Bristol Myers Squibb®

CAR T ACADEMY

Bridging Therapy and Lymphodepleting Chemotherapy

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 qualified treatment center

Monitoring and long-term follow-up[1,2,5]

- 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
- 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. **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

CAR T Academy: Bridging Therapy and Lymphodepleting Chemotherapy

01: BRIDGING THERAPY

02: LYMPHODEPLETION

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

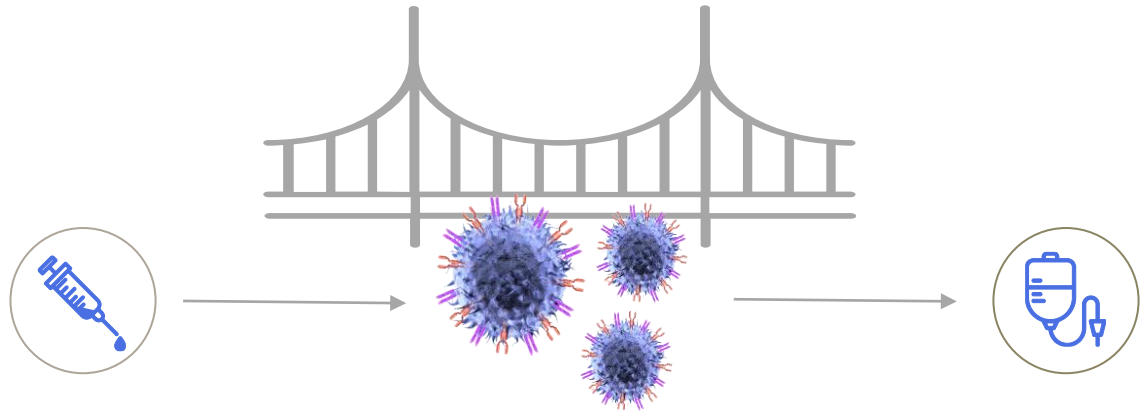
Following leukapheresis, it can take several weeks before the CAR T cell product can be manufactured and delivered to the patient[1,2]

Because most patients undergoing CAR T cell therapy have active disease, some will require bridging therapy during this period[1]

BRIDGING THERAPY GOALS[1]:

Maximize disease control

Minimize organ toxicity



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.

Coordination and Delivery of Bridging Therapy

The referring physician and CAR T cell therapy treatment center work together to carefully plan and select bridging therapy with the aim to avoid patient harm or delay CAR T cell infusion[1,2]

- Bridging therapy is typically delivered at the referring institution or CAR T cell therapy treatment center[2]
- Patients are closely monitored for infections and other toxicities during the bridging therapy phase[2]

Close communication between treating institutions and CAR T cell manufacturing sites is important for adjusting bridging therapy delivery (eg, if there are delays in CAR T cell manufacturing)[1]

References: 1. McGuirk J, et al. *Cytotherapy*. 2017;19:1015-1024. **2.** Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34.

Possible Bridging Therapy Options

Regimens are highly variable and depend on[1]:

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

Examples of bridging therapy regimens:

