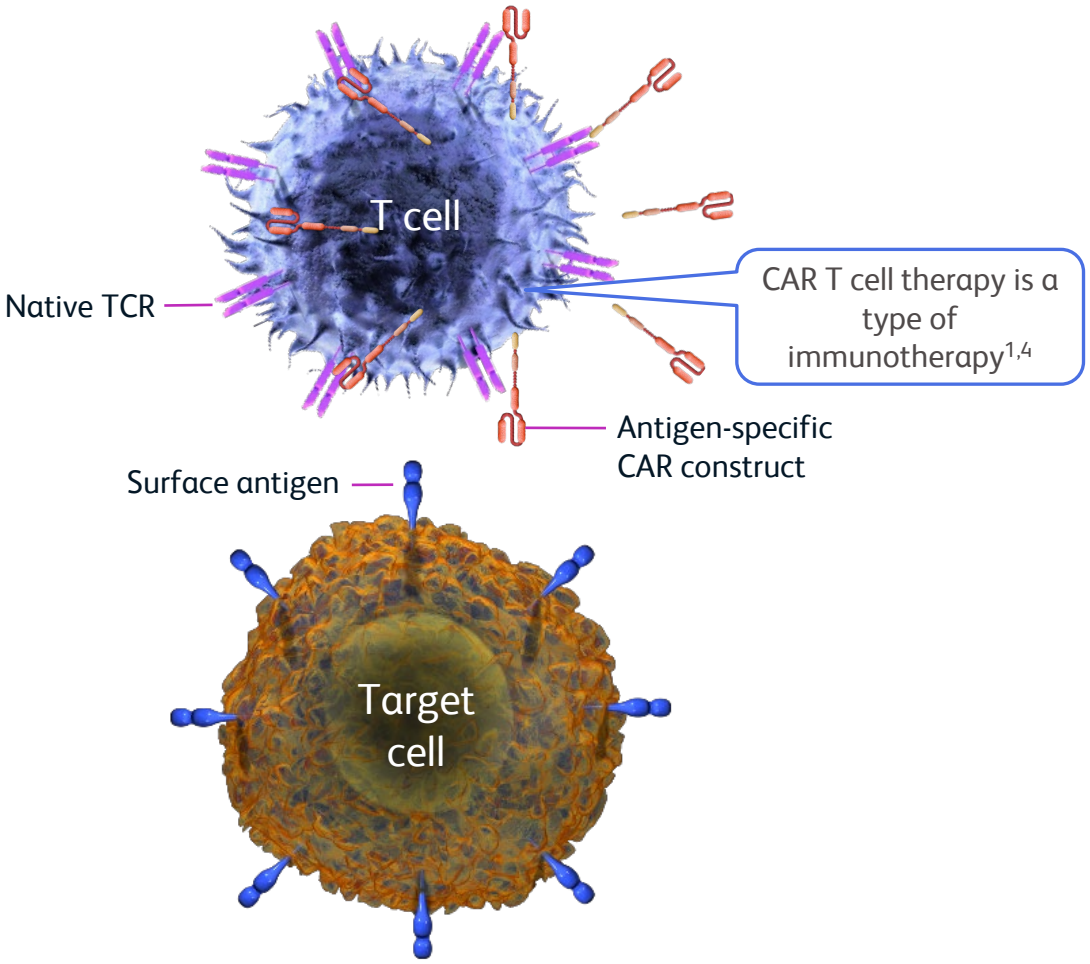
03: CAR T CELL THERAPY SIDE EFFECTS AND LONG-TERM FOLLOW-UP

What is CAR T Cell Therapy?

- **CAR T cell therapy is a type of immunotherapy that leverages the ability of T cells to detect and target specific antigen-expressing cells, including cancer cells[1]**
- Gene transfer technology is used to express CARs on T cells, conferring antigen specificity[2]
  - CAR T cells can be directed to a specific surface antigen found on target cells[2]
  - CAR T cell therapy takes advantage of the cytotoxic potential of T cells by binding target cells in an antigen-dependent manner[2]

CAR T Cell Persistence

- CAR T cells may also expand and persist, providing T cell memory for a period of time[2]
- Persistent CAR T cells consist of both effector (cytotoxic) and central memory T cells[3]

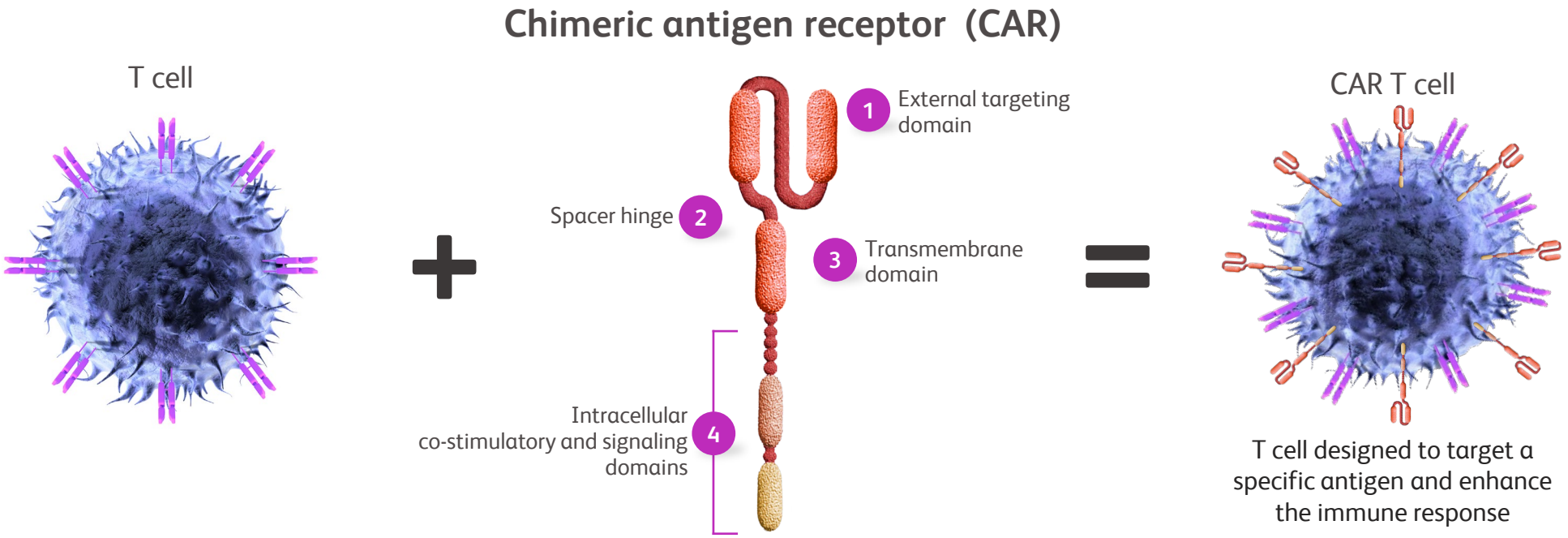


CAR, chimeric antigen receptor; TCR, T cell receptor.

