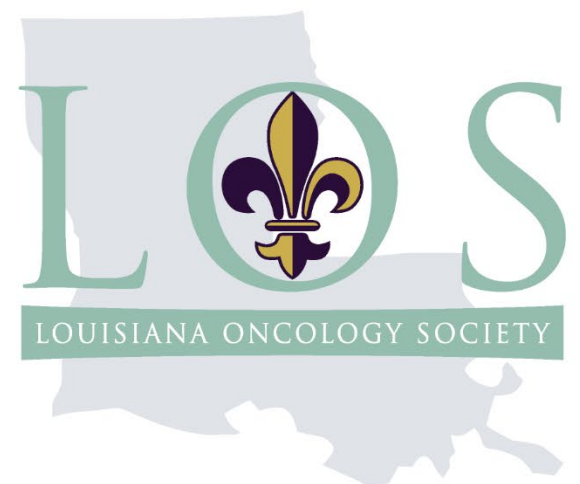


The CD19 CAR T-cell Therapy Journey

Clark Alsfeld, MD

Attending Physician

Ochsner MD Anderson Cancer Center



Learning Objectives

- Review qualifications for CD19 CAR T-cell therapy
- Describe the CAR T-cell therapy journey
- Discuss coping with CAR T-cell therapy both short- and long-term complications

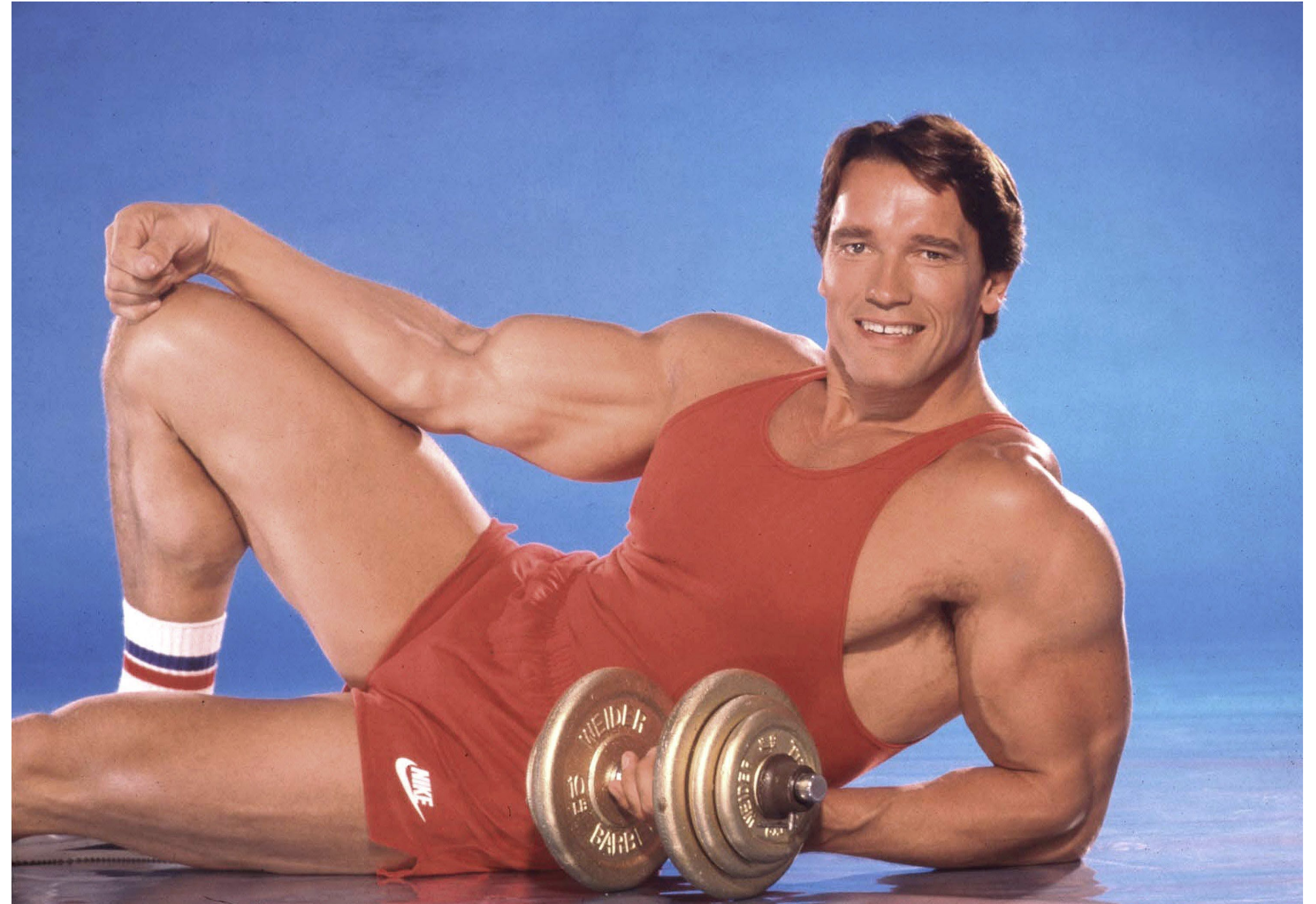
CAR T-cell Therapy Qualifications

FDA Approved CD19 CAR T-cell Products

<p>YESCARTA Axicabtagene ciloleucel</p>	<p>BREYANZI Lisocabtagene maraleucel</p>
<ol style="list-style-type: none"> 1. Refractory DLBCL 2. Two or more lines: <ul style="list-style-type: none"> • DBLCL • PMBCL • HGBCL • Transformed FL <ul style="list-style-type: none"> • FL 	<ol style="list-style-type: none"> 1. Refractory DLBCL 2. Two or more lines: <ul style="list-style-type: none"> • DLBCL • HGBCL • PMBCL • FL grade 3B • *CLL/SLL
<p>KYMRIAH Tisagenlecleucel</p>	<p>TECARTUS Brexucabtagene autoleucel</p>
<ol style="list-style-type: none"> 1. R/R B-cell ALL (<26 yo) 2. Two or more lines: <ul style="list-style-type: none"> • DLBCL • HGBCL • Transformed FL <ul style="list-style-type: none"> • FL 	<ol style="list-style-type: none"> 1. R/R MCL 2. R/R B-cell ALL

