CAR T Cell Therapy for Patients with Autoimmune Disease: An Overview for Referring Specialists

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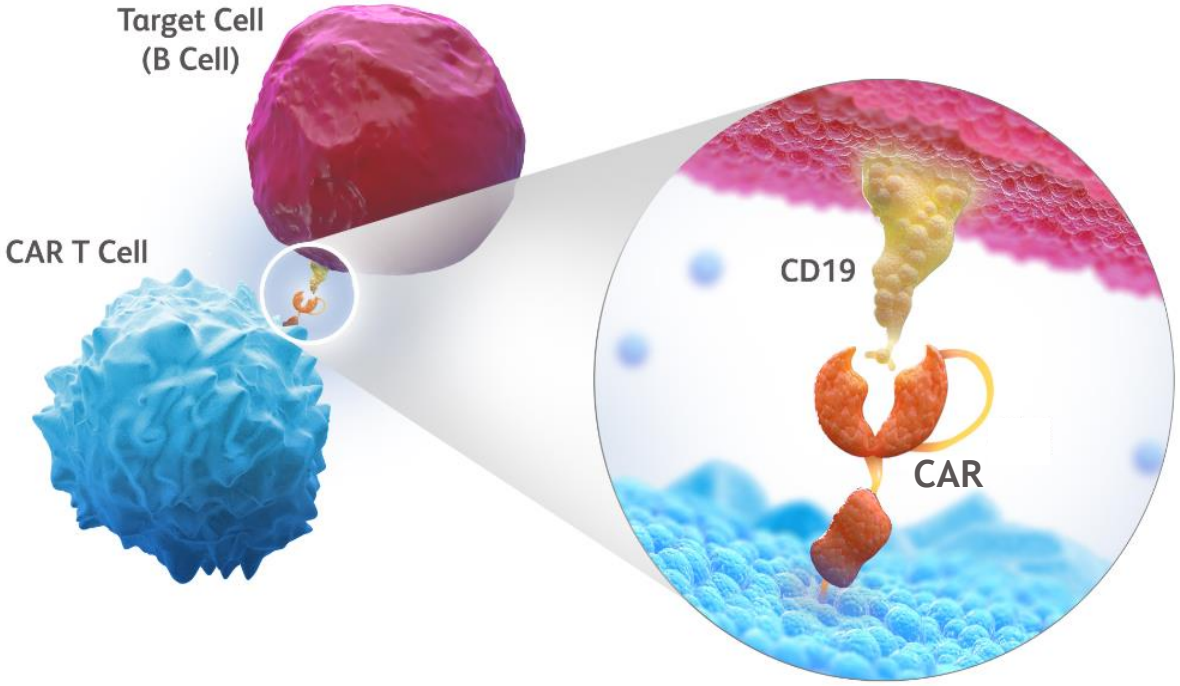
Important Context

- CAR T cell therapies are not approved for any uses in autoimmune diseases and are investigational only
- This presentation is intended to provide general background on the cell therapy process

CAR T Academy: CAR T Cell Therapy for Patients with Autoimmune Disease: An Overview for Referring Specialists

What is CAR T Cell Therapy?

Autologous chimeric antigen receptor (CAR) T cell therapy is a type of immunotherapy that reprograms T cells to express a CAR that binds to a specific antigen on target cells, leading to T cell activation, expansion, and cytotoxicity.[1]



- Gene transfer technology is used to express CARs on T cells, conferring antigen specificity[2]
- CAR T cell therapy targets specific cells that express the target antigen. An example of a target surface antigen is CD19 found on B lineage cells, which is highly specific and ubiquitously expressed from pro-B cells to plasma blasts[2,3]

After expansion, CAR T cells may also persist in the blood of patients for months and even years[4]

- Ultimately, CAR T-cell therapy combines the specificity of an antibody with the cytotoxic capabilities of a T cell[1,2,4]
- CD19-directed CAR T-cell therapy is now being explored in autoimmune disease[3,5-8]

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

References: 1. Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. Accessed October 30, 2023. https://www.lls.org/sites/default/files/2023-10/FSHP1_CART_Factsheet_June2022_rev.pdf. **2.** Oluwole OO, Davila ML. *J Leukoc Biol*. 2016;100:1265-1272. **3**. Mackensen A, et al. *Nat Med*. 2022;28:2124-2132. **4**. McLellan AD, Ali Hosseini Rad SM. *Immunol Cell Biol*. 2019;97(7):664-674. **5.** Schett G, et al. *Lancet*. 2023;402(10416):2034-2044. **6.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05869955. **7.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05938725. **8.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05474885.

CAR T Cell Mechanism of Action

Mechanism on the T Cell-Target Cell Level

1. CAR T cells are activated when they bind to a specific antigen on the target cell, leading to a signaling cascade that induces[1]:
   - cytotoxic activities
   - expresses proapoptotic molecules (FasL, TRAIL)
   - and secretes pro-inflammatory cytokines (IL-2, IFN-γ, TNF-α)