References: 1. Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. 2022. **2.** Oluwole OO, Davila ML. *J Leukoc Biol.* 2016;100:1265-1272. **3**. McLellan AD, Ali Hosseini Rad SM. *Immunol Cell Biol.* 2019;97(7):664-674. **4**. Leukemia & Lymphoma Society. Chimeric Antigen Receptor (CAR) T-cell Therapy. Accessed August 1, 2022. https://www.lls.org/treatment/types-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Components of a CAR T Cell

Autologous CAR T cell therapy helps equip a patient's T cells with the ability to detect and destroy target cells, including malignant cells, by combining the specificity of an antibody with the cytotoxic and memory capabilities of a T cell[1,2]



CARs consist of an extracellular domain, capable of binding tightly to a tumor antigen, which is fused to at least one intracellular costimulatory domain that transduces the key signal to initiate the signaling cascade[1,3]

References: 1. Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. 2022. **2.** Maus MV, Levine BL. *Oncologist*. 2016;21:608–617. **3.** Jayaraman J, et al. *EBioMedicine*. 2020;58:102931.

CAR T Cell Mechanism of Action

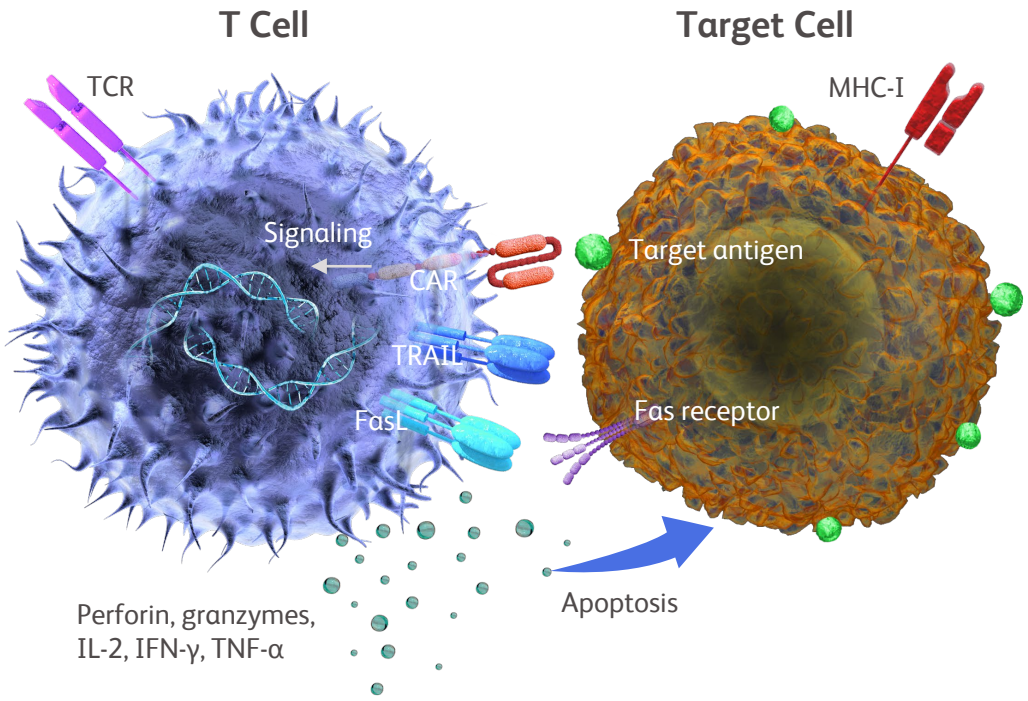
Current Understanding of the Mechanism

1. When a CAR binds to a specific antigen on the target cell, a signaling cascade is induced, leading to activation of the CAR T cell[1]

2. Once activated, the T cell[1]:
   - Induces cytotoxic activities
   - Expresses proapoptotic-molecules (eg, FasL and TRAIL) to induce apoptosis of the target cell
   - Secretes pro-inflammatory cytokines to activate other tumor-infiltrating immune cells

3. For hematologic malignancies, the target cells typically reside in the same locations as the migrating T cells, with none of the physical barriers or immunosuppressive microenvironments of solid tumors[2]

Target Cell Killing by CAR T Cells[1,3,4]



