CAR T Cell Infusion

Bristol Myers Squibb™

Patient Journey Through the CAR T Cell Therapy Process

Patient selection → Patient consent & education → Patient screening → Leukapheresis and cell transport → CAR T manufacturing → Bridging and lymphodepleting chemotherapy → **CAR T infusion & patient monitoring** → Post hospital discharge monitoring → Long-term monitoring

1 Patient Identification

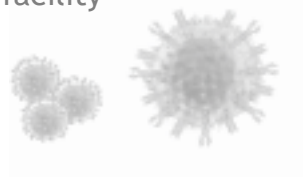
- Appropriate patients will be identified for treatment at qualified treatment sites or referring sites
- Company will be notified and leukapheresis and treatment dates will subsequently be scheduled

2 Leukapheresis

- Patient will undergo apheresis, which involves collection of white blood cells
- Collected apheresis product will be sent to the manufacturer for production

3 Manufacturing

The CAR T cell product is created at a manufacturing facility



4 Prep

- Patients may require bridging therapy to maintain disease control while the CAR T cell product is being manufactured
- Shortly prior to CAR T cell administration, the patient is prepared for treatment with lymphodepletion

5 Treat

- The CAR T cell product is delivered to the treatment site
- Product is administered

6 Monitor

- The patient is monitored closely for at least 4 weeks and side effects are promptly managed. Caregiver support is critical during this time
- Thereafter, the patient is periodically monitored long term

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

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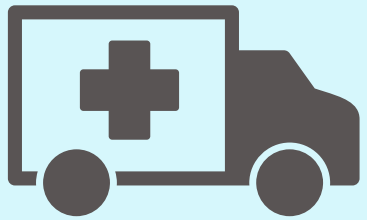
Please note: Each CAR T cell product is unique. Understanding the distinct features and toxicity profile for each product is essential for using these products in the clinic.

Shipment From Manufacturing Facility to Treatment Site

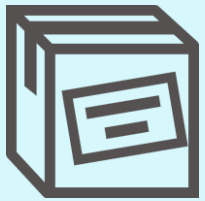
- Once successfully manufactured, CAR T cell products are formulated into a suspension and cryopreserved[1]
- Each product must pass quality tests before release for shipping as a frozen suspension[1–3]
- Each patient-specific product is typically packaged and stored in the vapor phase of liquid nitrogen[1,4]



The patient-specific product is then shipped to the treatment facility[1]

References: 1. Levine BL, et al. *Mol Ther - Methods Clin Dev*. 2017;4(March):92-101. **2.** Vormittag P, et al. *Curr Opin Biotechnol*. 2018;53:164-181. **3.** Li Y, et al. *Engineering*. 2019;5(1):122-131. doi:10.1016/j.eng.2018.12.003. **4.** Chen LN, et al. *Transfusion*. 2019;59(8):2506-2518.

Product Storage



CAR T cell products are delivered frozen and must be maintained in liquid nitrogen storage until being thawed immediately prior to use[2]

- Chain of Identity (COI) describes the ability to link a patient to their cells from the time of leukapheresis through product administration
- Throughout the CAR T cell therapy process, up through delivery to the treatment center and administration to the patient, it is critical that a CAR T cell product remains accurately linked to a specific patient at all times. Labels must be affixed to all product from collection to infusion to maintain COI[1,3,4]
  - Patient identifiers can include first name, last name, and date of birth
- If a site plans to store CAR T cell products on-site for a period of time, there may be regulatory or product-specific requirements for the site to meet in order to do so[2]

COI, chain of identity.

References: 1. Chen LN, et al. *Transfusion*. 2019;59(8):2506-2518. **2.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **3.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. 4. Papathanasiou MM, et al. *Cancer Gene Ther*. 2020.