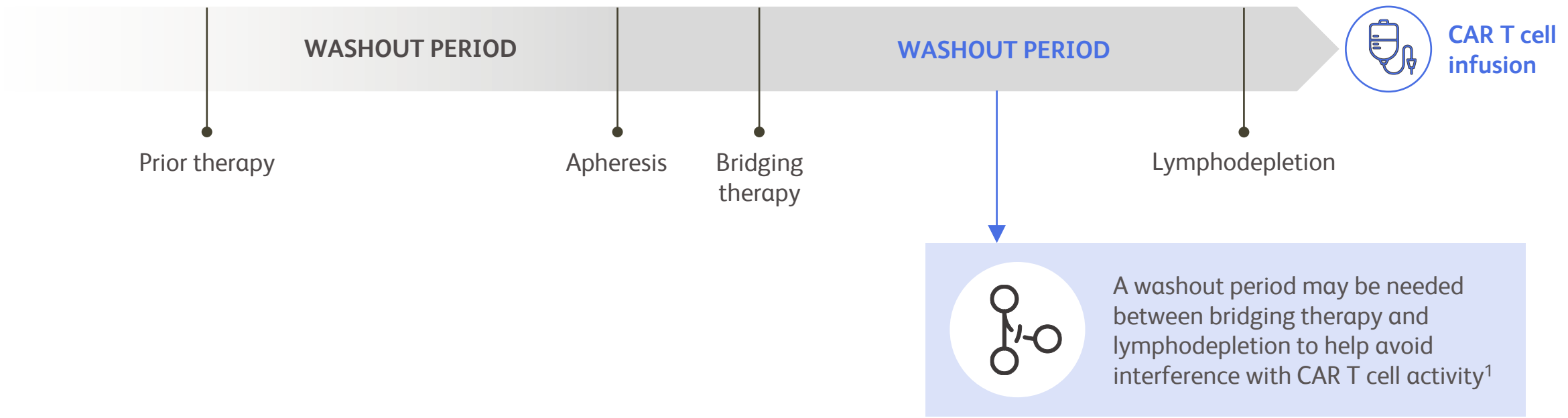
- Chemotherapy (oral or IV)
- Immunomodulatory agents[2]
- Radiation therapy[1]
  - For symptomatic or large masses
- Monoclonal antibodies[2]
- Antibody-drug conjugates[3]
- Corticosteroids, including high-dose steroids[1,2]
- Lower-intensity regimens (as appropriate for certain patients)[1]

Targeted agents and/or novel agents may also be utilized, provided they yield a rapid reduction in tumor burden and will not produce lasting effects that may adversely influence CAR T cell therapy[1]

IV, intravenous.

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

Washout Periods May be Needed Between Bridging Therapy and Lymphodepletion



Washout periods should be discussed and coordinated between the referring physicians and those treating with CAR T cell therapy[2]

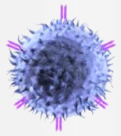
References: 1. Wall DA, et al. *Curr Oncol.* 2020;27(suppl 2):S115-S123. **2.** Beaupierre A, et al. *Clin J Oncol Nurs.* 2019;23:27-34.

CAR T Academy: Bridging Therapy and Lymphodepleting Chemotherapy

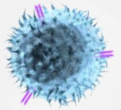
01: BRIDGING THERAPY

02: LYMPHODEPLETION

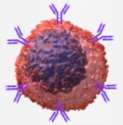
Key Immune Cells and Molecular Components Affected By Lymphodepleting Chemotherapy



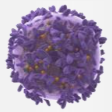
Cytotoxic T cell
- A type of lymphocyte that has antigen-specific surface receptors
- Functions involve killing infected/abnormal cells by inducing apoptosis



Regulatory T cell
- A type of lymphocyte that has antigen-specific surface receptors
- Functions involve suppressing immune responses through secretion of immunosuppressive cytokines or cell-to-cell contact



B cell
- A type of lymphocyte that has antigen-specific surface receptors
- Functions include presenting antigens to T cells and developing into plasma cells that produce antibodies



Natural killer cell
- A type of lymphocyte that lacks antigen-specific surface receptors
- Functions involve killing infected/abnormal cells by inducing apoptosis
- Important for tumor surveillance

Cytokines
- Polypeptides secreted by immune and other cells
- Serve as signaling molecules to influence the magnitude of inflammatory and immune responses
- Act sequentially, synergistically, or antagonistically