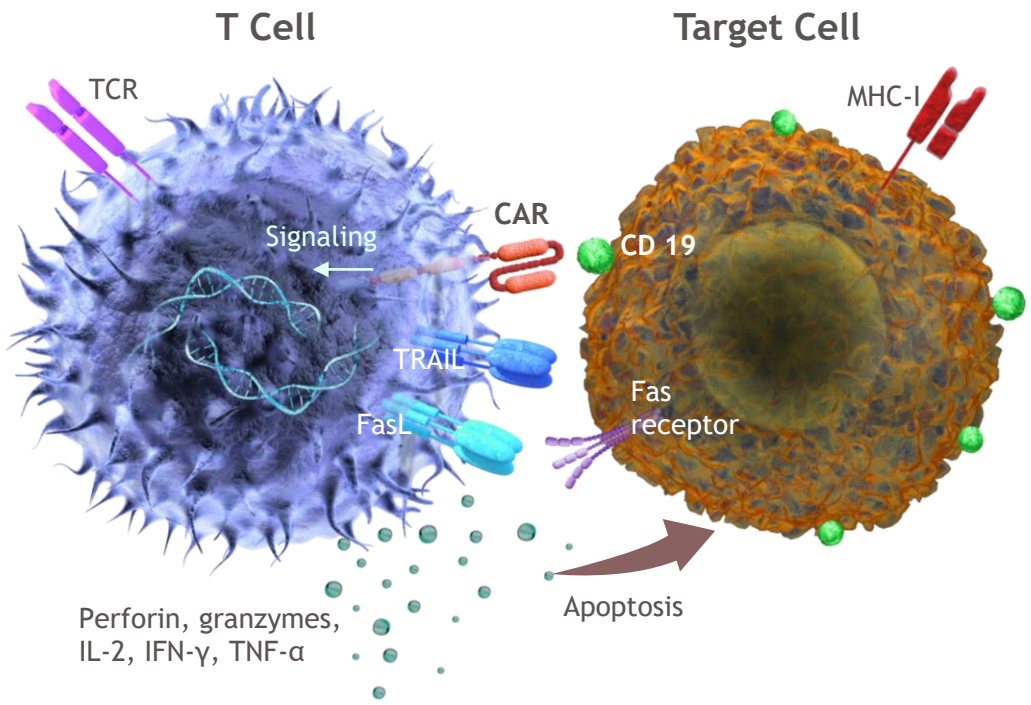
Rationale for Use in Autoimmune Diseases (AID)

2. B cells play a central role in the pathogenesis of AID, as they then exhibit impaired antigen presentation and are precursors to the cells that produce autoantibodies[2,3]

3. CD19-directed CAR T cells migrate and stay in the tissues, such as the lymph nodes and the bone marrow, resulting in the extensive killing of B cells[2]

4. The deep depletion of B cells via CAR T cell therapy results in the rapid and sustained breakdown of B cell-mediated immune response and has been theorized to reboot the immune system in autoimmune diseases[2,3]

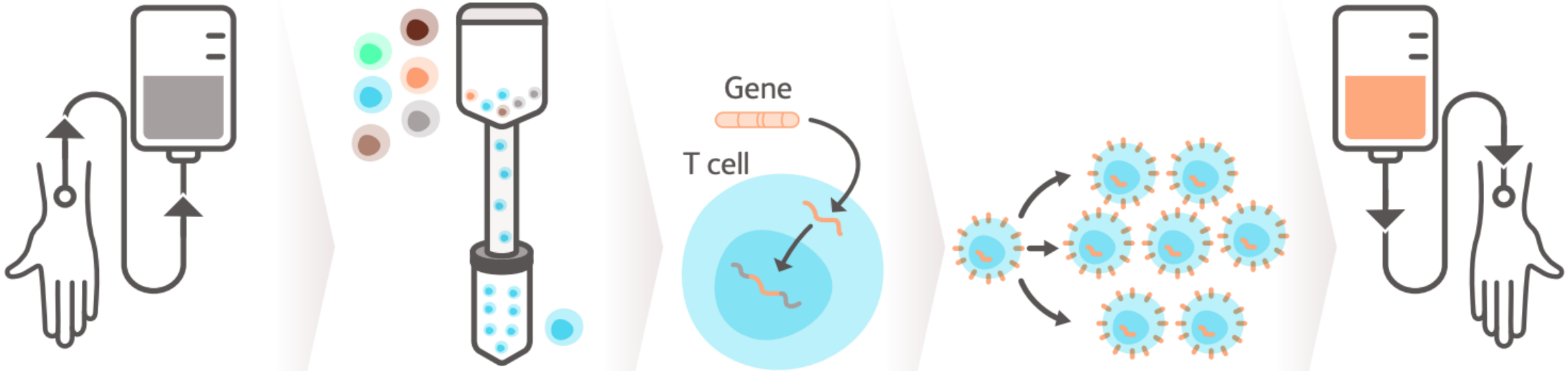
Target Cell Killing by CAR T Cells[1,4-6]



FasL, Fas ligand; IFN, interferon; IL-2, interleukin-2; MHC, major histocompatibility complex; 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.** Mackensen A, et al. *Nat Med*. 2022;28:2124-2132. **3.** Schett G, et al. *Lancet*. 2023;402(10416):2034-2044. **4.** British Society for Immunology. (2021). T-cell activation. Accessed October 30, 2023. https://www.immunology.org/public-information/bitesized-immunology/systems-processes/t-cell-activation. **5.** Maus MV, Levine BL. *Oncologist*. 2016;21:608-617. **6.** Benmebarek MR, et al. *Int J Mol Sci*. 2019;20(6).