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Preparing the Patient for Treatment

Before CAR T Cell Infusion

- Administer the lymphodepleting chemotherapy regimen[1]
- Schedule the patient's CAR T cell infusion after completion of lymphodepleting chemotherapy[2]
- Reasons for potential delay of infusion include, but are not limited to[1,3-6]:
  - Unresolved serious adverse reactions
  - Pulmonary reactions
  - Cardiac reactions
  - Hypotension
  - Active uncontrolled infections
  - Active graft-versus-host disease

Before CAR T Cell Infusion

- Premedication with acetaminophen and diphenhydramine (or another H1 antihistamine) are generally recommended to minimize the risk of infusion reactions[1,3-7]
- Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of CAR T cell therapy[1]

References: 1. Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **2.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. **3.** National Institutes of Heath. DailyMed. Accessed August 5, 2021. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **4.** National Institutes of Health. Accessed August 5, 2021. DailyMed. Available at https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **5.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. **6.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. **7.** National Institutes of Health. DailyMed. Accessed October 25, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022.

Pretreatment Considerations

Before you begin treatment with CAR T cell therapy, note the following:

- **Ensure that tocilizumab and emergency equipment are available prior to infusion and during the recovery period[1]**
- Monitor patients for signs and symptoms of infection before and after CAR T cell administration and treat appropriately.[2] CAR T cell therapy should not be administered to patients with clinically significant active systemic infections[3]
- Monitor complete blood counts prior to and after CAR T cell therapy administration[2]
- CAR T cell therapy may cause a false-positive HIV test result by some commercial tests[4,5]

HIV, human immunodeficiency virus

References: 1. Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24(6):1135-1141. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **3.** Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **4.** Hauser JR, et al. *J Clin Microbiol*. 2019;58:e01420-19. **5.** Ariza-Heredia EJ, et al. *Diagn Microbiol Infect Dis*. 2017;88(4):305-307.

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Product Preparation for Infusion[1-5]

Confirm the infusion time in advance, and adjust the start time of product thaw, if necessary

Match the patient's identity with the patient identifiers on the CAR T cell product documentation

Remove the CAR T cell product and verify that the contents match the product documentation

(continued on next slide)

References: 1. National Institutes of Heath. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **2.** National Institutes of Health. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **3.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. **4.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. **5.** National Institutes of Health. DailyMed. Accessed October 25, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022.

Product Preparation for Infusion (cont.)

Inspect the product for any breaches of container integrity (breaks, cracks) and confirm appropriate patient identifiers upon receipt[1]

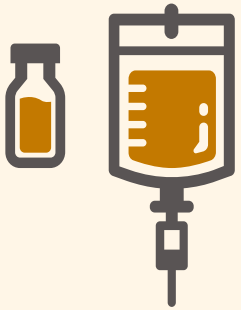
Thaw the CAR T cell product per the product manufacturer's specific guidance[2-6]

Refer to the product's specific prescribing information for the expiration time following thawing. Ensure that the dose is administered to the patient before the expiration period[2-6]

References: 1. Yakoub-Agha I, et al. *Haematologica*. 2020;105(2):297-316. **2.** National Institutes of Heath. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **3.** National Institutes of Health. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **4.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. 5. National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. **6.** National Institutes of Health. DailyMed. Accessed October 25, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022.

Line Set Up and Infusion[1-5]

- Refer to the CAR T cell product's specific prescribing information for details on how to administer the particular CAR T cell product
- Before, during, and after administration, follow universal precautions and local biosafety guidelines for handling and disposal to avoid potential transmission of infectious diseases



Please refer to the product prescribing information for specific guidance regarding line set up and infusion[6]

IV, intravenous.

References: 1. National Institutes of Heath. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **2.** National Institutes of Health. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **3.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. **4.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. 5. National Institutes of Health. DailyMed. Accessed October 25, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022. **6.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34.