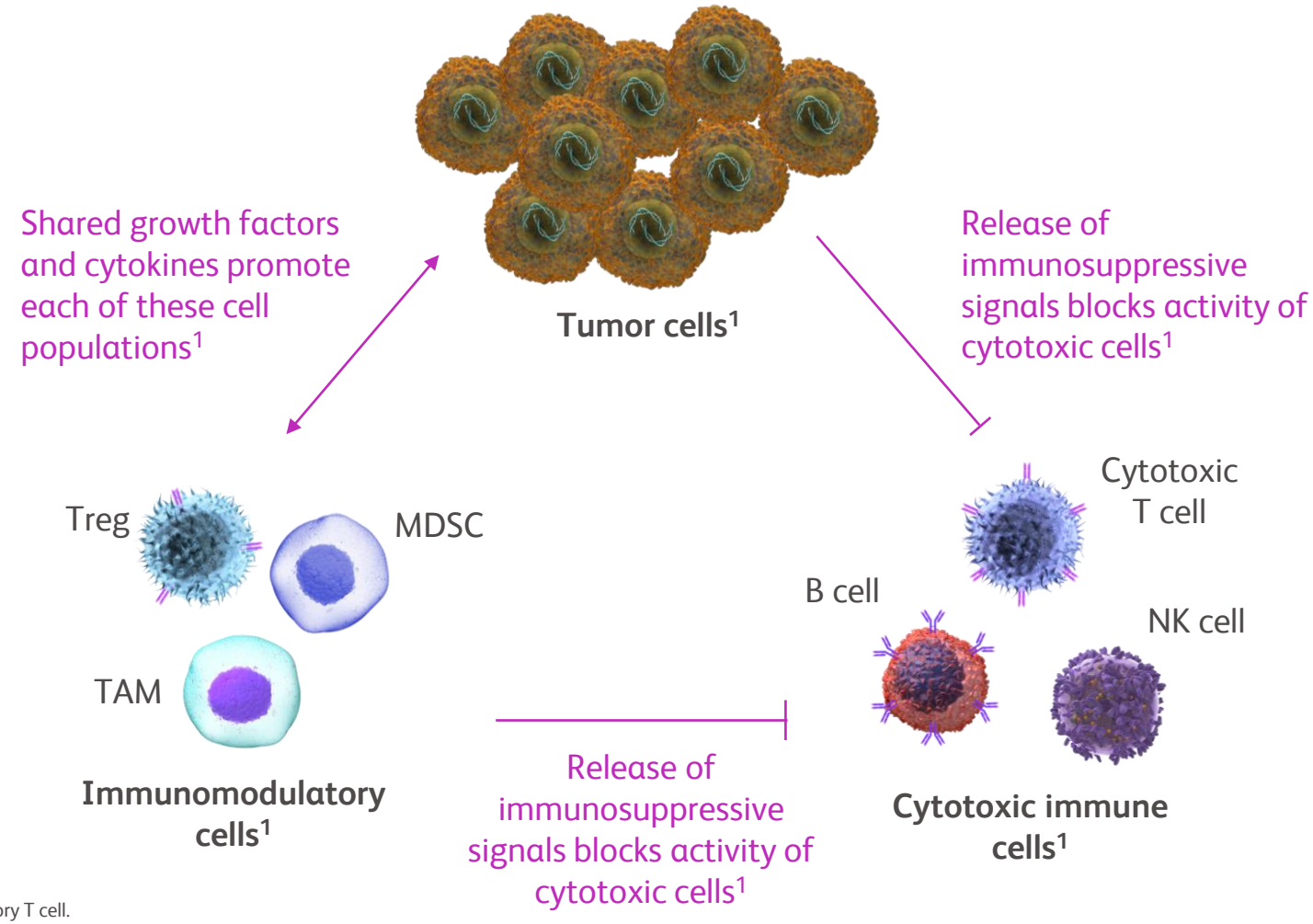
Reference: Delves PJ. *Merck Manual Professional Version.* Last updated Dec 2018.