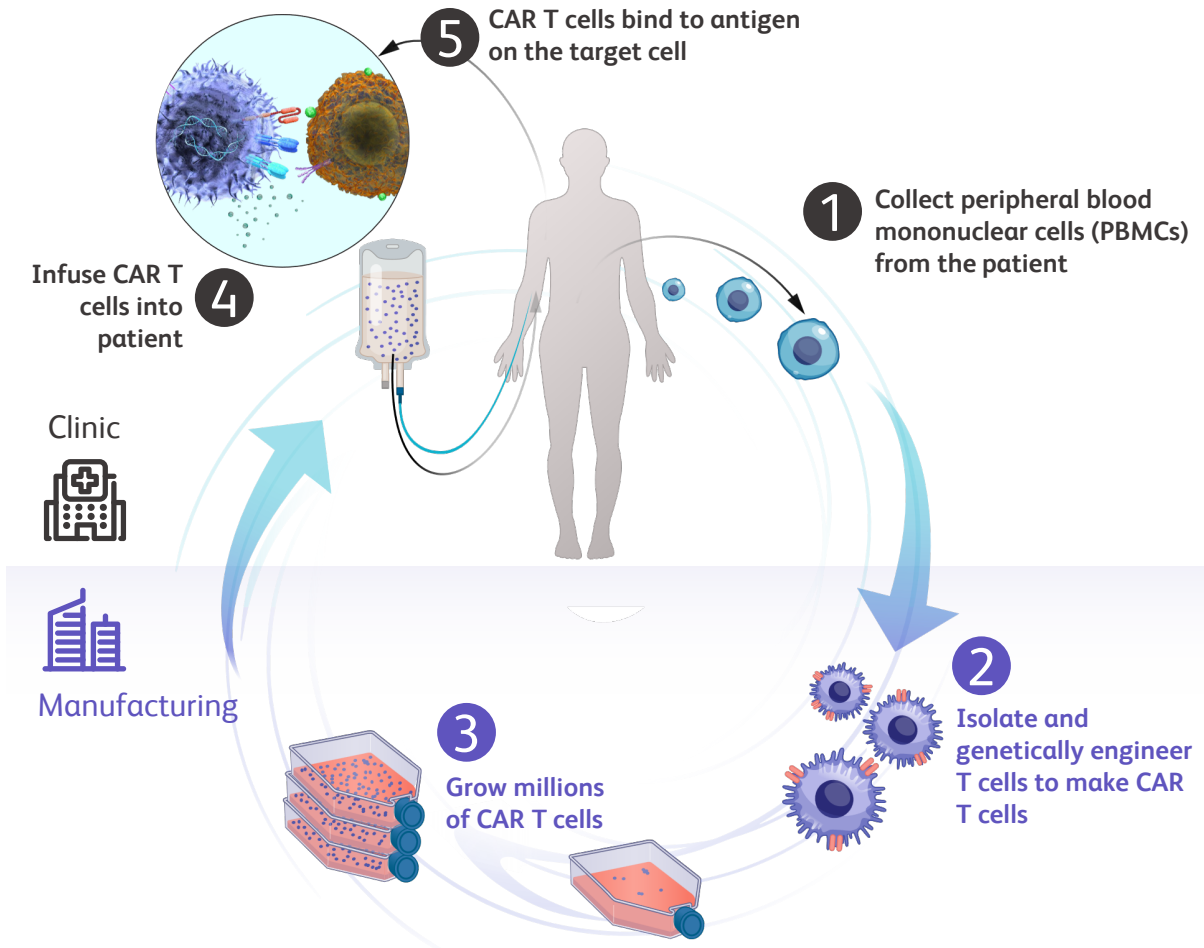
FasL, Fas ligand; IFN, interferon; IL-2, interleukin-2; MHC, major histocompatibility complex; TCR, T cell receptor; TRAIL, tumor necrosis factor-related apoptosis inducing ligand; TNF, tumor necrosis factor.

References: 1. Cartellieri M, et al. *J Biomed Biotechnol*. 2010;2010:956304. **2**. Filley AC, et al. *Front Oncol*. 2018;8(OCT):1-19. **3**. Maus MV, Levine BL. *Oncologist*. 2016;21:608–617. **4.** Benmebarek MR, et al. *Int J Mol Sci*. 2019;20(6).

Overview of the CAR T Cell Therapy Process

The autologous CAR T cell therapy process generally involves[1-3]:

- Collecting a patient's T cells via apheresis
- CAR T cell manufacturing
  - Genetically engineering T cells to express the CAR
  - Expanding CAR T cells to generate sufficient cell numbers for therapy
  - During the manufacturing period, some patients may receive bridging therapy
- Infusion of CAR T cells to the patient after the patient has received preparative chemotherapy, or lymphodepleting chemotherapy
- Short- and long-term patient monitoring after infusion of CAR T cells



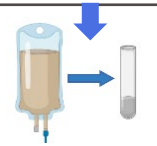
References: 1. National Cancer Institute. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. Accessed August 5, 2022. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells **2**. Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. 2022. **3**. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024.

Autologous CAR T Cell Manufacturing Methods

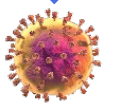
Overview of the CAR T Cell Manufacturing Process[1,2]

1. **Leukapheresis**
   - Patients undergo leukapheresis to collect PBMCs; the PBMCs are then shipped to a manufacturing facility
   - Collected apheresis products may be processed differently depending on the downstream procedures using one of several commercially available devices

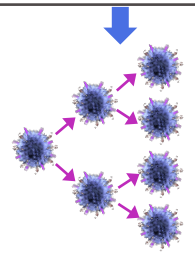
2. **Selection & Activation**
   - Lymphocytes are isolated from the PBMCs and T cells are activated



3. **Gene Transfer**
   - Isolated patients T cells are transduced with a viral vector to insert the CAR genetic sequence



4. **Cell Expansion**
   - Engineered T cells are expanded to a therapeutic dose
   - Cellular product is concentrated and cryopreserved in container(s) before being shipped to the treatment site for infusion to the patient



CAR T cell total manufacturing time may range from ~2—5+ weeks, varying by product and manufacterer[3]

PBMC, peripheral blood mononuclear cells.

References: 1. Wang X, Rivière I. *Mol Ther Oncolytics*. 2016;3:16015. **2.** Levine BL, et al. *Mol Ther Methods Clin Dev*. 2016;4:92-101. **3.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141.

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Icon indicates areas of collaboration between the non-CAR T and CAR T treatment teams

Patient Journey Through the CAR T Cell Therapy Process

Referring hematologist/ oncologist → **At CAR T cell therapy treatment center** → **Referring hematologist/ oncologist**

Patient identification and referral[1]

- Patient identification begins with the referring hematologist/ oncologist
- Early collaboration may facilitate timely referral and eligibility evaluation

Consultation at CAR T cell therapy treatment center[1]

- Referred patients meet the CAR T cell therapy multidisciplinary team to determine if CAR T cell therapy is right for them

Apheresis[2,3]

- Peripheral blood mononuclear cells (PBMC) are collected by leukapheresis, then shipped for manufacturing
- Apheresis may occur at the treatment center or a qualified external apheresis center

Bridging and lymphodepleting chemotherapy (LDC)[2,3]

- Bridging therapy may be given to maintain disease control during CAR T cell manufacturing
- Appropriate bridging therapy should be discussed and coordinated between the referring and CAR T cell therapy treating physicians
- LDC is administered prior to CAR T cell infusion to deplete endogenous T cells and create an environment for CAR T cell expansion

Infusion and monitoring[1,4]

- Infusion occurs at a qualified treatment center
- After infusion, patients are closely monitored for at least 2 weeks at the CAR T cell therapy treatment site, and side effects are promptly managed
- After at least 2 weeks, patients may be discharged back to the referring physician's care

Long-term follow-up[1,2]

- Following treatment, patients receive ongoing care to monitor and manage any persistent or delayed complications of therapy
- Communication continues between the CAR T cell therapy treatment center and the primary hematologist/ oncologist as patients are monitored long-term

References: 1. Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **2.** Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23:27-34. **3.** McGuirk J, et al. *Cytotherapy.* 2017;19(9):1015-1024. **4.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor

