CAR T 102: Introduction to the Patient Cell Therapy Journey

Bristol Myers Squibb™

Journey Through the CAR T Cell Therapy Process

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

Manufacturing

Patient identification[1,2]

- Appropriate patients are identified for treatment at qualified treatment sites or referring sites
- Early collaboration may facilitate timely referral and eligibility evaluation
- Once a patient is confirmed as eligible, leukapheresis is scheduled

Apheresis[1-4]

- Before apheresis, patients undergo a washout of prior medications that may affect T cell health to ensure optimal collection
- Physicians, APPs, and nurse coordinators all play a role in ensuring a proper washout occurs before apheresis
- Patients then undergo apheresis, which involves collection of white blood cells
- The collected apheresis product is then sent to the manufacturer

Bridging[1,3]

- 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 physicians and those treating with CAR T cell therapy

LDC and Infusion[1-3]

- LDC is administered prior to CAR T cell infusion to deplete endogenous T cells and create an environment for CAR T cell expansion
- Infusion will then occur at the certified treatment center

Monitoring and long-term follow-up[1,2]

- After infusion, patients are closely monitored for at least 4 weeks at the CAR T cell therapy treatment site, and side effects are promptly managed
- After at least 4 weeks, patients may be discharged back to the referring physician's care
- Communication continues between the CAR T cell therapy treatment center and the primary hematologist/ oncologist as patients are monitored long-term

APP, advanced practice provider; CAR, chimeric antigen receptor; LDC, lymphodepleting chemotherapy.

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.** Qayed M, et al. *Cytotherapy*. 2022;S1465-3249(22)00641-7.

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]
- Absence of clinically relevant comorbidities (eg, select cardiovascular, neurologic, or immune disorders)[3]
- 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 4 weeks after CAR T cell infusion[6]

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.

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.

Washout Periods Can Help Support Optimal T Cell Collection

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]

Washout periods prior to apheresis should be discussed between referring physicians and those treating with CAR T cell therapy to help minimize the impact of prior therapies on quality of circulating T cells[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.

Collection of T Cells Through Leukapheresis

T cells are collected for CAR T cell therapy through apheresis[1]

- Centrifugation is used to separate blood cells by density which allows for the collection of specific cell types[2]

Leukapheresis, the collection of white blood cells, may be performed in the outpatient setting[1,3]

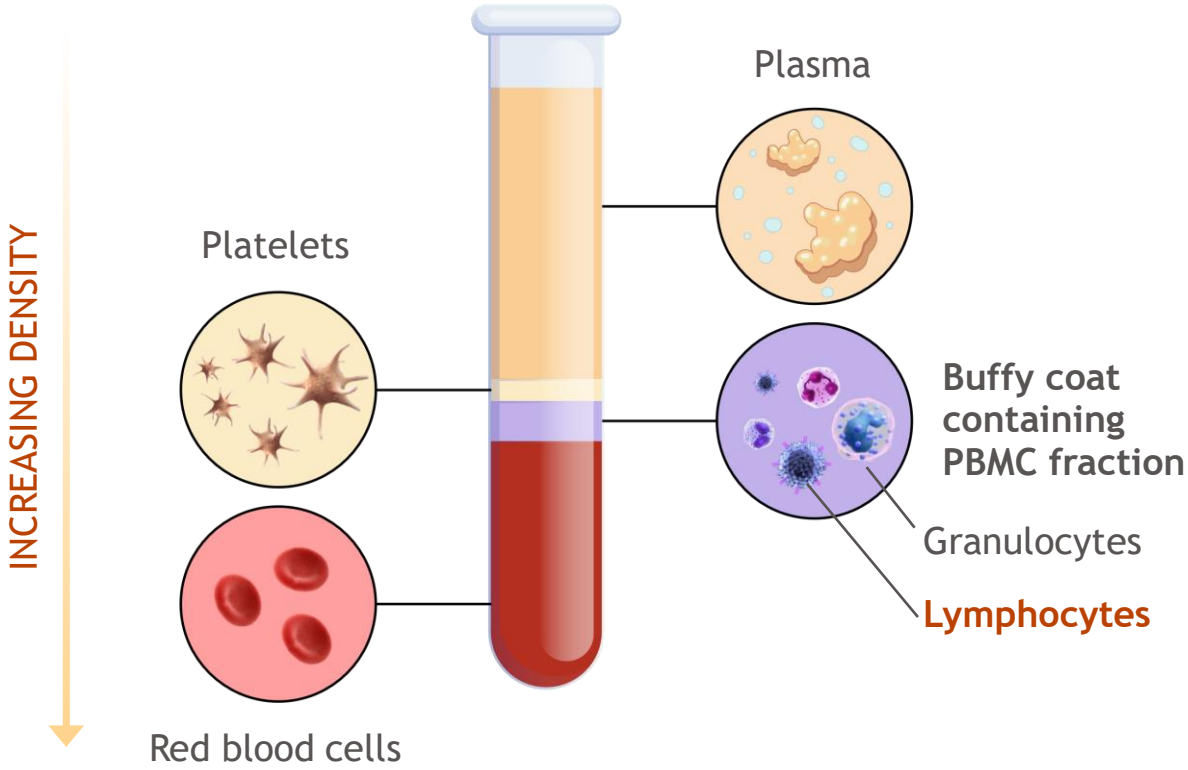
Coordination across the multidisciplinary team can help achieve an efficient leukapheresis collection[3]