5 Key Steps in CAR T Manufacturing: Cell Collection to Final Product



Leukapheresis

Collection of peripheral blood mononuclear cells (PBMCs) from the patient; the PBMCs are then shipped to a manufacturing facility[1-3]

Selection & Activation

Lymphocytes are isolated from the PBMCs and T cells are activated[2]

Gene Transfer

Genetic modification of the T cells via viral vectors to express CARs[2,4]

CAR T Cell Expansion

Cells are expanded by the millions, concentrated to achieve therapeutic doses, cryopreserved, and then shipped to the treatment site for patient infusion[2,4]

Infusion

Following delivery of final product. Includes lymphodepletion followed by a **one-time** CAR T cell infusion[3,5]

Manufacturing turnaround time approximately ~ 2 to 5+ Weeks[3,5]

References: 1. Levine BL, et al. *Mol Ther Methods Clin Dev*. 2016;4:92-101. **2.** Abou-El-Enein M, et al. *Blood Cancer Discov*. 2021 Sep;2(5):408-422. **3.** Mackensen A, et al. *Nat Med*. 2022;28:2124-2132. **4.** Wang X, Rivière I. *Mol Ther Oncolytics*. 2016;3:16015. **5.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141.

CAR T Academy: CAR T Cell Therapy for Patients with Autoimmune Disease: An Overview for Referring Specialists

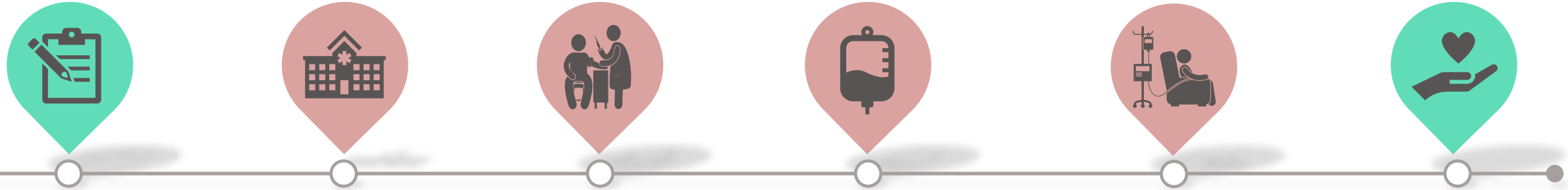
01 Introduction to CAR T Cell Therapy

02 Patient Journey and Joint Care Model

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

Patient Journey Through the CAR T Cell Therapy Process - Overview

Referring Specialist → **At CAR T cell therapy treatment center** → **Referring Specialist**



Patient identification and referral[1-3]

- Patient identification begins with the referring specialist (eg, rheumatologist, neurologist)
- Early collaboration may facilitate timely referral and eligibility evaluation

Consultation at CAR T treatment center[1,4]

- Patients referred for CAR T cell therapy meet with a multi-disciplinary team to determine eligibility and receive care from both a member of the referring specialty (eg, rheumatologist or neurologist) and a hematologist (CAR T treater) during visits to the CAR T center

Apheresis[5,6]

- Peripheral blood mononuclear cells (PBMC) are collected by leukapheresis and then transported to a manufacturing facility where they undergo genetic engineering to express chimeric antigen receptors (CARs)

Bridging Therapy[5,7]

- Bridging therapy that may be used for disease control during CAR T cell manufacturing should be coordinated between the referring physician and CAR T cell therapy treatment team

Lymphodepleting Chemotherapy (LDC) and CAR T Infusion[3,5,8-10]

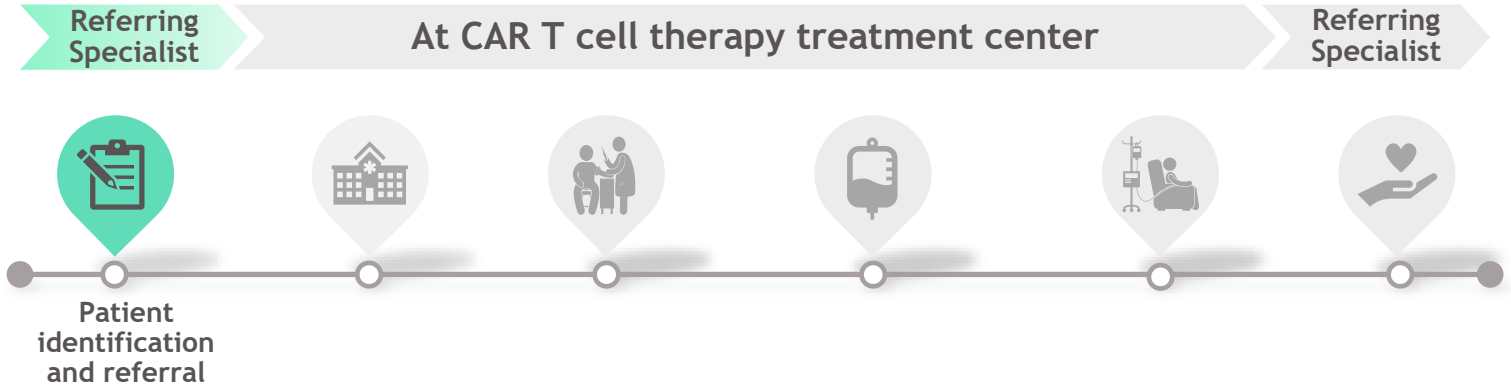
- Patients undergo LDC prior to CAR T cell infusion at a certified center to remove endogenous T cells and promote CAR T cell expansion. Patients are monitored for side effects for at least 4 weeks and then discharged to the referring physician's care