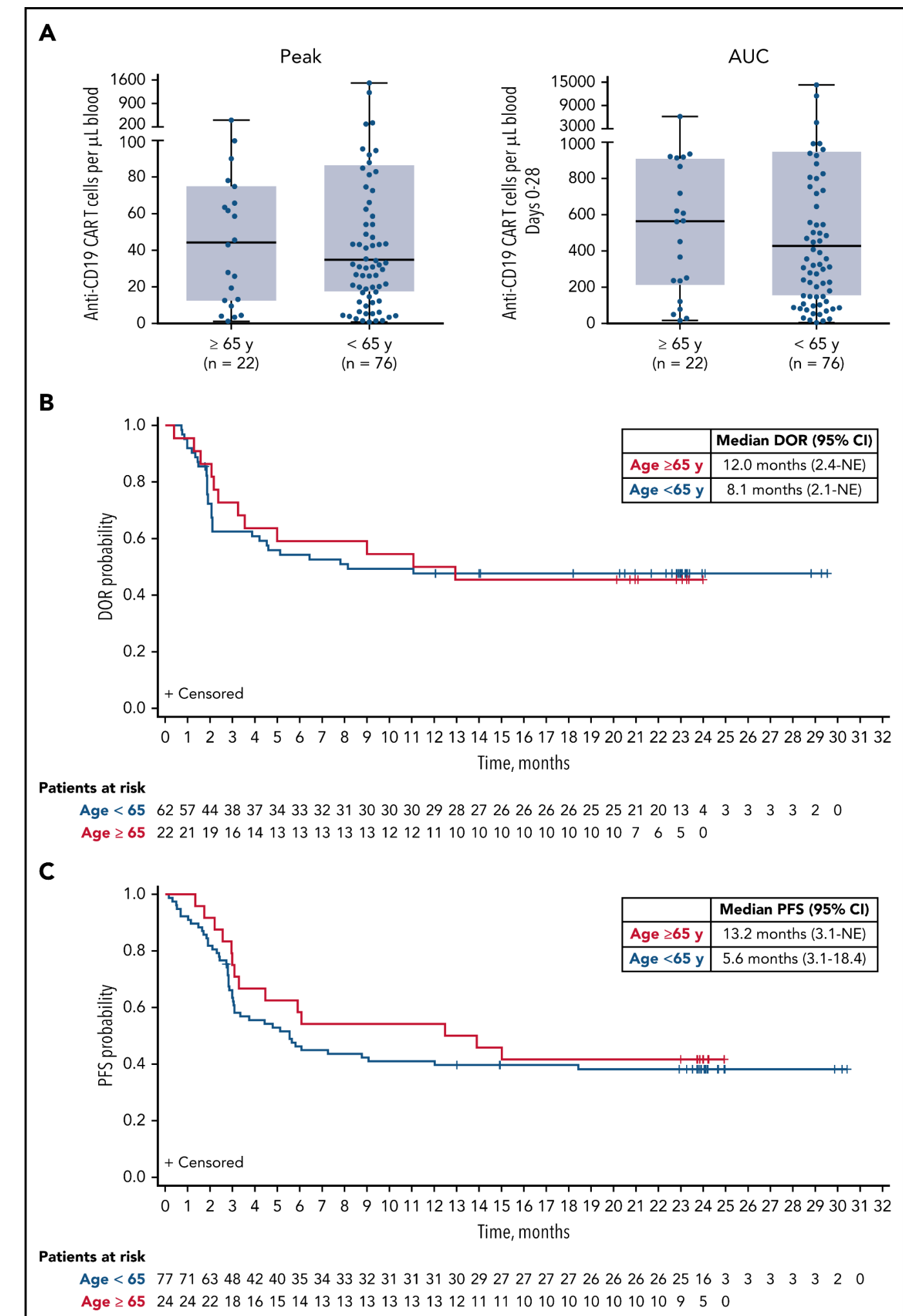
Patient Characteristics

- Age
- Organ function
- Disease status
- Infection
- Prior treatment
 - Bendamustine



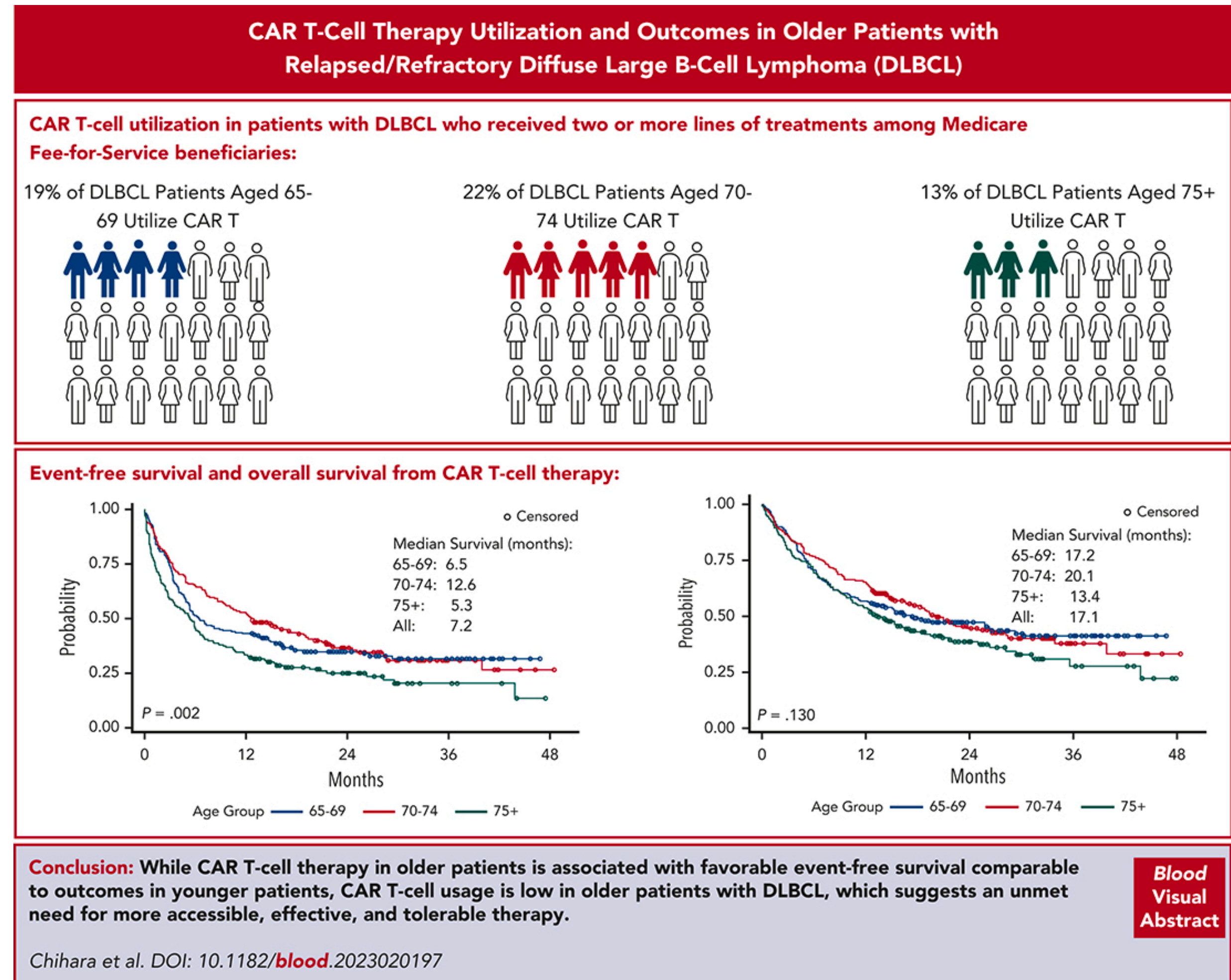
CART in Older Patients

- Subgroup analysis of ZUMA-1:
 - Response rates similar (ORR 92%, CR 75%)
 - No increase in adverse events
 - G3-4 CRS: 7%
 - G3-4 neurotox: 44%
 - G3-4 infections: 19%
 - Outcomes were better compared to SCHOLAR-1



CART in Older Patients

- Real world data for CART in patients age >65 in 3L setting:
 - EFS and OS comparable (lower in >75)
 - Utilization of CART was poor (20%)



Pre-CART Evaluation

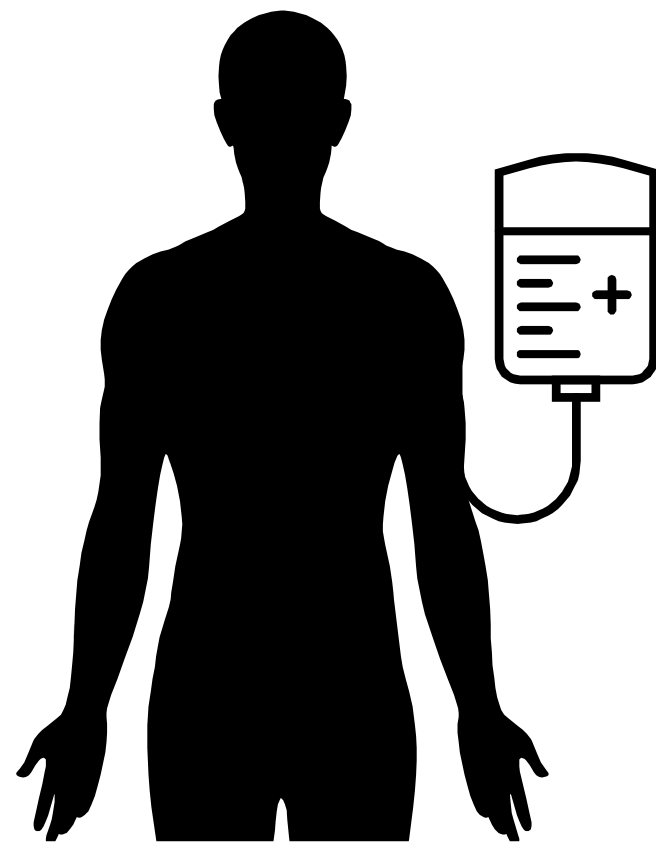
- Baseline labs
- Infectious workup (including CMV)
- Echocardiogram
- Electrocardiogram
- Pulmonary function test
- PET/CT
- MRI brain
- SW assessment
- Psychological assessment
- Pharmacist evaluation