Different machines and techniques may be employed to collect and ship leukapheresis products in accordance with the manufacturer's CAR T cell product-specific apheresis protocols and standards[1,2,a]

[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.** 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.

Separation of Blood Components for CAR T Cell Therapy[2]



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]

Refer to the Apheresis module for more information

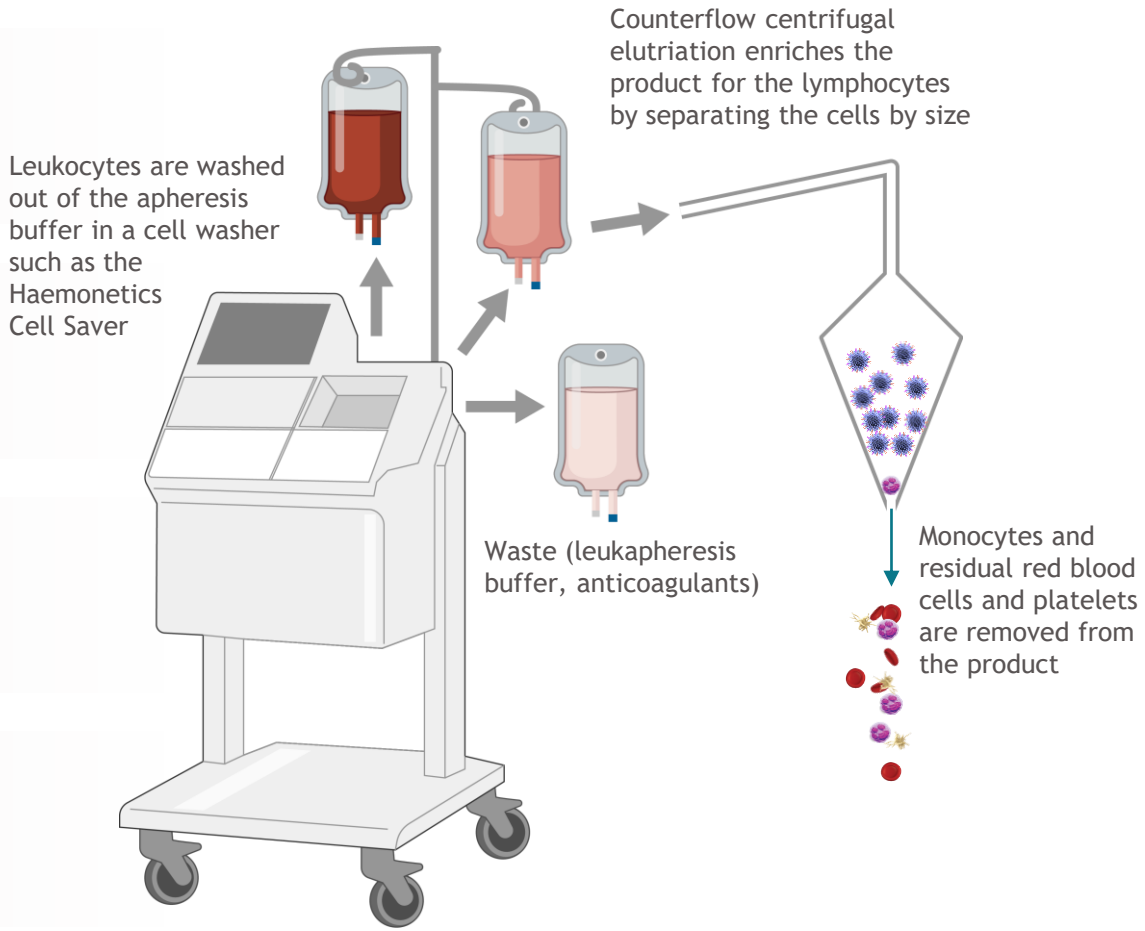
Selection and Activation of T Cells

Following collection at the treatment center, cells are shipped (fresh or frozen per product protocol) to the manufacturing site[1]

After a sufficient number of leukocytes has been harvested, the leukapheresis product is enriched for T cells. This can be done using a variety of methods, including counterflow centrifugal elutriation or antibody-specific beads[2]

This enrichment procedure involves washing the collected T cells, which may be further processed to remove any cells that inhibit T cell activation and expansion, such as monocytes[2]

The washed T cells are then activated with primary and costimulatory signals; a step necessary to prepare the cells for gene transfer[3]