Long-term follow-up[5]

- Patients receive ongoing care to monitor and manage any complications after treatment
- Communication continues between the treatment center and community specialists for long-term monitoring

References: 1. Schett G, et al. *Lancet*. 2023;402(10416):2034-2044. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **3.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10 (Suppl 3). **4.** FAU. 20-year-old patient with systemic lupus erythematosus treated with a new therapeutic approach for the first time worldwide. Access November 13, 2023. https://www.fau.eu/2021/08/11/news/research/world-exclusive-car-t-cell-therapy-successfully-used-against-autoimmune-disease/. **5.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **6.** Abou-El-Enein M, et al. *Blood Cancer Discov*. 2021 Sep;2(5):408-422. **7.** Pecher AC, et al. *JAMA*. 2023;329(24):2154-2162. **8.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05869955. **9.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05938725 **10.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05474885.

Patient Identification & Referral



YOU MAY CONSIDER REFERRING YOUR PATIENT WITH AUTOIMMUNE DISEASE (AID) FOR A CAR T CLINICAL TRIAL, IF YOUR PATIENT:

- … has autoreactive B cell-caused AID, which can be targeted by CAR T cells and is being investigated in a clinical trial.[1-4]
- … has refractory or relapsed AID that does not respond to conventional therapies, such as immunosuppressants, biologics, or monoclonal antibodies or has become intolerant to them.[1-5]
- … has a window of opportunity for symptom reversal and reducing the risk of permanent organ damage.[1]

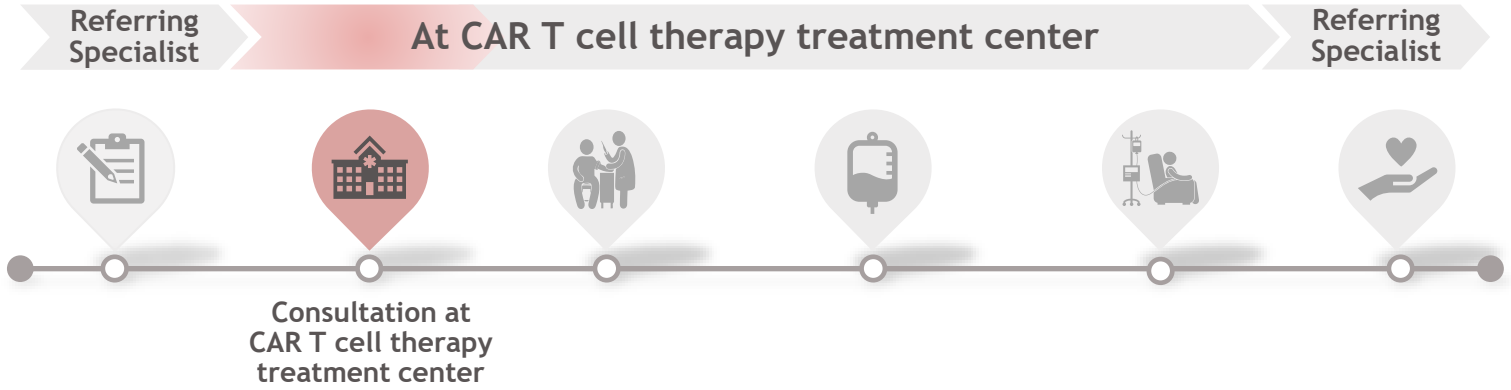
REFERRING FOR A CAR T CLINICAL TRIAL: IMPORTANT ELIGIBILITY AND SUPPORT SYSTEM FACTORS OF YOUR PATIENT

The patient's performance status permits them to undergo the multi-step CAR T cell therapy process, and they are willing to do so.[1,6]

Additional considerations: Caregiver support, socioeconomic factors, ability to stay in close proximity to the CAR T treatment center for at least 4 weeks following infusion.[7]

References: 1. Schett G, et al. *Lancet*. 2023;402(10416):2034-2044. **2.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05869955. **3.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05938725. **4.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05474885. **5.** Mackensen A, et al. *Nat Med*. 2022;28:2124-2132. **6.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **7.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10 (Suppl 3).

Patient Eligibility Evaluation at CAR T Treatment Center



WORKUP AT THE CAR T THERAPY TREATMENT CENTER TO DETERMINE PATIENT ELIGIBILITY

Review of disease assessment and medical and treatment history[2-5]

Assessment of organ function, comorbidities, and physical fitness[2-5]

Laboratory studies[5]

- Hematology, coagulation & chemistry
- Creatinine Clearance
- Serum pregnancy
- Inflammatory markers
- Viral serology
- Immunoglobulins
- Immunology

Precise criteria for eligibility vary by disease, treatment regimen or protocol, and CAR T cell product[6]