CAR T-cell Journey

Autologous CAR T-Cell Therapy: Underlying Principles

Leukapheresis

Collect patient's white blood cells

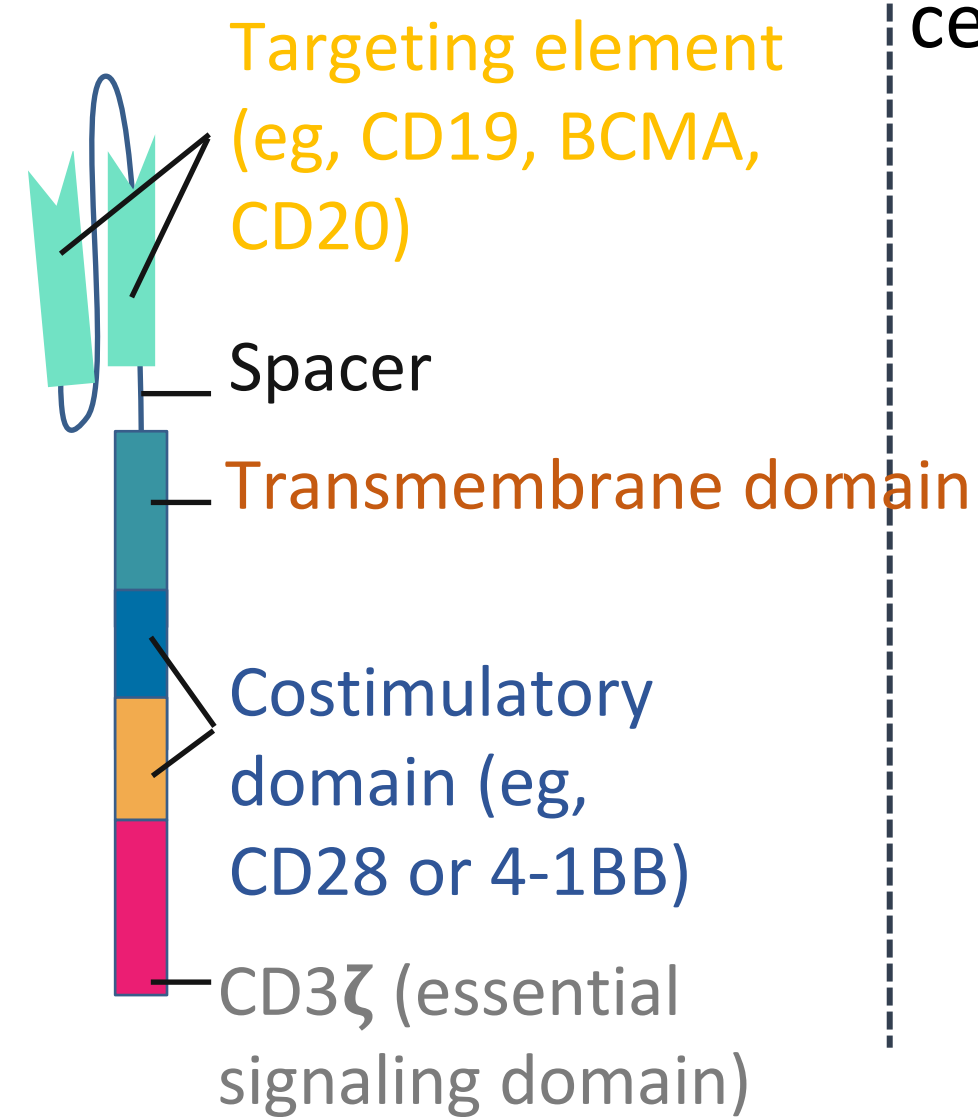
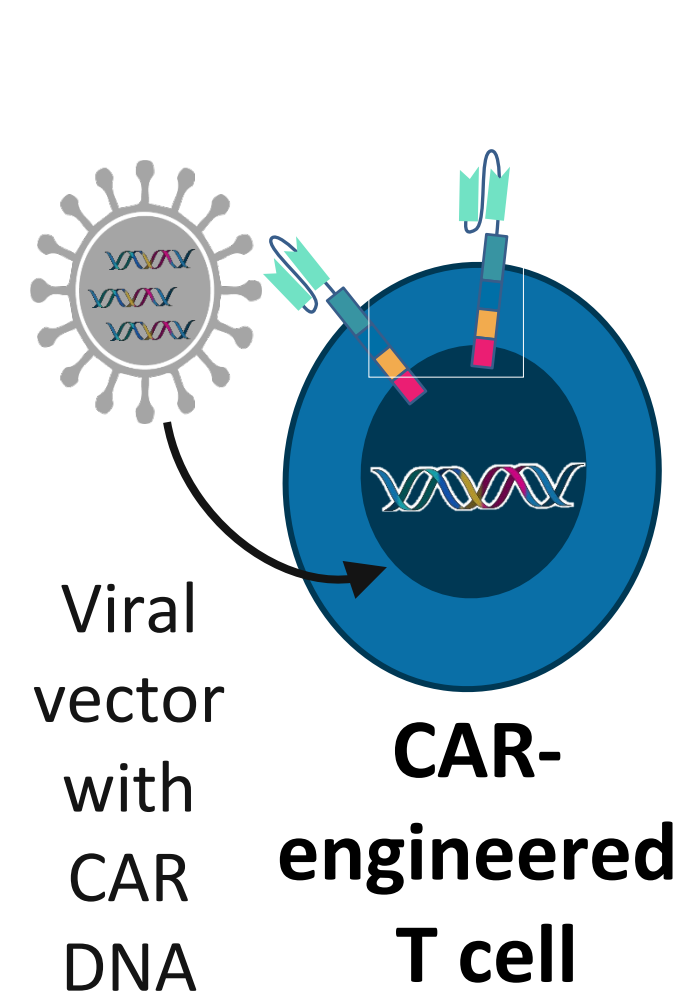