Immunosuppression Results in Imbalances in Cell Activity

Tumor cells acquire the ability to escape detection and killing by cytotoxic immune cells by:

- Production of signals that downregulate anti-tumor immune responses[1]
- Downregulation of signals that activate anti-tumor immune responses[1]
- Recruitment of immunomodulatory cells (eg, MDSCs, Tregs, TAMs) that suppress anti-tumor immune responses[1,2]

These various mechanisms may contribute to the typically poor response of aggressive tumors and late-stage cancers to immunotherapies[1]

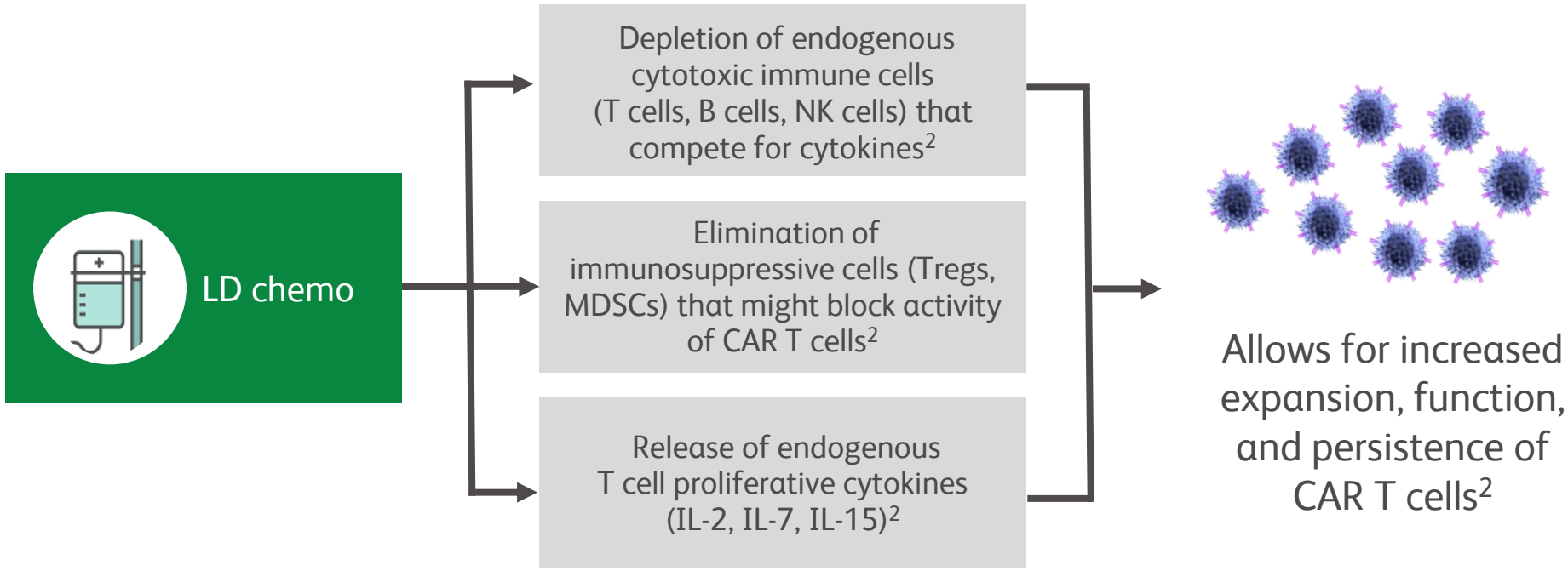


MDSCs, myeloid-derived suppressor cells; NK, natural killer; TAM, tumor-associated macrophage; Treg, regulatory T cell.

References: 1. Wang Y, et al. *Cancer Drug Resist.* 2019;2:1-20. **2.** Sterner RC, Sterner RM. *Blood Cancer J.* 2021;11(4):69.

Purpose of Lymphodepleting Chemotherapy (LD Chemo)

Primary aim: prepare the patient for CAR T cell infusion by depleting endogenous immune cells; not used to control disease[1]



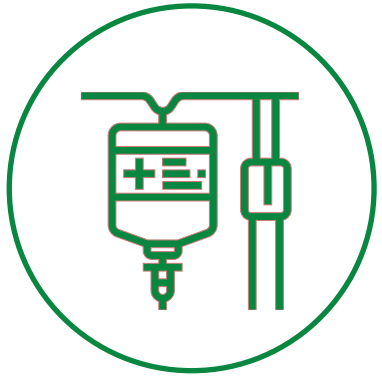
IL, interleukin; MDSCs, myeloid-derived suppressor cells; NK, natural killer; Tregs, regulatory T cells

References: 1. Beaupierre A, et al. *Clin J Oncol Nurs*. 2019;23:27-34. **2.** Neelapu SS. *Blood*. 2019;133:1799-1800.