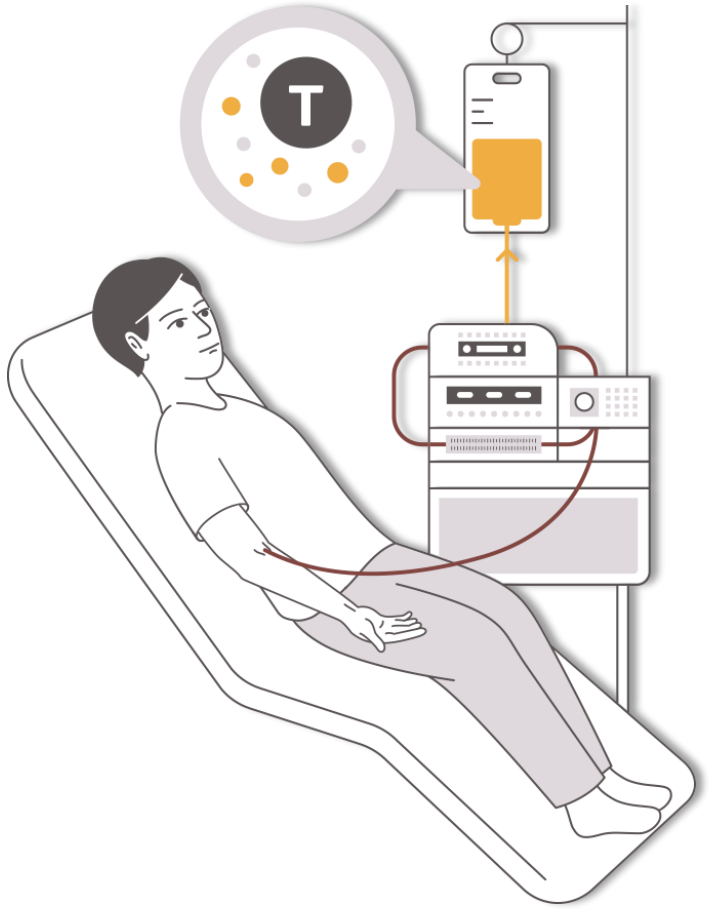
Referrers should communicate with their colleagues in the same specialty at the treatment site.[1]

Referring specialists are often responsible for providing current patient records including[7]:

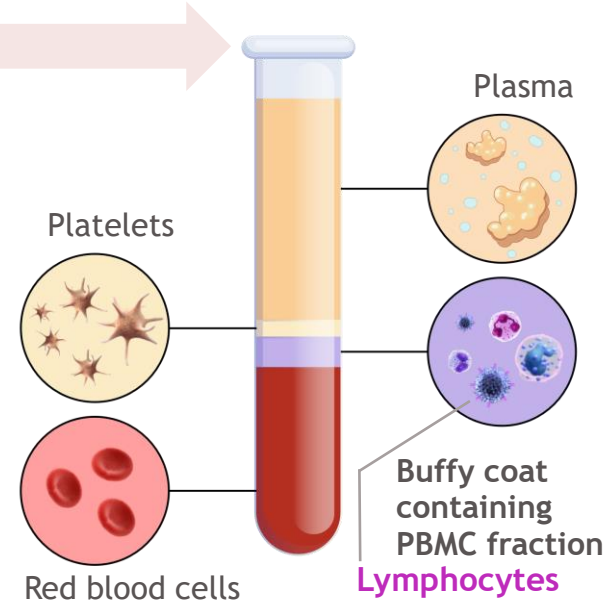
- Diagnostic scans
- Pathology reports
- Recent laboratory data
- Complete history and physical

References: 1. Schett G, et al. *Lancet*. 2023;402(10416):2034-2044. **2.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05869955. **3.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05938725. **4.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05474885. **5.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **6.** Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. Accessed October 30, 2023. https://www.lls.org/sites/default/files/2023-10/FSHP1_CART_Factsheet_June2022_rev.pdf. **7.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Collection of T Cells Through Leukapheresis



- Apheresis is the removal of blood from a patient, and the subsequent separation into its components[1,2]
  - Leukapheresis specifically refers to the collection of white blood cells[1]
- Leukapheresis performed at an authorized clinic or infusion center[1,3]
  - Coordination across the multidisciplinary team can help achieve an efficient leukapheresis collection[3]



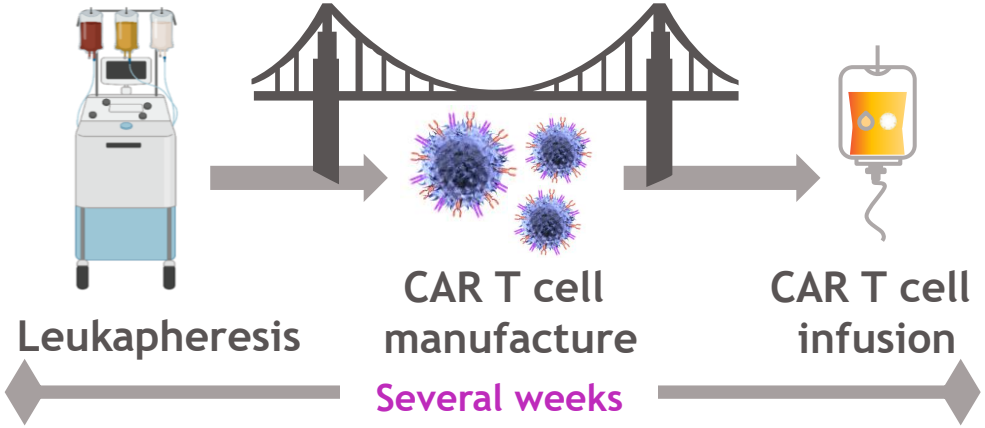
A single leukapheresis session of 2-5 hours is typically sufficient to harvest the required number of cells for CAR T cell manufacturing[1,4]

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

Potential Bridging Therapy to Control Disease Until CAR T Cells Are Ready for Infusion