References: **1**. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2**. Levine BL, et al. *Mol Therapy Methods & Clin Dev*. 2017;4:92-101. **3**. Wang X, Riviere I. *Mol Ther Oncolytics*. 2016;3:16015.

Gene Transfer Equips T Cells With Target-Specific Receptors

Gene transfer technology is used to express a chimeric antigen receptor (CAR) on T cells, conferring antigen specificity. These CAR T cells can thus be directed to a specific target by binding its surface antigen[1]

Gene delivery of the CAR may occur by viral or nonviral gene transfer systems[1-3]

Viral machinery may be used to introduce the genetic material that encodes the receptor for the CAR target via transduction of a ribonucleic acid (RNA) vector[2,3]

- This genetic material could encode any target currently utilized for CAR T cell therapy, such as B cell maturation antigen (BCMA)[4]

The RNA is then transcribed by the patient's cells and incorporated into the patient's deoxyribonucleic acid (DNA), allowing for CAR expression on the surface of T cells[2,3]

- For example, a BCMA CAR T cell would target the BCMA antigen expressed on myeloma cells[4]

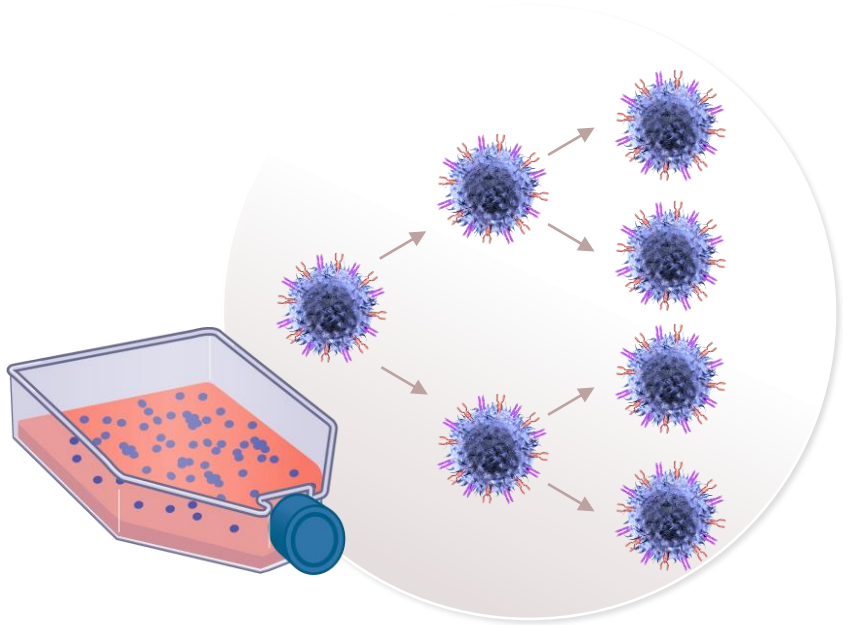
Refer to the CAR T 101 module for more information on target antigens

TCR, T cell receptor.