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Sites of Infusion

Some clinical trials or products require **inpatient admission** for administration and post-infusion monitoring

- Inpatient admission may be necessary to manage the unique toxicities (eg, CRS, neurotoxicity) associated with CAR T cell therapy

Outpatient Centers

Certain CAR T cell products were administered in the outpatient setting in clinical trials

- Whether or not outpatient administration is appropriate will be up to the prescribing physician, dependent on what is appropriate for the patient, based on patient-specific considerations, including but not limited to severity of disease, caregiver support, and proximity to the treatment center
- Feasibility will also depend on the product and institutional infrastructure

CRS, cytokine release syndrome.

Reference: 1. Chow VA, et al. *Blood*. 2018;132:777-781.

REMS Requirements for CAR T Cell Infusion

Given the risk of CRS and neurotoxicity, approved CAR T cell products are available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)[1-7]

Select required components:

- Healthcare facilities that dispense and administer a specific CAR T cell product must be enrolled and comply with the REMS requirements for that product[1]
- Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after CAR T cell infusion, for the potential treatment of CRS[3-7]
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense, or administer the CAR T cell product are trained about the management of CRS and neurologic toxicities[3-7]

Please refer to the product prescribing information for REMS requirements specific to the product and additional AEs associated with CAR T therapy

AE, adverse event; CRS, cytokine release syndrome.

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23(2):27-34. **2.** FDA. Accessed July 23, 2020. https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. **3.** National Institutes of Heath. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=594bb413-af3b-4b97-afb3-bfe2b174f2ed. **4.** National Institutes of Health. DailyMed. Accessed August 5, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b90c1fe7-f5cc-464e-958a-af36e9c26d7c. **5.** National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=aad3ba54-dfd3-4cb3-9e2b-c5ef89559189. 6. National Institutes of Health. DailyMed. Accessed August 10, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59. **7.** National Institutes of Health. DailyMed. Accessed October 25, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a16108c2-7ca7-45af-965e-54bda4713022.

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Team Coordination Is Key Before, During, and After CAR T Cell Infusion

Before Infusion[1]

Evaluate the patient for CAR T cell therapy based on physical assessment, medical records, laboratory assessment, treatment history, and other relevant information

During Infusion[1]

Infusion should be conducted by staff appropriately trained on the specific CAR T cell therapy

After Infusion[2]

Nursing staff, pharmacists, treating physicians, and primary hematologists should maintain close communication to identify patients experiencing toxicity and rapidly intervene

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019:34:45-55.

Summary (1)

Handling Guidelines

- Patient-specific CAR T cell products are typically cryopreserved, individually packaged, and shipped to the treatment facility
- The CAR T cell product typically will be stored frozen in the vapor phase of liquid nitrogen until ready for infusion

Patient Preparation

- Lymphodepleting chemotherapy should be administered prior to CAR T cell infusion, with CAR T cell administration scheduled following completion
- Patients should be evaluated by a healthcare provider qualified in delivering CAR T cell therapy on the day of infusion to assess for any clinical concerns that might require a delay in treatment delivery
- To minimize risk of infusion reactions, patients should receive acetaminophen and H1 antihistamines just before CAR T cell product infusion

Summary (2)

Product Preparation

- Because autologous CAR T cell products are patient-specific therapies, it is important to match the patient's identity to that of the product at all steps prior to infusion
- When the patient is ready to receive the CAR T cell product, the therapy must be thawed before use, which requires coordinated timing and reference to the product-specific guidance for thawing and preparation
- Intravenous line set up and infusion should be performed in accordance with product-specific labeling

Product Guidelines

- CAR T cells can be administered at the treating physician's discretion in the inpatient and/or outpatient settings, depending on the product and patient considerations, as well as the capabilities of the treatment site
- Due to the risk of CRS and neurologic toxicities, CAR T cell products are only available through restricted REMS programs, and treatment sites and healthcare providers need to be trained on the product-specific REMS programs in order to treat patients

Multidisciplinary Team Coordination

- Delivering optimal care to patients receiving CAR T cell therapy requires multidisciplinary collaboration before, during, and after CAR T cell infusion

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/car-t-academy-cell-infusion-acknowledgment.pdf
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