Considerations for CAR T Cell Therapy

General considerations for CAR T cell therapy:

- Have a disease as defined in commercial indication or in clinical trial[1]
- Adequate marrow and organ function, as well as patient fitness and performance status[2,3]
- Do not administer to patients with active infections or inflammatory disorders[3,4,a]
- Prior chemotherapy exposure may adversely affect quality of circulating T cells[2]
- Allogeneic stem cell transplant before CAR T cell therapy may increase the risk of graft-versus-host disease (GVHD)[5]

These considerations are typically part of the general workup conducted and do not necessarily disqualify patients from CAR T cell therapy

Additional considerations:

- Socioeconomic factors[1]
- Caregiver support[6]
- Social work evaluation[7]
- Stay in close proximity of treating institution for at least 2 weeks after CAR T cell infusion[8]

Centers and manufacturers may have resources to assist eligible patients

Precise criteria for eligibility vary by malignancy, treatment regimen or protocol, and CAR T cell product[3]

[a] Including hepatitis B, hepatitis C, HIV, and CMV.
CMV, cytomegalovirus; HIV, human immunodeficiency virus.

References: 1. Taylor L, et al. *Clin J Oncol Nurs.* 2019;23:20-26. **2.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **3.** Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. 2022. **4.** Hill JA, Seo SK. *Blood* 2020;136(8):925-935. **5.** Wall DA, Krueger J. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **6.** Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **7.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. **8.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor

Patient Eligibility Evaluation

Patient workup may include:

Disease assessment and review of medical and treatment history[1,2]
- May require confirmatory biopsy of disease if not recently completed or reviewed[2]

Assessment of organ function, comorbidities, and performance status[1]

Laboratory studies
- CRP[2]
- Ferritin[2]
- LDH[2]
- CBC with differential[2]
- Comprehensive metabolic panel[2]
- Screening for infections including hepatitis B, hepatitis C, and HIV[3]

Referring centers are often responsible for providing current patient records, including[2]:

- Diagnostic scans
- Pathology reports and slides
- Recent laboratory data
- Complete history and physical

Refer to the Patient Considerations module for more information

CBC, complete blood count; CRP, C-reactive protein; LDH, lactate dehydrogenase.

References: 1. McDermott K, Spendley L. *J Adv Pract Oncol.* 2019;10(Suppl 3):11-20. **2.** Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23:27-34. **3.** Yakoub-Agha I, et al. *Haematologica.* 2020;105(2):297-316.

Collection of T Cells Through Leukapheresis

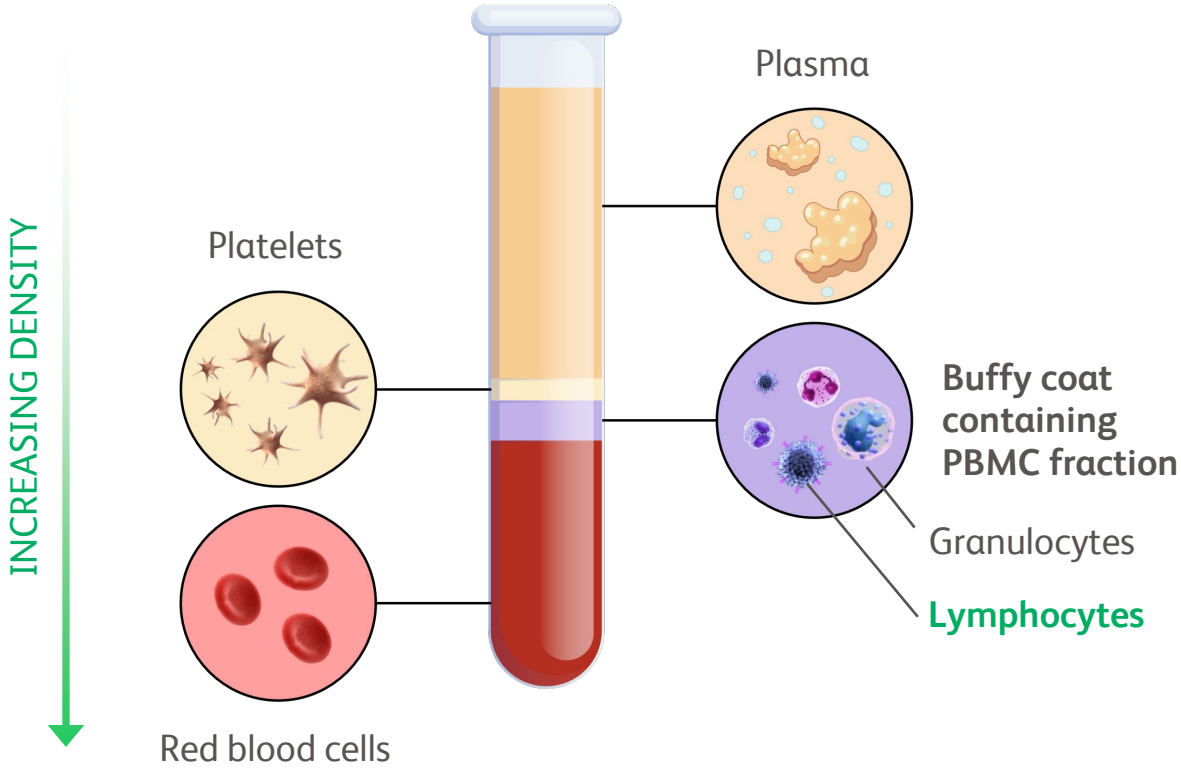
Apheresis is the removal of blood from a patient, and the subsequent separation into its components[1]

- Leukapheresis specifically refers to the collection of white blood cells[1]

Leukapheresis may be performed in the outpatient setting[2]

Coordination across the multidisciplinary team can help achieve an efficient leukapheresis collection[2]

Separation of Blood Components for CAR T Cell Therapy[4]



A single leukapheresis session of **2-5 hours is typically sufficient** to harvest the required number of cells for CAR T cell manufacturing[1,3]

Refer to the Apheresis module for more information

[a] Physicians should consult product-specific information and/or clinical trial information for any patients treated on a clinical study.
PBMC, peripheral blood mononuclear cell.

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Qayed M, et al. *Cytotherapy*. 2022;S1465-3249(22)00641-7. **3.** Korell F, et al. *Cells*. 2020;9:1225. **4.** Fesnak A, et al. *Transfus Med Rev*. 2016;30:139-145.