Manufacturing

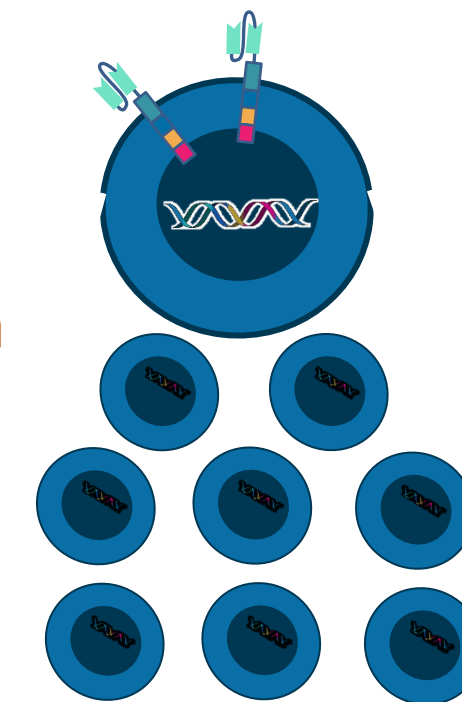
Isolate and activate T cells



Engineer T cells with CAR gene

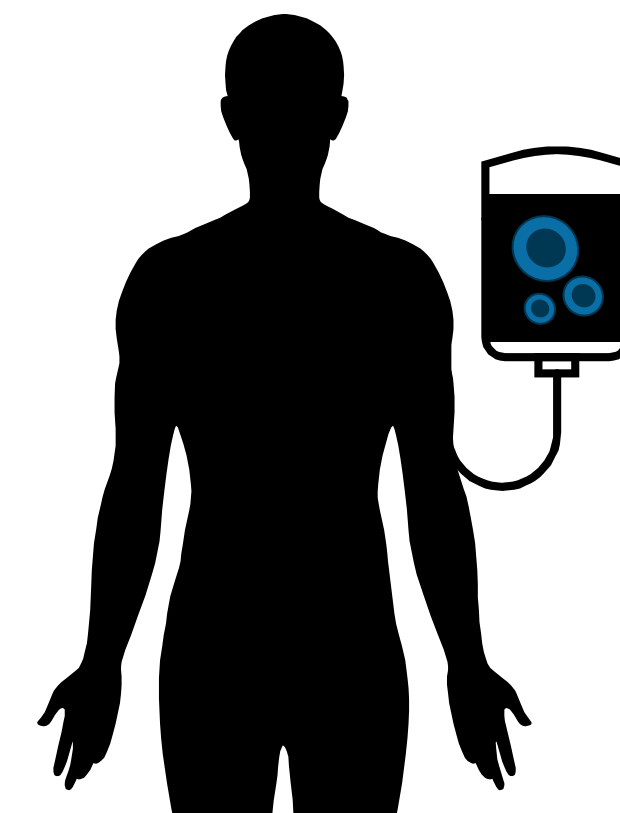


Expand CAR T cells

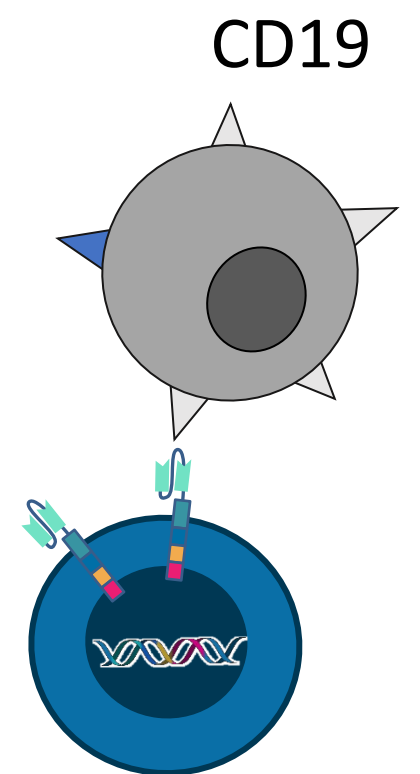


Infusion

Infuse same patient with CAR T cells



Activity



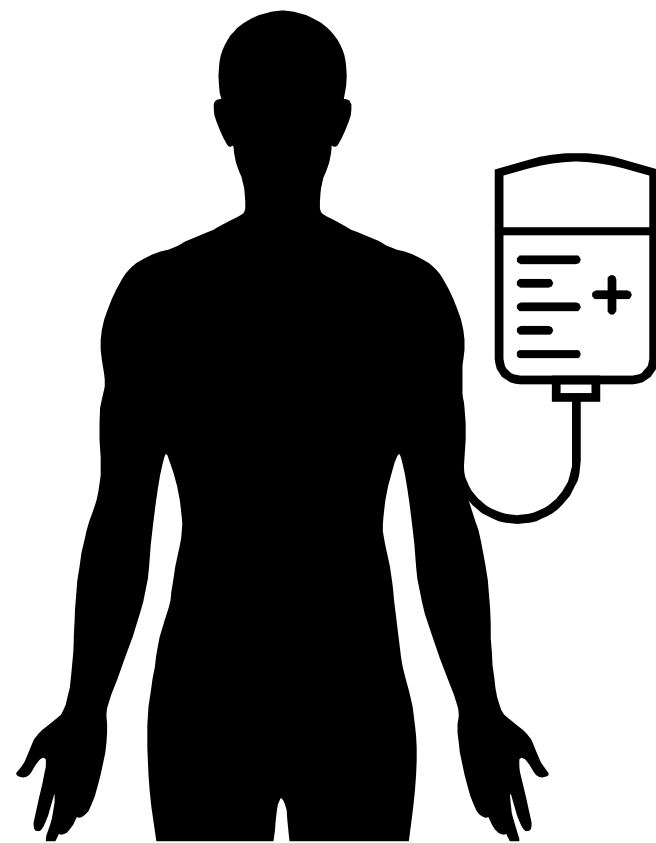
Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

Autologous CAR T-Cell Therapy: Underlying Principles

Leukapheresis

Collect patient's white blood cells

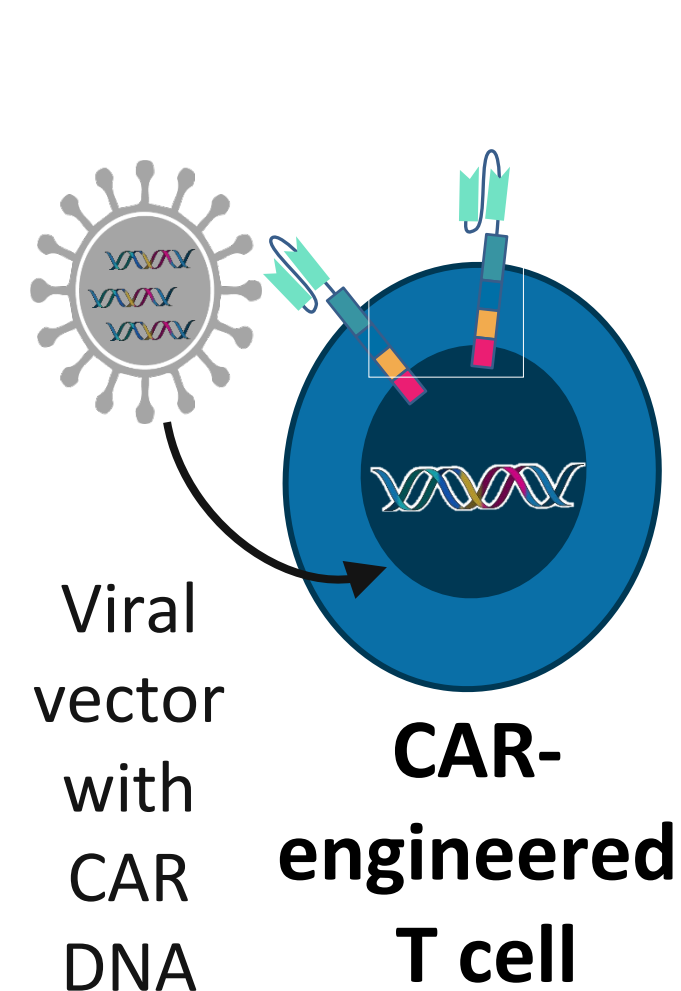


Manufacturing

Isolate and activate T cells



Engineer T cells with CAR gene



Targeting element (eg, CD19, BCMA, CD20)

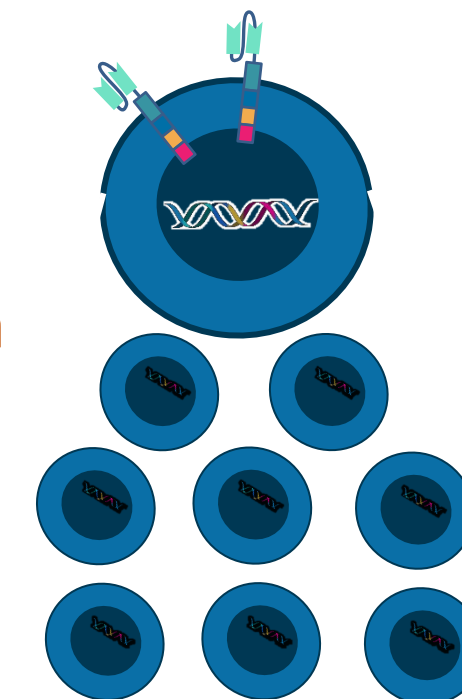
Spacer

Transmembrane domain

Costimulatory domain (eg, CD28 or 4-1BB)

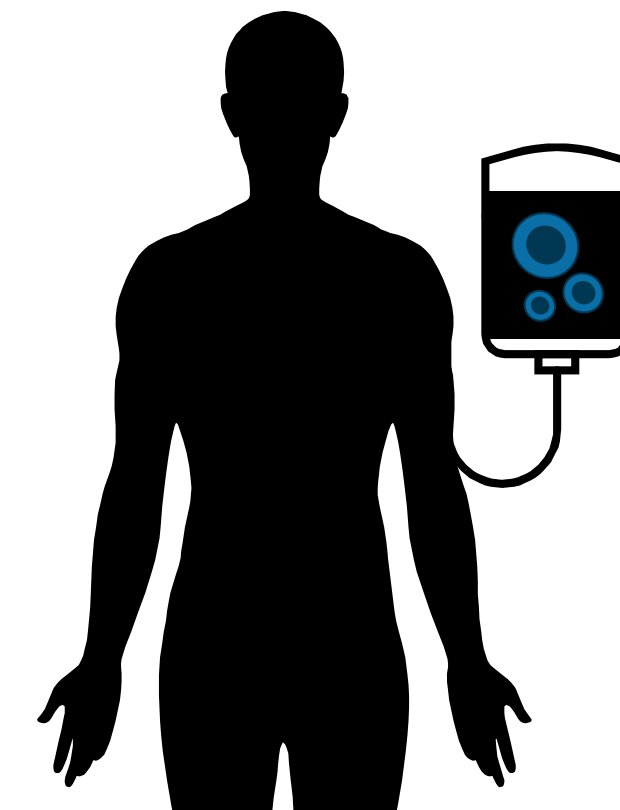
CD3 ζ (essential signaling domain)