Bridging therapy goals[1]:

Maximize disease control
Minimize organ toxicity



- It can take several weeks before the CAR T cell product is manufactured and delivered to the patient[1,3,4]
- Bridging is carefully planned and selected with the aim to control disease during this period and avoid patient harm or delay of CAR T cell infusion[1]
- Patients are closely monitored for infections and other toxicities[4]

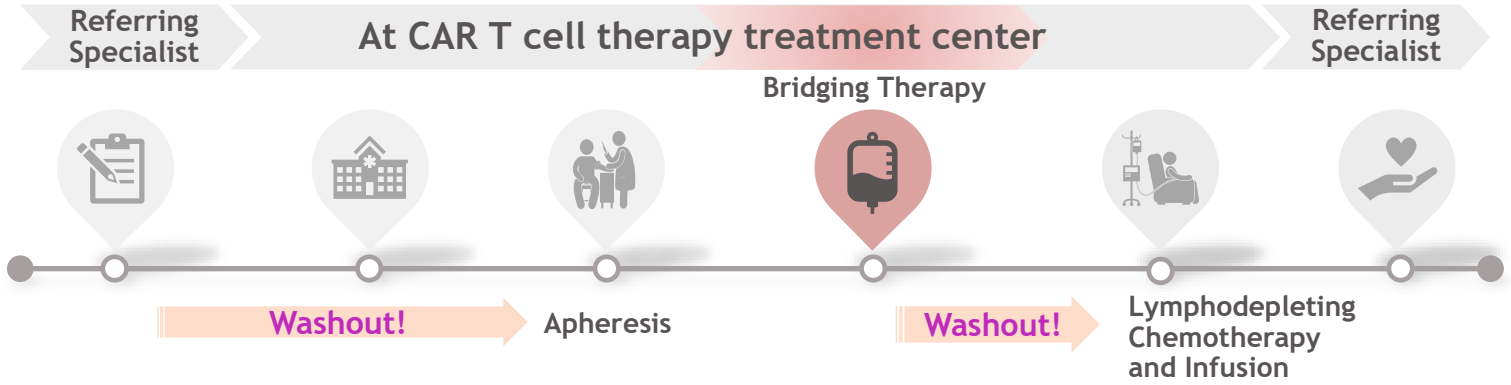
Close communication between the referring center and CAR T cell therapy treating institutions is important for coordination of bridging therapy delivery, especially when it is initiated at the referring center[1]

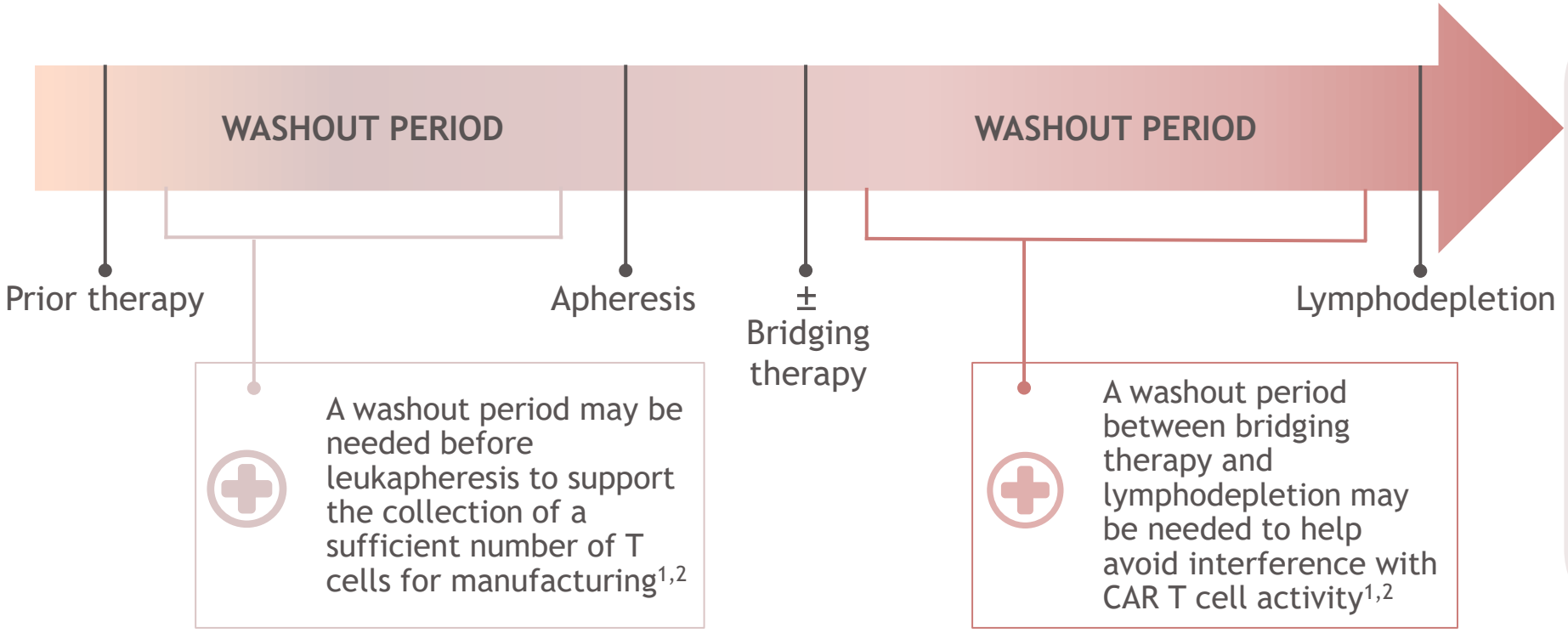
Regimens are highly variable and depend on: Disease Burden, Age, Co-morbidities, prior Response to Therapy etc.[1,2] **Examples** include[6-8]: Immuno-modulatory Agents, Corticosteroids, Monoclonal Antibodies.