Bridging Therapy May Help Control Disease Until CAR T Cells Are Ready for Infusion

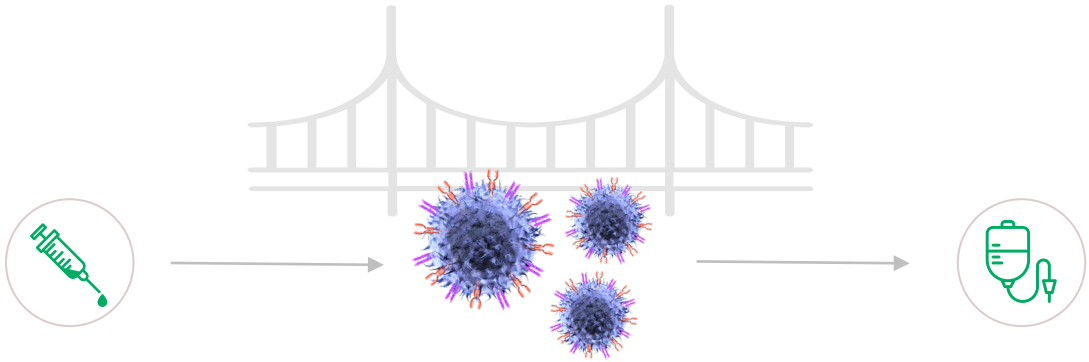
It can take several weeks before the CAR T cell product is manufactured and delivered to the patient, therefore patients that have active disease may require bridging therapy during this period[1,2]

Patients undergoing CAR T cell therapy may have active disease and may require bridging therapy during this period[1]

BRIDGING THERAPY GOALS[1]:

Maximize disease control

Minimize organ toxicity



Appropriate bridging therapy should be discussed and coordinated between the referring physicians and those treating with CAR T cell therapy[3,4]

Refer to the Bridging Therapy module for more information

Bridge icon attribution: round PNG Designed By Ylivdesign from https://pngtree.com/

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **3.** Wall DA, et al. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **4.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(Suppl 3):29-40.

Washout Periods May be Needed Between Bridging Therapy and Lymphodepletion

A washout period may be needed before leukapheresis to support the collection of a sufficient number of T cells for manufacturing[1]

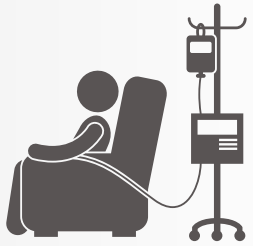
Prior treatments, including anthracycline-containing regimens, may affect T cell health and should be washed out to ensure optimal T cell collection[2,3]

A washout period may be needed between bridging therapy and lymphodepletion to help avoid interference with CAR T cell activity[1]

Washout periods should be discussed and coordinated between the referring physicians and those treating with CAR T cell therapy[4,5]

References: 1. Wall DA, et al. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **2.** Das RK, et al. *Blood Adv*. 2020;4(19):4653-4664. **3.** Yakoub-Agha I, et al. *Hematologica*. 2020;105(2):297-316. **4.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(Suppl 3):29-40. **5.** Qayed M, et al. *Cytotherapy*. 2022;S1465-3249(22)00641-7.

Coordination and Delivery of Bridging Therapy



Regimens are highly variable and depend on[1]:

- Specific malignancy
- Disease burden
- Patient age
- Comorbidities
- Prior response to therapy

- Bridging therapy is carefully planned and selected with the aim to control disease and avoid patient harm or delay of CAR T cell infusion[1]
- Patients are closely monitored for infections and other toxicities[2]
- Bridging therapy delivery may take place at either the treating or referring center[1]

When bridging takes place at the referring center, close communication with CAR T cell therapy treating institutions is important for coordination of bridging therapy delivery[1]

Examples of bridging therapy:

Chemotherapy, immunomodulatory agents, radiation therapy, monoclonal antibodies, antibody-drug conjugates, corticosteroids, and lower-intensity regimens (as appropriate for certain patients)[2-4]

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **3.** Raje N, et al. *N Engl J Med*. 2019;380:1726-1737. **4.** Hashmi H, et al. *Hematol Oncol Stem Cell Ther*. 2021;S1658-3876(21)00062-5.

CAR T Cell Therapy Setting of Care Considerations

- Under certain circumstances, outpatient administration and monitoring may be appropriate per the CAR T cell therapy treating physician's discretion or clinical trial protocol[1]
  - In these cases, patients are usually observed in the treating center for a few hours after CAR T cell therapy infusion to monitor for acute reactions; if none occur, they may be permitted to leave the treatment center[2]
  - Patients should stay within vicinity of the CAR T cell therapy treatment center for at least 2 weeks as directed by the CAR T cell therapy treating physician, or as indicated per clinical trial protocol[3,4]
  - Hospitalization may be necessary if toxicities develop[2]

Determining the setting for CAR T cell therapy infusion is based on several factors[1,5]:

- Treatment center infrastructure
- Ability to provide patient coverage 24/7
- Anticipated onset and severity of AEs
- Training, education, and protocols for managing AEs
- CAR T cell product offered
- Availability of reliable caregiver(s)
- Patient and/or physician preference

References: 1. Brudno JN, Kochenderfer JN. *Blood* Rev. 2019:34:45-55. **2.** Maus MV, Levine BL. *Oncologist*. 2016;21:608-617. **3.** Santomasso BD, et al. *J Clin Oncol*. 2021;39:3978-3992. **4.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor **5.** Taylor L, et al. *Clin J Onc Nurs*. 2019;23(2):20-26.

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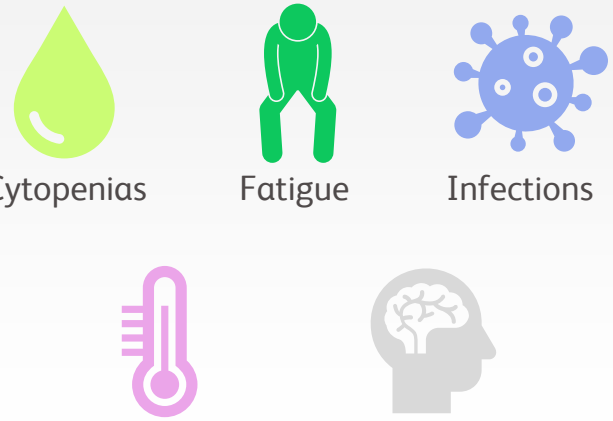
Post-CAR T Cell Therapy Side Effects[1-5]