Expand CAR T cells

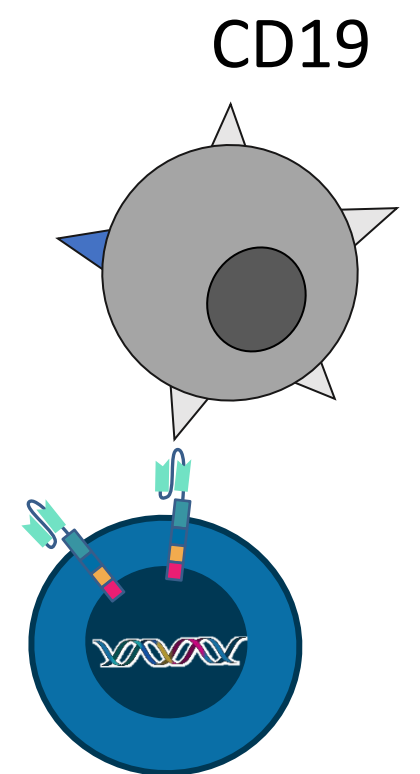


Infusion

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Activity



Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

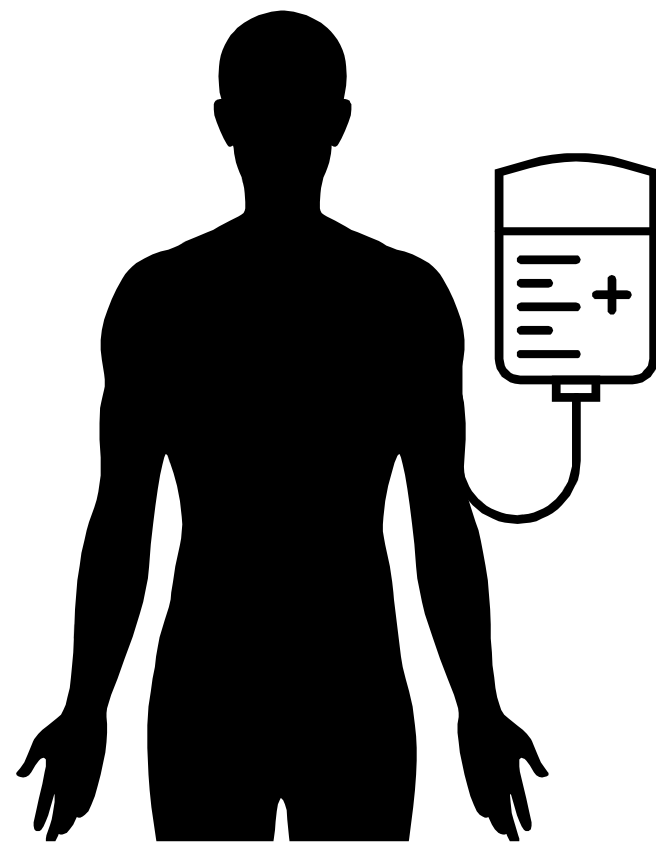
Apheresis



Autologous CAR T-Cell Therapy: Underlying Principles

Leukapheresis

Collect patient's white blood cells

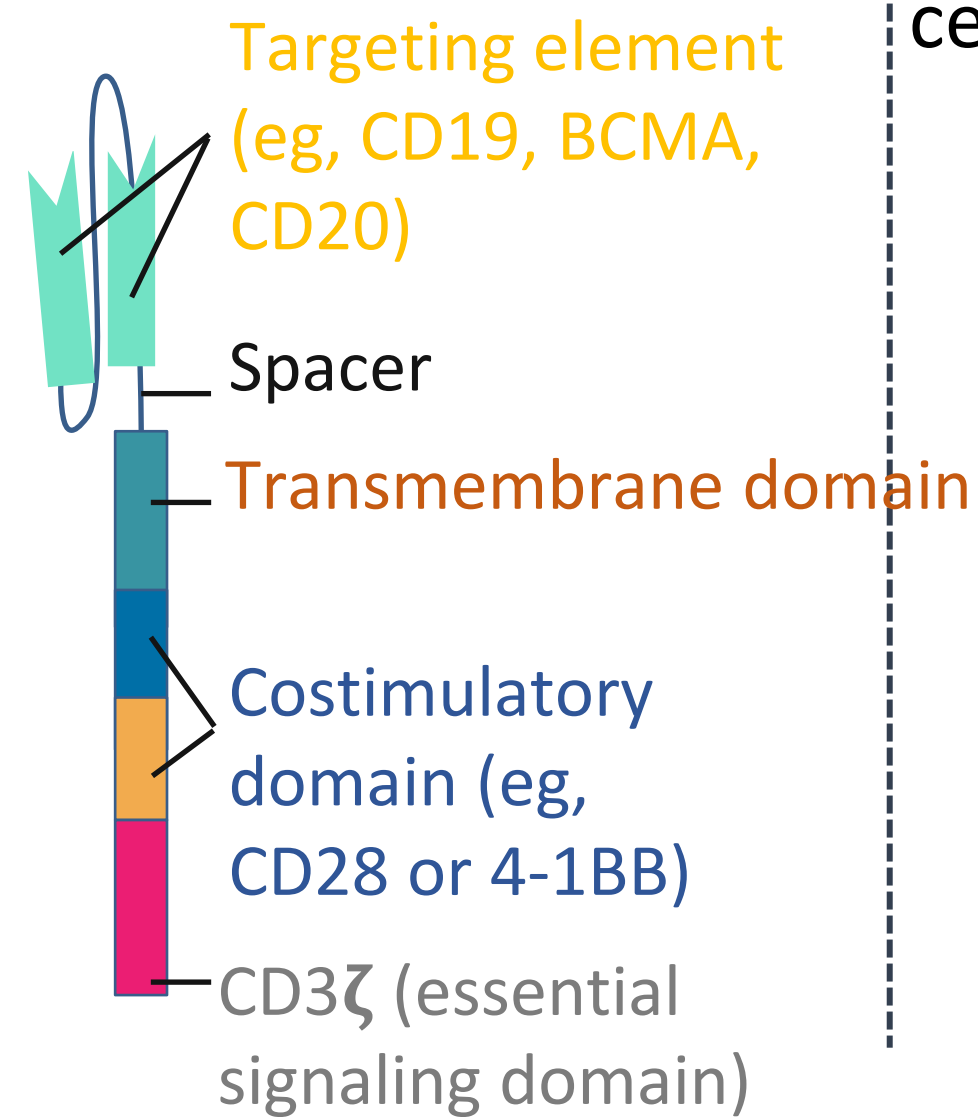
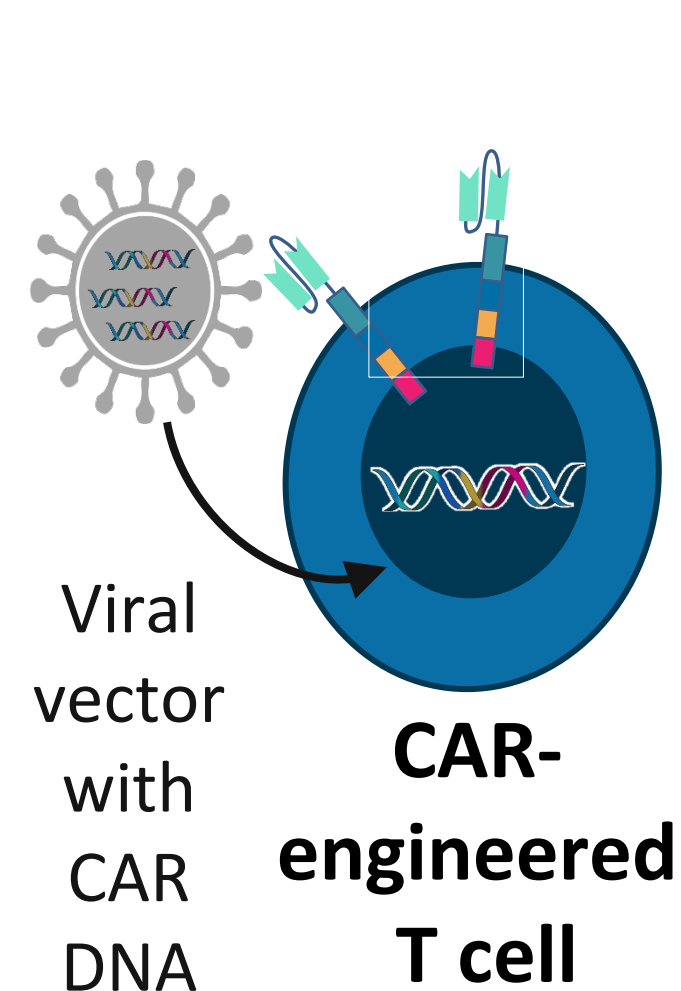