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

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **3.** Levine BL, et al. *Mol Ther Methods Clin Dev*. 2016;4:92-101. **4.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **5.** Wall DA, Krueger J. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **6.** Pecher AC, et al. *JAMA*. 2023;329(24):2154-2162. **7.** Haghikia A et al. *Lancet Neurol*. 2023;22(12):1104-1105. **8.** Yuan Y et al. Presented at: ACR Convergence 2023; November 13, 2023; San Diego, CA. Abstract 1493.

Washout Periods May be Needed After Prior Therapy and/or Bridging Therapy





Washout periods should be discussed and coordinated between the referrer and CAR T cell therapy treatment team.[3]

References: 1. Wall DA, Krueger J. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **2.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **3.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10 (Suppl 3).

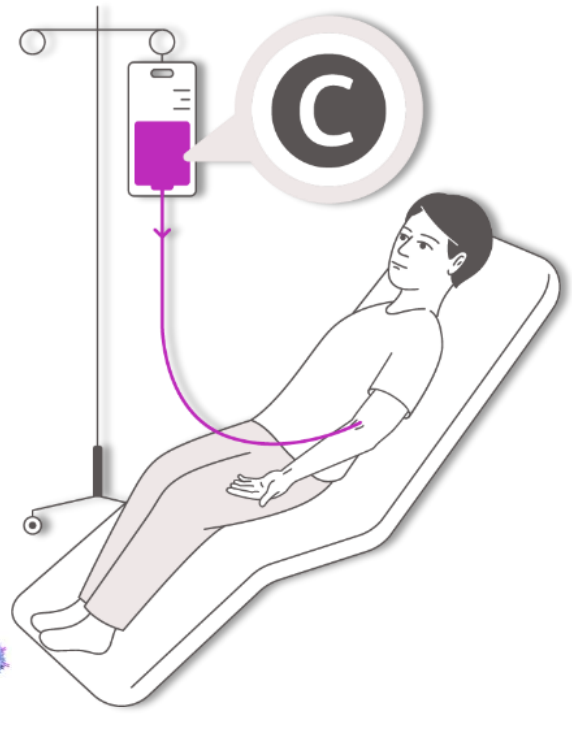
Lymphodepleting Chemotherapy to prepare the patient for CAR T cell Infusion

Main Goal: to prepare the patient so that the CAR T cells work and grow better after infusion[1]

CAR T recipients receive lympho-depleting chemotherapy (LDC) to prevent their immune system from destroying the infused CAR T cells.[2]

Lymphodepletion induces a favorable cytokine environment for CAR T cells and eliminates immunosuppressive elements, such as endogenous immune cells.[2]

These effects improve expansion, function and persistence of CAR T cells[1]



Typically, LDC is administered to patients on an outpatient basis for 3 days, a few days prior to CAR T cell infusion. The most frequently used combination for LDC is fludarabine/cyclophosphamide (flu/cy).[3-7]

LDC is given at lower doses. For the patient, this means that they may experience fewer side effects from LDC than they would from conventional chemotherapy.[3,8]

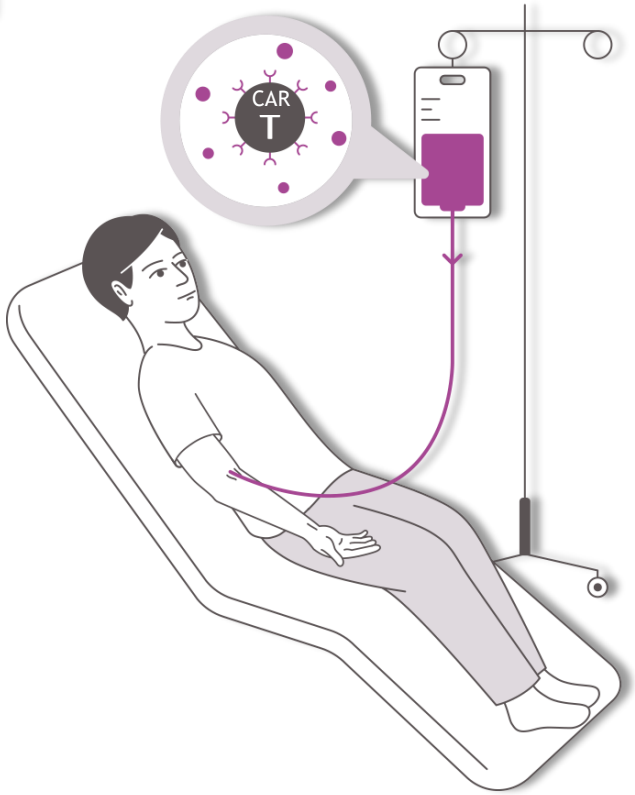
Major side effects of LDC include[9,10]: nausea, fatigue, edema, low blood counts, hair thinning (no major hair loss)