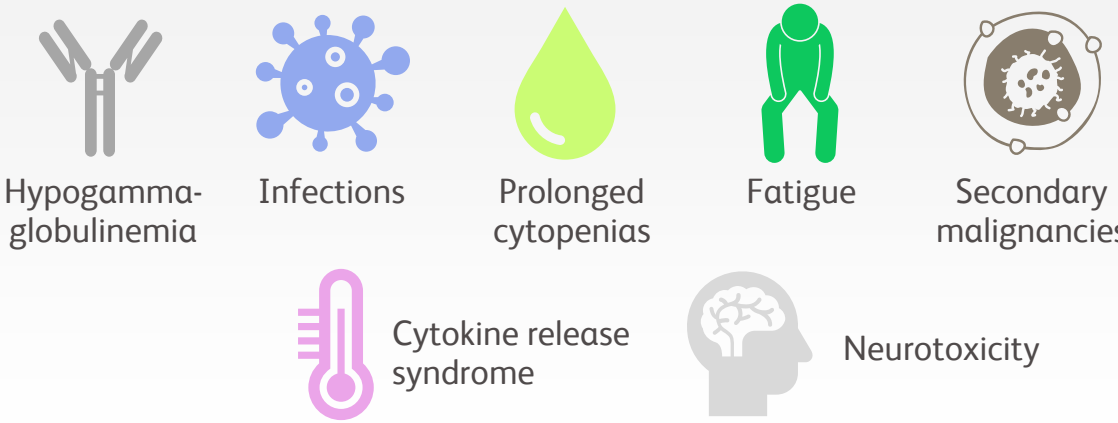
Close monitoring after CAR T cell therapy infusion enables providers to help manage persistent and/or delayed complications and monitor disease status[1]

Adverse reactions post-CAR T cell therapy may include[2,3a]:

Short-term (≤2 weeks)



Long-term (>2 weeks)



Because of the risk of delayed neurologic events, patients should not drive or operate machinery for at least 2 weeks after CAR T cell infusion[4,5]

[a] Note, other adverse reactions may occur that are not listed on slide.

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23(2):27-34. **2.** Hayden PJ, et al. *Ann Oncol.* 2021;33(3):259-275. **3.** Buitrago J et al. *Clin J Onc Nurs.* 2019;23(2):42-48. **4.** Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **5.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor

CRS and Neurotoxicity Are Serious Adverse Effects of CAR T Cell Therapy[a]

Short-term

Following CAR T cell therapy, patients should be closely monitored for at least 2 weeks by the CAR T treatment center for cytokine release syndrome (CRS) and neurotoxicity[1,2]

CRS		Neurotoxicity
Typical time to onset: 1-7 days (range: 1-63)[3-9] Typical duration: 4-10 days (range: 1-63)[3-9]		Typical time to onset: 2–8 days (range: 1-368)[3-9] Typical duration: 7–21 days (range: 1-578)[3-9]
Signs and symptoms of CRS may include fever, hypotension, hypoxia and potentially organ dysfunction[10]		Signs and symptoms of CAR T neurotoxicity may include tremor, impaired attention, lethargy, dysgraphia and apraxia[10]

It is important to watch for signs as both of these events may require hospitalization[11]
In some instances, delayed onset of CRS and/or neurotoxicity may occur. Notify the CAR T treatment center if CRS or neurotoxicity is suspected[1]

Refer to the Acute Management module for more information

References: **1**. Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **2**. US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor **3.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed **4.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c **5**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189 **6.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2 **7**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022 **8.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59 **9.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538&audience=consumer **10.** Alexander M, et al. *Transplant and Cell Ther.* 2021;27(7):558-570.**11.** Jain M, et al. *Blood.* 2023;141(20):2430-2442.

Long-Term Monitoring Post-CAR T Cell Therapy

Long-term

After at least 2 weeks, or when toxicities resolve, patients can be transferred back to their primary hematologist/oncologist[1,2]

- Long-term follow-up may be conducted by a multidisciplinary team to monitor disease status and long-term side effects[3]

Close communication between the non-CAR T hematologist and the treatment site is needed for ongoing patient follow-up[1]

  - Follow-up with non-CAR T practitioners is personalized and may vary on a case-by-case basis[4]

- The long-term follow-up phase occurs up to 15 years post-infusion, as recommended by the FDA.[5] Patients should also be monitored life-long for secondary malignancies[6-12]

Elements of long-term follow-up can include[1,4]:

— Managing persistent and/or delayed complications

— Monitoring disease status and for occurrence of secondary malignancies

References: **1**. Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **2**. US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor **3**. Hayden PJ, et al. *Ann Oncol.* 2021;33(3):259-275. **4.** Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23(2):27-34. **5**. US Food and Drug Administration. Updated March 11, 2024. Accessed July 7, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products **6**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed **7**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c 8. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189 **9**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2 **10**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022 **11**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59 **12**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538&audience=consumer

Considerations for Management of Prolonged Cytopenias[a]

Long-term

Prolonged cytopenias

- Patients may exhibit cytopenias for weeks to months following lymphodepleting chemotherapy and CAR T cell therapy infusion[1]
- Incidence, duration, and severity of cytopenias varies between products and indications. Incidence of Grade 3-4 cytopenias 28+ days after CAR T cell infusion has been reported to range from 12-41% for neutropenia and 13-49% for thrombocytopenia. While less frequent, prolonged anemia may also occur[2-9]
- While cytopenias often recover within a few months post-CAR T cell infusion[10], cytopenias have been observed in patients up to 24 months following CAR T cell infusion[11,12]
- **Consider supportive care, growth factors, and/or corticosteroids to support patients with severe cytopenias, when appropriate[13]**

[a] Physicians should consult product-specific information and/or clinical trial information, and/or their institutional guidelines.

References: **1**. Jain T, et al. *Blood.* 2023;141(20):2460-2469. **2**. Hayden PJ, et al. *Ann Oncol.* 2021;33(3):259-275. **3.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed **4**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c **5**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189 **6**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2 **7**. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022 **8.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59 **9.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538&audience=consumer **10.** Jain T, et al. *Blood Adv*. 2020;4(15):3776-3787. **11.** Cordeiro A, et al. *Biol Blood Marrow Transplant*. 2020;26(1):26-33. **12.** Munshi NC, et al. *N Engl J Med.* 2021;384(8):705-716. **13**. Santomasso BD, et al. *J Clin Oncol.* 2021;39:3978-3992.