Manufacturing

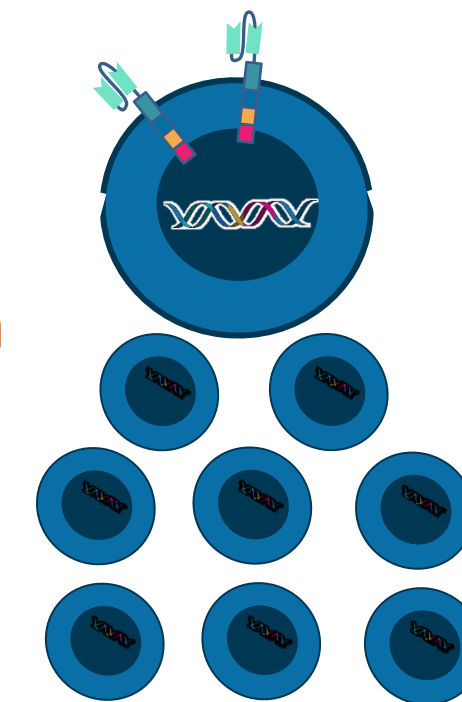
Isolate and activate T cells



Engineer T cells with CAR gene

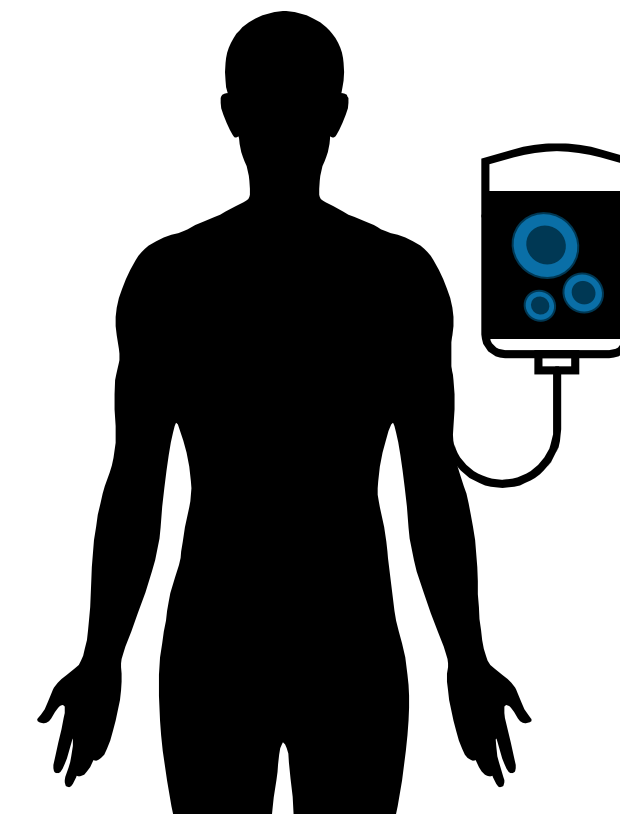


Expand CAR T cells

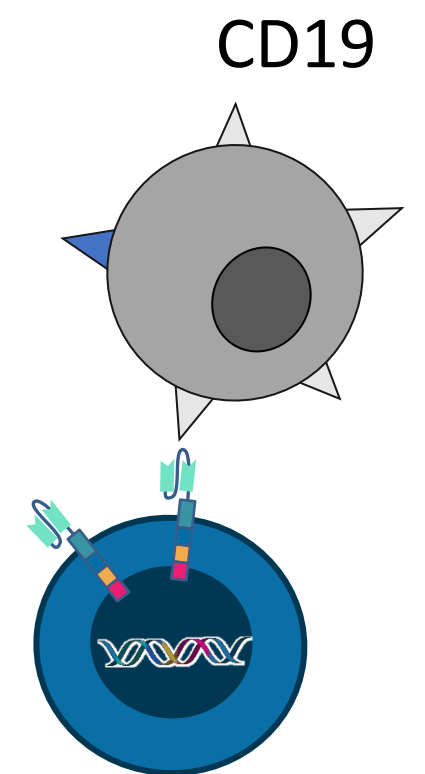


Infusion

Infuse same patient with CAR T cells



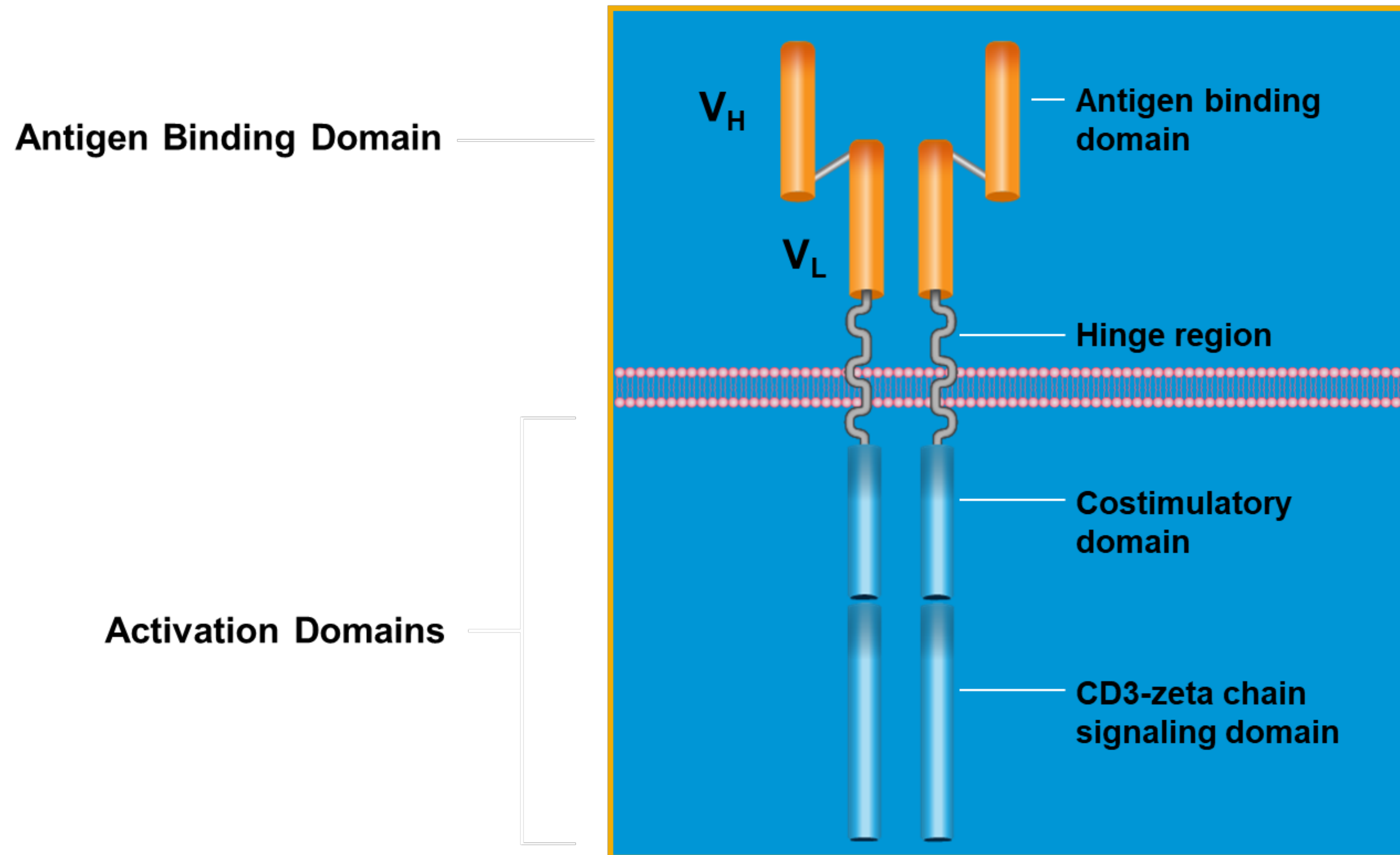
Activity



Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

CAR T-cell Construct



scFv

Single-chain variable fragment (scFv) bypasses MHC antigen presentation, allowing direct activation of T cell by cancer cell antigens