References: 1. Oluwole OO, et al. *J Leukoc Biol*. 2016;100:1265-1272. **2.** Levine BL, et al. *Mol Therapy Methods & Clin Dev*. 2017;4:92-101. **3.** Wang X, et al. *Mol Ther Oncolytics*. 2016;3:16015. **4.** Roex G, et al. *J Hematol Oncol*. 2020; 13:164.

CAR T Cells Are Expanded to a Therapeutic Dose Prior to Infusion

Once the T cells expressing CAR are selected, they are expanded, or grown, outside the body to an appropriate therapeutic dose[1,2]



When the cell expansion process is finished, the cell culture must be concentrated to a volume that can be infused into the patient[1]

The washed and concentrated cells are cryopreserved and transported to the treatment center. Depending on whether the product was shipped fresh or frozen, cells may need to be thawed prior to infusion[1]

References: 1. Levine BL, et al. *Mol Therapy Methods & Clin Dev*. 2017;4:92-101. **2.** Wang X, et al. *Mol Ther Oncolytics*. 2016;3:16015.

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

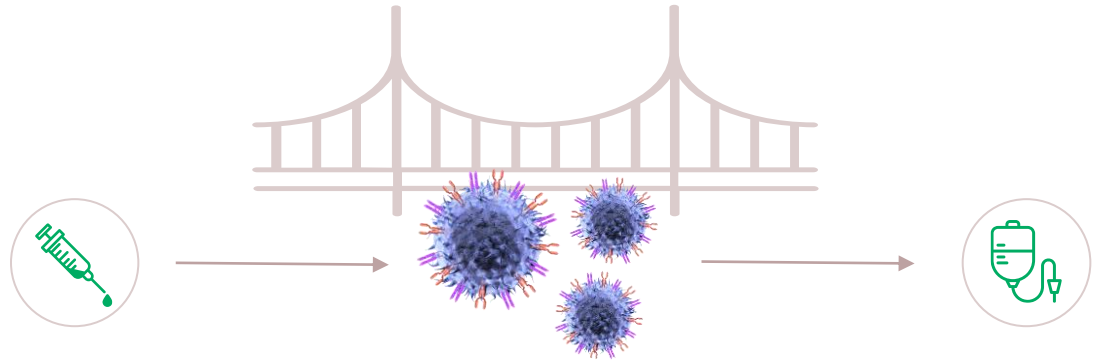
It can take several weeks before the CAR T cell product is manufactured and delivered to the patient, therefore patients that have active disease may require bridging therapy during this period[1,2]

Bridging chemotherapy regimens are variable and the treatment type utilized depends on the diagnosis, disease burden, prior toxicities, and age of the patient[1,3]

BRIDGING THERAPY GOALS[1]:

Maximize disease control

Minimize organ toxicity

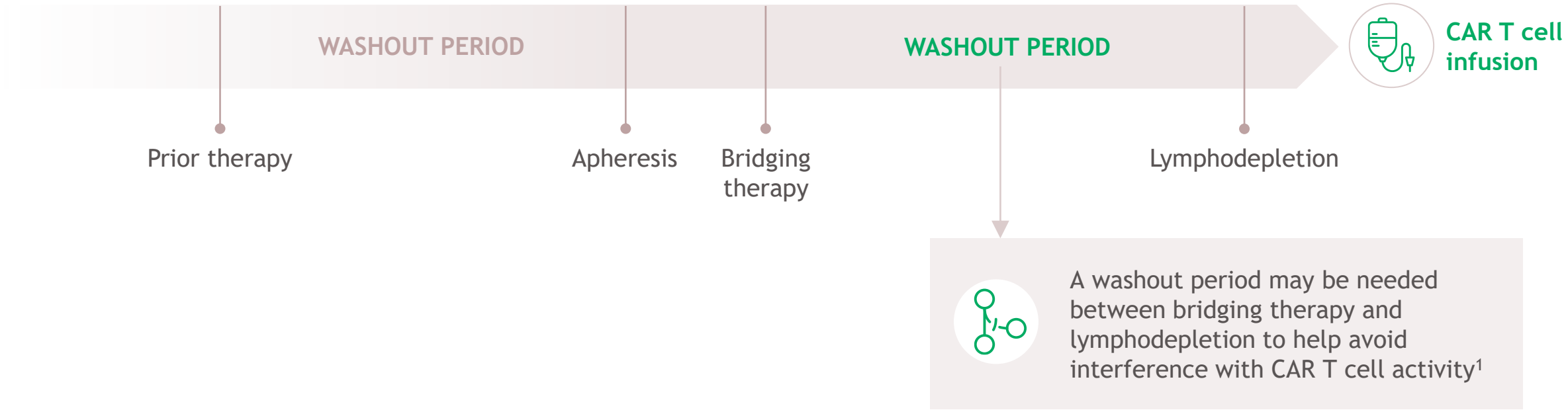


Appropriate bridging therapy should be discussed and coordinated between the referring physicians and those treating with CAR T cell therapy[4]

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



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References: 1. Wall DA, et al. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Lymphodepletion Creates a Favorable Environment for CAR T Cell Therapy Infusion

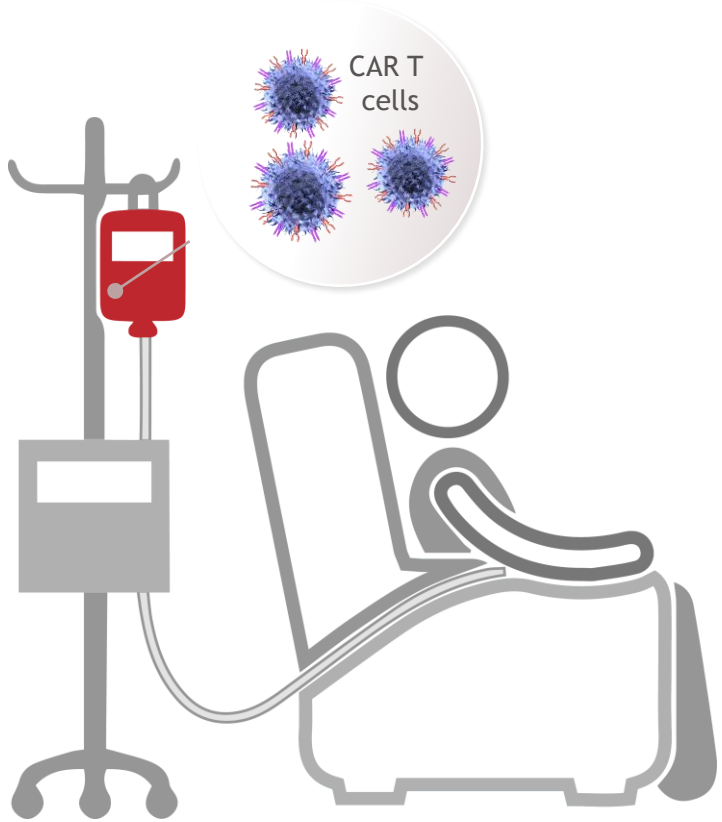
Lymphodepletion[1-3]

- The patient's healthcare team administers lymphodepleting chemotherapy (LDC; eg, low-dose fludarabine and cyclophosphamide) prior to infusion with CAR T cell therapy to deplete lymphocytes
- LDC is administered prior to CAR T cell infusion to deplete endogenous T cells and create an environment for CAR T cell expansion

Infusion[2,4,5]

Following completion of lymphodepletion, the patient's healthcare team administers the prepared CAR T cell therapy