Considerations for Management of Hypogammaglobulinemia[a]

Long-term

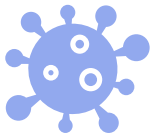
Hypogamma-globulinemia

- Hypogammaglobulinemia develops in approximately 50% of patients that receive CAR T cell therapy[1]
- For these patients, as well as immunologically-immature pediatric patients, intravenous immunoglobulin (IVIG) replacement is routine[1]
- **Consider IVIG treatment monthly for select patients until reaching a steady state[1,2]**

[a] Physicians should consult product-specific information and/or clinical trial information, and/or their institutional guidelines.
[b] Antibacterial and antifungal prophylaxis may be considered based on patient characteristics and history.
References: **1**.Hayden PJ, et al. *Ann Oncol*. 2021;33(3):259-275. **2**. Santomasso BD, et al. *J Clin Oncol*. 2021;39:3978-3992.

Considerations for Management of Infections[a]

Long-term



Infections

- Infections following CAR T cell therapy are common, and the incidence rate can range from 50-69%[1]
- Most early infections are bacterial or respiratory viral infections[2]
- Beyond 30 days, viral infections predominate, and long-term antiviral prophylaxis may be considered[2,3,b]
  - Antibacterial and antifungal prophylaxis may also be considered as needed (eg, in high-risk patients, patients with prolonged neutropenia)[2,4]
- When eligible, vaccination may also reduce infection rates[2]
- **Consider inactivated vaccines ≥6 months after CAR T cell therapy and ≥2 months after IVIG[2,5]**
- **Consider live vaccines ≥6-12 months after CAR T cell therapy and immune reconstitution[2,5]**
- Patients should have CMV serology at baseline. In patients at high risk for viral reactivation or infection or those with sequelae of infectious or neurological symptoms that are unexplained by alternative diagnoses, viral PCRs should be checked[4]

[a] Physicians should consult product-specific information and/or clinical trial information, and/or their institutional guidelines.
[b] Antibacterial and antifungal prophylaxis may be considered based on patient characteristics and history.

References: **1**. Ahmed N, et al. *Clin Hematol Int*. 2024;6(2):31-45. **2**. Hayden PJ, et al. *Ann Oncol*. 2021;33(3):259-275. **3**. Santomasso BD, et al. *J Clin Oncol*. 2021;39:3978-3992. **4**. Shadhid Z, et al. *Transplant and Cell Ther*. 2024:30(955-969). **5**. Hill JA, Seo SK. *Blood* 2020;136(8):925-935.

Considerations for Management of Fatigue and Secondary Malignancies[a]

Long-term

Fatigue

- Fatigue can be a common and difficult-to-manage side effect of CAR T cell therapy with incidence ranging from 23-52% in clinical trials[1-8]
- **Consider ruling out any possible contributing factors, such as anemia and hypothyroidism[9]**
- **Consider avoiding steroid use due to potential T cell suppression that may limit activity of CAR T cells[1]**
- **Consider nonpharmacologic interventions including exercise, yoga, and meditation[1]**

Secondary malignancies

- Because genetic alteration is used to create CAR T cells, there is a possibility that these products can cause insertional mutagenesis, resulting in secondary malignancies[1]
- In a meta-analysis of clinical trials that were randomized to CAR T vs standard of care, there was a similar risk of secondary malignancies with either treatment strategy[10]
  - The median time from first infusion to diagnosis for subsequent malignancies was 2 to 16 months, depending on the type of malignancy[11]
- **Patients should be monitored lifelong for secondary malignancies[11]**
  - **Secondary malignancies should be treated per disease-specific protocols[12]**

[a] Physicians should consult product-specific information and/or clinical trial information, and/or their institutional guidelines.

References: 1. Buitrago J et al. *Clin J Onc Nurs.* 2019;23(2):42-48. **2.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed 3. National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c **4.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189 **5.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2 **6.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022 **7.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59 **8.** National Institutes of Health. DailyMed. Accessed July 7, 2025. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=4fef6986-b988-45e4-8c20-b14f0ef1f538&audience=consumer **9.** American Cancer Society. Cancer-related fatigue. Updated July 16, 2024. Accessed July 7, 2025. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/fatigue/what-is-cancer-related-fatigue.html **10.** Tix t, et al. *Clin Cancer Res.* 2024;30(20):4690-4700. **11.** Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **12.** Cordeiro A et al. *Biol Blood Marrow Transplant.* 2020;26(1):26-33.

Example Clinical Testing in the First Year Post-CAR T Cell Therapy[a]

Long-term

Day +14 to 1 year | Day +100 to 1 year | 1-2 years | 2-15+ years

Delayed and prolonged events can occur, therefore more frequent testing should be considered in collaboration with treating physician to monitor for the onset of complications

Example Clinical Testing Panel and Frequency per EBMT/EHA

Tests	Purpose
Biochemistry blood panels	Assess bone marrow recovery, organ health, and supportive care needs
Viral presence	Infection/ viral reactivation
Immunoglobulin or serum protein testing	Immune reconstitution
Peripheral blood immunophenotyping	Immune recovery
CAR T cell monitoring	CAR T cell persistence

- Additional tests and imaging should be carried out as clinically indicated and/or per institutional guidelines
- Collaboration between the CAR T cell therapy treatment site and the non-CAR T hematology practitioner is important for monitoring and management of patients after CAR T cell therapy
  - The frequency and timing for testing should be determined in collaboration between the CAR T cell therapy treatment team and the non-CAR T hematology practitioner

[a] Physicians should consult product-specific information and/or clinical trial information, and/or their institutional guidelines.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CRP, C-reactive protein; EBMT, European Society for Blood and Marrow Transplantation; EBV, Epstein-Barr virus; EHA, European Hematology Association; FBC, full blood count; HCT, hematopoietic cell transplantation; LDH, lactate dehydrogenase.