Hinge region

Essential for optimal antigen binding

Costimulatory Domain: CD28 or 4-1BB

Enhances proliferation, cytotoxicity and persistence of CAR T cells

Signaling Domain: CD3 ζ chain

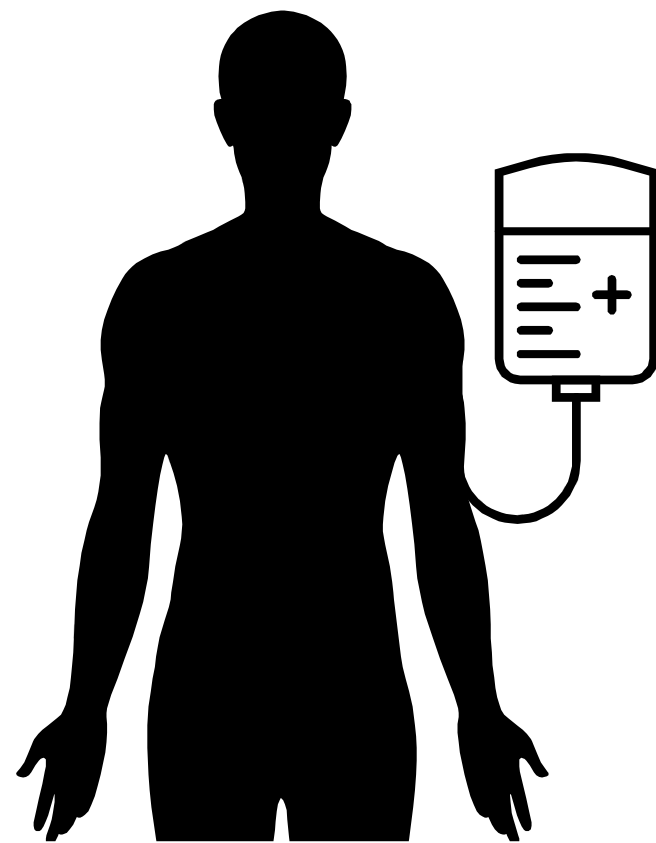
Proliferation and activation of CAR T cells
CAR T-cell-mediated killing of tumor cells

Slide created by E Squared Communications
Courtesy of the CAR T Working Group

Autologous CAR T-Cell Therapy: Underlying Principles

Leukapheresis

Collect patient's white blood cells

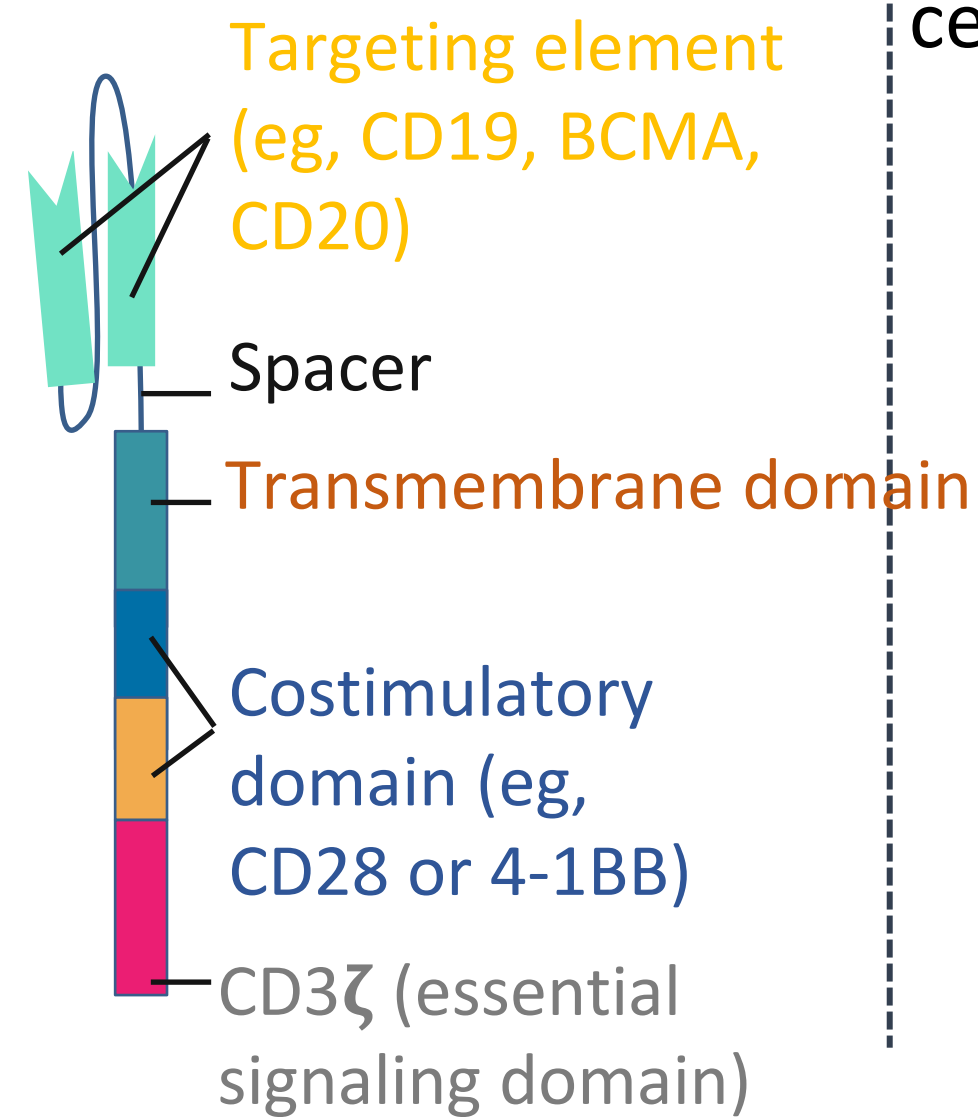
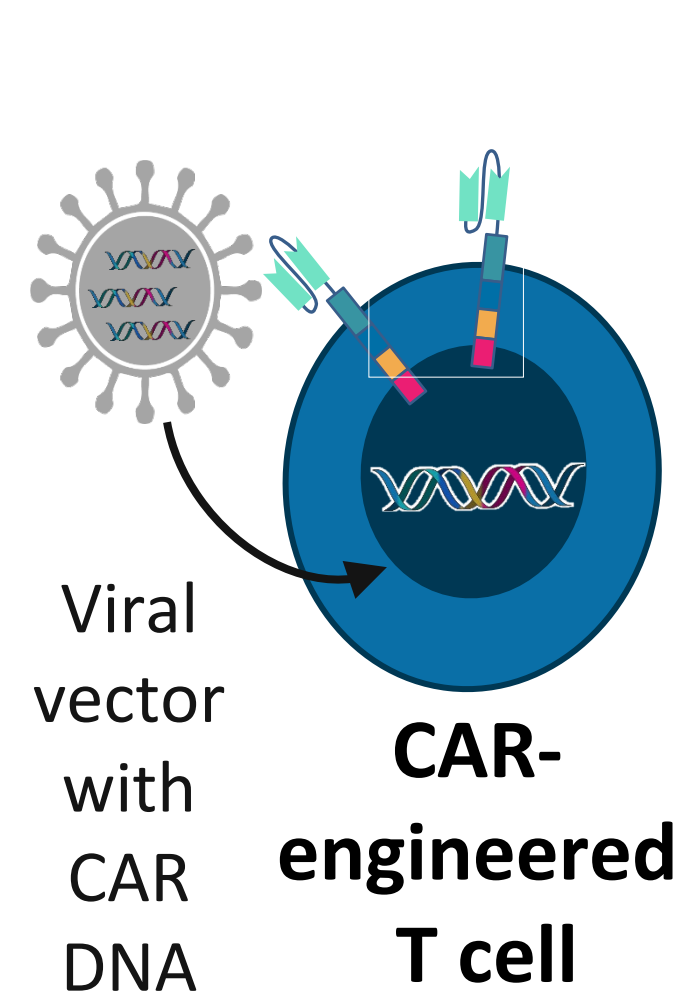