- CAR T cell therapy may be administered in an outpatient setting depending on the patient's fitness and proximity to a hospital
- Administration guidelines vary depending on the CAR T cell therapy product

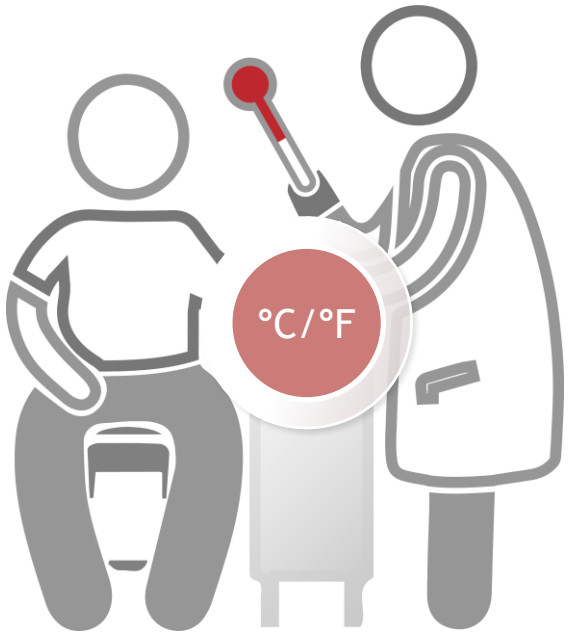


Refer to the Infusion module for more information

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.** Neelapu S. *Blood*. 2019;133(17):1799-1800 **4.** Wall DA, et al. *Curr Oncol*. 2020;27(suppl 2):S115-S123. **5.** Brudno J, et al. *Blood Revs*. 2019;34:45-55.

Monitoring Begins Promptly After Infusion

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



Patients should remain within proximity of the certified treatment center for at least 4 weeks following infusion[2]

- In the days following infusion, patients are monitored frequently for signs and symptoms of adverse events (eg, cytokine release syndrome and neurotoxicity)[2]

After at least 4 weeks, or when toxicities resolve, the patient may return to their referring provider for long-term follow-up (LTFU)[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.

Long-Term Monitoring Post-CAR T Cell Therapy

The LTFU phase occurs up to 15 years post-infusion, as recommended by the FDA.[4]
Patients should also be monitored life long for secondary malignancies[5-10]

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]

Refer to the Long-Term Follow-Up and Outpatient Monitoring modules for more information

LTFU may be conducted by a multidisciplinary team to monitor disease status and long-term side effects[2]

- Close communication between the non-CAR T hematologist and the treatment site is needed for ongoing patient follow-up[3]
- After 4 weeks post-CAR T cell therapy infusion, the CAR T specialist and non-CAR T hematologist/oncologist will work together to arrange the patients' return to the referring center[1]
  - The CAR T treatment center often provides clear guidance throughout the patient transition and is available to the referring center if questions arise once a patient has returned to their care[1]

References: **1**. Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(Suppl 3):29-40. **2**. Hayden PJ, et al. *Ann Oncol*. 2021;33(3):259-275. **3**. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **4**. US Food and Drug Administration. Accessed August 15, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products **5**. National Institutes of Health. DailyMed. Accessed June 27, 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed **6**. National Institutes of Health. DailyMed. Accessed August 15, 2023. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c **7**. National Institutes of Health. DailyMed. Accessed June 27, 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189 **8**. National Institutes of Health. DailyMed. Accessed June 27, 2022. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7d040b91-3fb8-41db-ba7f-60a36f06e2c2 **9**. National Institutes of Health. DailyMed. Accessed August 15, 2023. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022 **10**. National Institutes of Health. DailyMed. Accessed August 15, 2023. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59

Journey Through the CAR T Cell Therapy Process

Other steps of the CAR T journey will be covered in subsequent modules

Manufacturing

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Thank you for completing this module of CAR T Academy

We hope you found it informative and educational

- Follow this link to download a printable acknowledgment of completion: https://www.car-t-academy.com/pdf/intro-to-patient-cell-therapy-journey-acknowledgment.pdf
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- For more information and access to other CAR T Academy modules, please visit: https://www.car-t-academy.com