References: **1.** Hayden PJ, et al. *Ann Oncol*. 2021;33(3):259-275. **2.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor

Possible Frequency of Clinic Visits for Patients Through the LTFU[a]

- CAR T cells may persist in some patients, underscoring the need for long-term monitoring for late effects of treatment[1,3]
- The FDA recommends 15 years of observation for patients who receive CAR T cell therapies[4,5]
- Patients should be monitored lifelong for secondary malignancies[6]
- After CAR T cell therapy, referring physicians remain in ongoing communication with the treatment site to report patient data during the long-term follow-up period[6]
  - This data may then be reported to the CIBMTR registry, and/or to the FDA, who capture long-term follow-up data for patients that received CAR T cell therapies[4,7]
  - To report SUSPECTED ADVERSE REACTIONS, contact the product manufacturer or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Long-term

Day +14 to 1 year	Day +100 to 1 year	1-2 years	2-15+ years
	Consider monthly assessments from day +100 to 1 year after CAR T cell therapy[8,b]	Consider biannual assessments from 1-2 years after CAR T cell therapy[8,b]	Consider annual assessments recommended up to 15+ years after CAR T cell therapy[8,b]
	Disease assessment, vaccination guidance, and review of medical and treatment history[8]		
	Assessment of organ function, comorbidities, and performance status[8]		
	Laboratory studies for immune reconstitution, viral infection, CAR T persistence and standard follow-up[8]		

CIBMTR, Center for International Blood & Marrow Transplant Research; FDA, Food and Drug Administration.

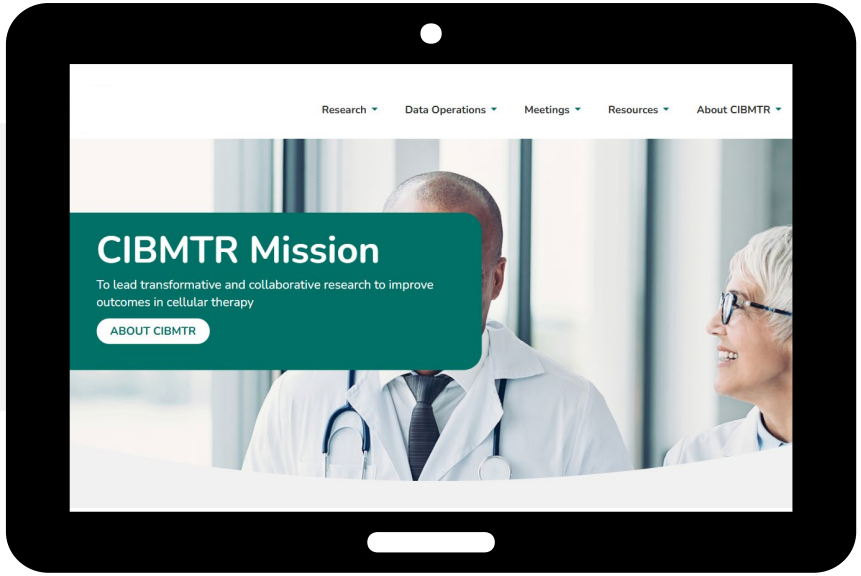
[a] Physicians should consult product-specific information and/or clinical trial information, and/or their institutional guidelines.

[b] Some patients may warrant more frequent or closer monitoring depending on prognosis, disease characteristics, and/or patient characteristics.

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** US Food and Drug Administration. Accessed June 27, 2025. https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/fda-eliminates-risk-evaluation-and-mitigation-strategies-rems-autologous-chimeric-antigen-receptor **3.** Oluwole OO, Davila ML. *J Leukoc Biol.* 2016;100:1265-1272. **4.** Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638. **5.** US Food and Drug Administration. Accessed June 24, 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products. **6.** Beaupierre A, et al. *J Adv Pract Oncol.* 2019;10(Suppl 3):29-40. **7.** CIBMTR. CIBMTR Communication Packet: Resources for potential centers. Accessed July 7, 2025. https://cibmtr.org/Files/New-Center-Resources/New-Center-Communication-Packet.pdf. **8.** Hayden PJ, et al. *Ann Oncol*. 2021;33(3):259-275.

Patient Registry and Data Capture

The CIBMTR Cellular Therapy Registry:



- Offers a platform for standardized, comprehensive data collection
  - After infusion, data captured at 3 months, 6 months, 1 year, and yearly thereafter

- Aligns with FDA regulatory recommendations to capture relevant CAR T cell–associated toxicities
  - Specific outcomes captured include CRS, neurotoxicities, neutrophil and platelet recovery, hypogammaglobulinemia, severe infections, nonhematologic grade 4 toxicities, death from any cause
  - Event-driven forms can be used to report subsequent neoplasms and pregnancies

CIBMTR, Center for International Blood and Marrow Transplant Research; CRS, cytokine release syndrome; FDA, US Food and Drug Administration

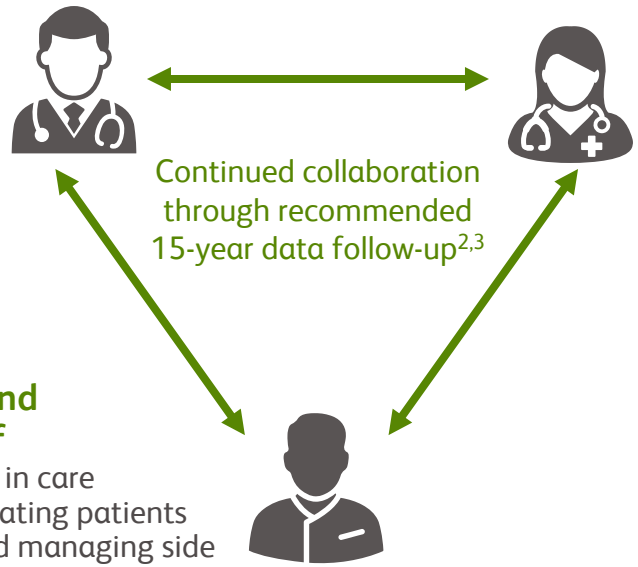
Reference: Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

Treatment and Management Requires Open Communication Between Non-CAR T Hematology Practitioners and Treating Institutions

Patients will be co-managed by the primary hematologist and CAR T specialist leading up to infusion and following the initial post-infusion monitoring period. Care can then be transitioned back to the primary hematologist[1]

Non CAR T Hematologist/ Oncologist

Refers patients for CAR T cell therapy[1]



CAR T Specialist

The treating provider at a qualified treatment facility[1]

Nurses, APPs, and Pharmacy Staff

Have a critical role in care coordination, educating patients and caregivers, and managing side effects including potential long-term effects[2-4]

Example topics of discussion for referring physicians and CAR T cell treatment sites when coordinating patient care

- ✓ Appropriate bridging therapy
- ✓ Washout periods pre-apheresis and pre-lymphodepletion
- ✓ Timing and coordination of patient care at each institution after CAR T cell infusion
- ✓ Methods of efficient communication between practices

APP, advanced practice providers.

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23:27-34. **2**. Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40. **3**. Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **4**. Hayden PJ, et al. *Ann Oncol*. 2021;33(3):259-275.

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