Multiple LD Chemo Regimens Have Been Used in CAR T Cell Therapy Trials

Examples of lymphodepleting therapy regimens:

- Cyclophosphamide[1]
- Fludarabine + cyclophosphamide[1]
- Pentostatin + cyclophosphamide[1]
- Bendamustine-based regimens[1]
- Disease-specific regimens[1]



Fludarabine + cyclophosphamide is a commonly used regimen[1,2]

LD, lymphodepletion.

References: 1. Brudno JN, Kochenderfer JN. *Blood Rev.* 2019;34:45-55.
2. Perica K, et al. *Biol Blood Marrow Transplant.* 2018;24:1135-1141.

Lymphodepleting Chemotherapy is an Important Step in the CAR T Process But May Cause Toxicity

Lymphodepleting chemotherapy may contribute to the development of adverse effects, such as cytopenias and infections[1]

With the goal of reducing adverse events, clinicians should:[1-3]

- Remain vigilant for myelosuppression and infections
- Consider dose-reductions for patients with increased sensitivity to fludarabine and cyclophosphamide (eg, existing cytopenias, renal insufficiency)

References: 1. Lickefett B, et al. *Front Immunol.* 2023;14:1-19. **2.** Amini L, et al. *Nat Rev Clin Oncol.* 2022; 19(5):342-355. **3.** LymphmaHub. Accessed September 26, 2025. https://lymphomahub.com/medical-information/preparing-for-car-t-cell-therapy-patient-selection-bridging-therapies-and-lymphodepletion

Delivery of LD Chemo

- Patients are treated with LD chemo several days before CAR T cells are infused[1]
- Coordinated by the treating facility, and can be delivered in the inpatient or outpatient setting[2]
- Active infection must be excluded or under control prior to the start of LD chemo[3]

Patients should have a caregiver that meets certain expectations[2]

Expectations for Caregivers During LD Chemo[2]

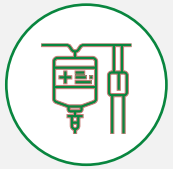
- ✓ Be at least 18 years old
- ✓ Be able to drive
- ✓ Stay with the patient 24 hours/day in the outpatient setting
- ✓ Live with the patient at a place within close proximity of the treating facility
- ✓ Transport patient to/from appointments
- ✓ Actively engage with the medical team
- ✓ Manage and administer the patient's medications
- ✓ Practice good home precautions
- ✓ Contact the medical team with any questions or regarding any symptoms or adverse events

References: 1. Perica K, et al. *Biol Blood Marrow Transplant.* 2018;24:1135-1141. **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.

Summary

Bridging therapy[1]

- Some patients may receive bridging therapy while CAR T cell therapy is being manufactured
- The purpose is to maximize disease control and minimize organ toxicity until CAR T cell therapy can be delivered
- The specific regimens used depends on the specific disease diagnosis, disease burden, patient age, comorbidities, and prior response to therapy
- Treatment is carefully planned and selected so as not to cause patient harm or delay CAR T cell infusion



Lymphodepleting chemotherapy[2-5]

- The purpose is to prepare the patient for CAR T cell infusion by depleting endogenous T cells—not to control disease
- This treatment elicits several effects that help increase the expansion, function, and persistence of CAR T cells
- Patients typically receive lymphodepleting chemotherapy several days prior to CAR T cell infusion
- Fludarabine + cyclophosphamide is a commonly used regimen

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.** Neelapu SS. *Blood*. 2019;133:1799-1800. **4.** Perica K, et al. *Biol Blood Marrow Transplant*. 2018;24:1135-1141. **5.** Brudno JN, Kochenderfer JN. *Blood Rev*. 2019;34:45-55.

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