References: **1.** Turtle, CJ, et al. *Blood* 2015;126(33):184. **2.** Neelapu SS. *Blood*. 2019;133(17):1799-1800. **3.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **4.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05869955. **5.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05938725. **6.** ClinicalTrials.gov. Accessed October 30, 2023. https://clinicaltrials.gov/study/NCT05474885. **7.** Műzes G, Sipos F. *Cells*. 2023;12(11):1534. Published 2023 Jun 2. **8.** Owen K et al. *Cancer Immunol Immunother*. 2023;72(4):805-814. **9.** Krina Patel (MD Anderson Cancer Center). HealthTree University Myeloma YouTube page. What is Lymphodepleting Chemotherapy? Accessed November 15, 2023. https://www.youtube.com/watch?v=4-tSO18tCLI. **10.** BMT infonet.org. Steps Involved in CAR T-cell Therapy. Accessed December 14, 2023. https://www.bmtinfonet.org/car-t-cell/Steps%20Involved%20in%20CAR%20T-cell%20Therapy.

Infusion of CAR T cell Therapy Product and Short-Term Monitoring

CAR T cell infusion is usually done in an inpatient setting, and patients may remain hospitalized in a specialized CAR T unit ranging from at least 1 to 2 weeks.[1]

CAR T cells are infused into the patient generally over the course of 30 to 60 minutes, and is scheduled following the completion of lymphodepleting chemotherapy.[2]



Patients are monitored for signs and symptoms of cytokine release syndrome, neurotoxicity, and other adverse events at the CAR T treatment center ranging from at least 1 to 2 weeks following infusion at the certified healthcare facility.[2]

Patients will remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.[3,4]

References: 1. Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **2.** Lymphoma Canada. CAR-T Protocol Overview. Accessed October 30, 2023. https://www.lymphoma.ca/wp-content/uploads/2020/09/CAR-T-Protocol-Overview.pdf. **3.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10 (Suppl 3). **4.** McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024.

Long-term Monitoring following CAR T Infusion

Patients can be transferred back to their referring community specialist after at least 4 weeks of close monitoring and resolution of toxicities.[1]

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

Follow-up with the local specialist is personalized and may vary on a case-by-case basis[2]

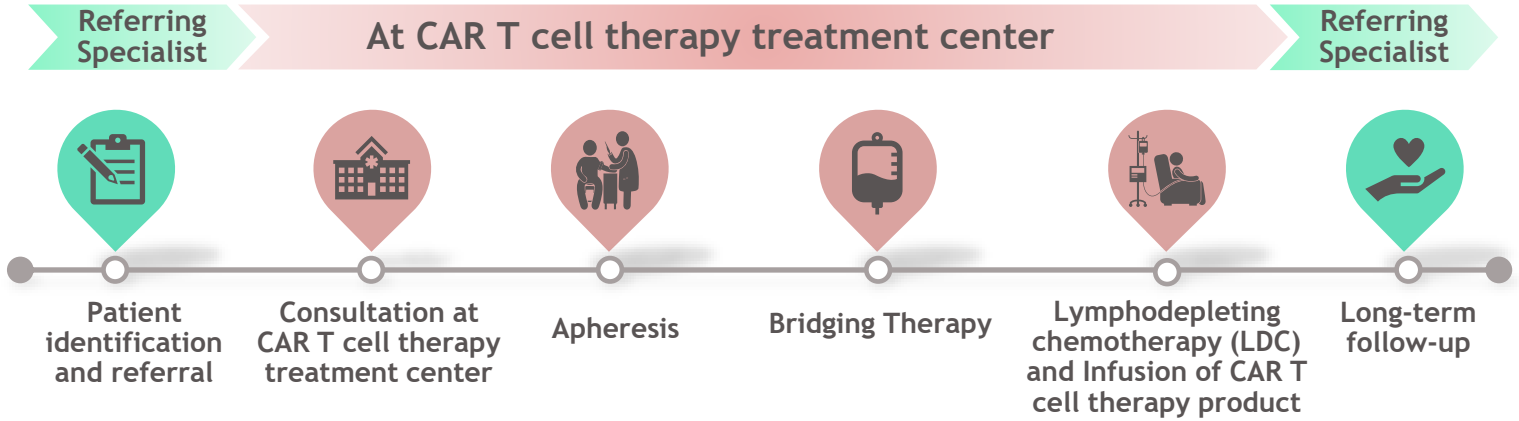
Elements of the long-term follow-up phase* include[3]:

- Monitoring disease status
- Managing persistent and/or delayed complications

*Follow-up of 15 years post-infusion mandated by the FDA.[4]

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.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **4.** U.S. Food and Drug Administration. Accessed October 30, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products.

Collaboration between Community Specialists and CAR T Treating Centers is Key



Patients will be co-managed by the community specialist (eg, rheumatology, neurology) and CAR T specialist leading up to infusion and following the initial post-infusion monitoring period.[1,2] Care can then be transitioned back to the community specialist.[3]

Non CAR T Specialist
Refers patients for CAR T cell therapy[1,3]

CAR T Treatment Team
The treating provider at a qualified treatment facility[4]

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[2,3,5]

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 provider.

References: 1. Schett G, et al. *Lancet*. 2023;402(10416):2034-2044. **2.** Hayden PJ, et al. *Ann Oncol*. 2022;33(3):259-275. **3.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(suppl 3):29-40. **4.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **5.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316.

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