Manufacturing

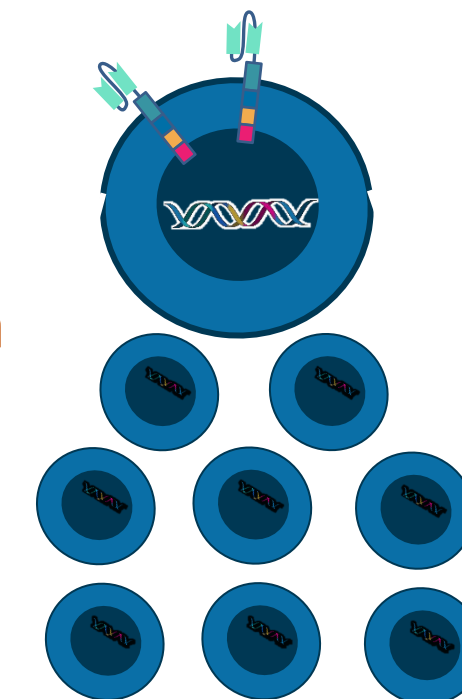
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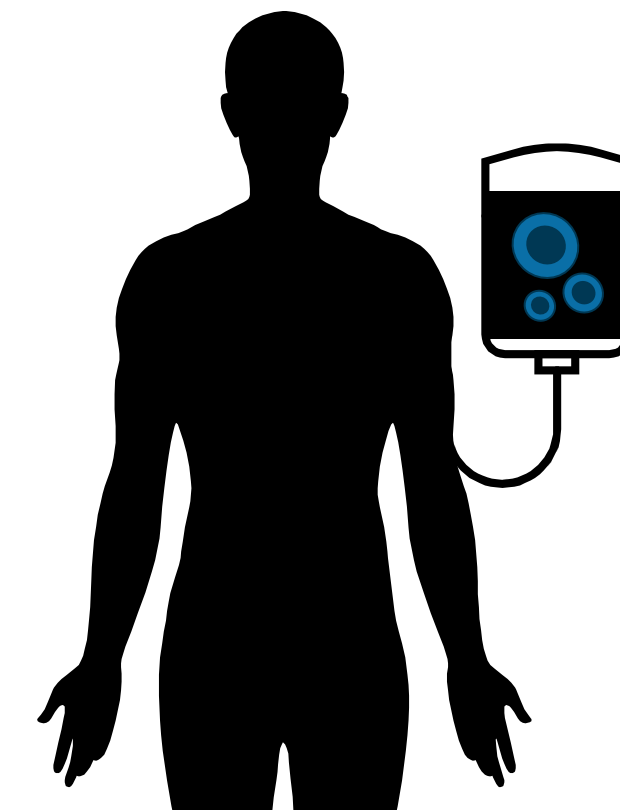


Expand CAR T cells

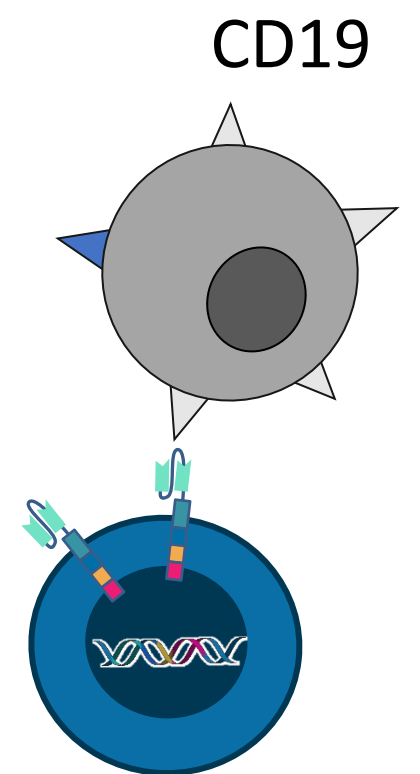


Infusion

Infuse same patient with CAR T cells



Activity



Median manufacturing time: 17-28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

CAR T-cell Infusion

- Lymphodepleting chemotherapy (fludarabine + cyclophosphamide)
Wednesday – Friday (day -5 to -3)
- Admission on Sunday (day -1)
- CAR T-cells are infused on Monday (day 0)

CAR T-cell Hospitalization

- Patients are hospitalized for approximately 14 days to monitor for toxicities.
- Discharge if no active issues and resolution of CRS/ICANS.

Acute Toxicities

- Cytokine release syndrome (CRS)
- Immune effector cell associated neurotoxicity syndrome (ICANS)
- Infections
- Cytopenias

Cytokine Release Syndrome (CRS)

- Cytokine-mediated systemic inflammatory response
- What are the symptoms associated with CRS?
 - Fevers, hypotension, hypoxia, end-organ dysfunction
 - Rarely: arrhythmias, renal failure, pleural effusions, transaminitis, coagulopathy, IEC-HS (HLH)
- Rising inflammatory markers (ferritin, CRP, etc)
 - IL-2, IL-6, IL-15, IFN-gamma, TFN-alpha
- Can occur with or without ICANS

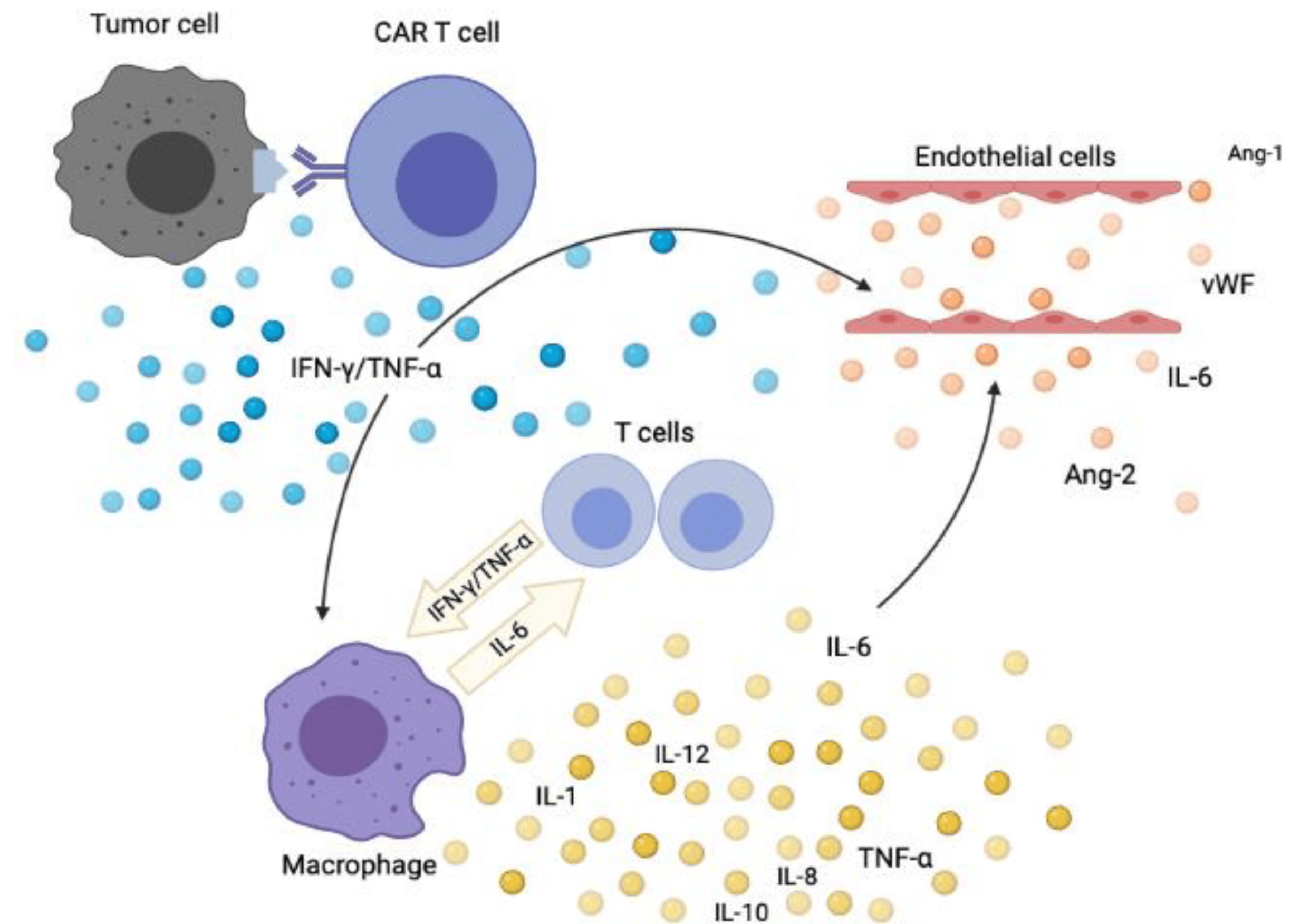
Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

- What is ICANS?

- Clinical and neuropsychiatric syndrome developing post-CAR T-cell therapy

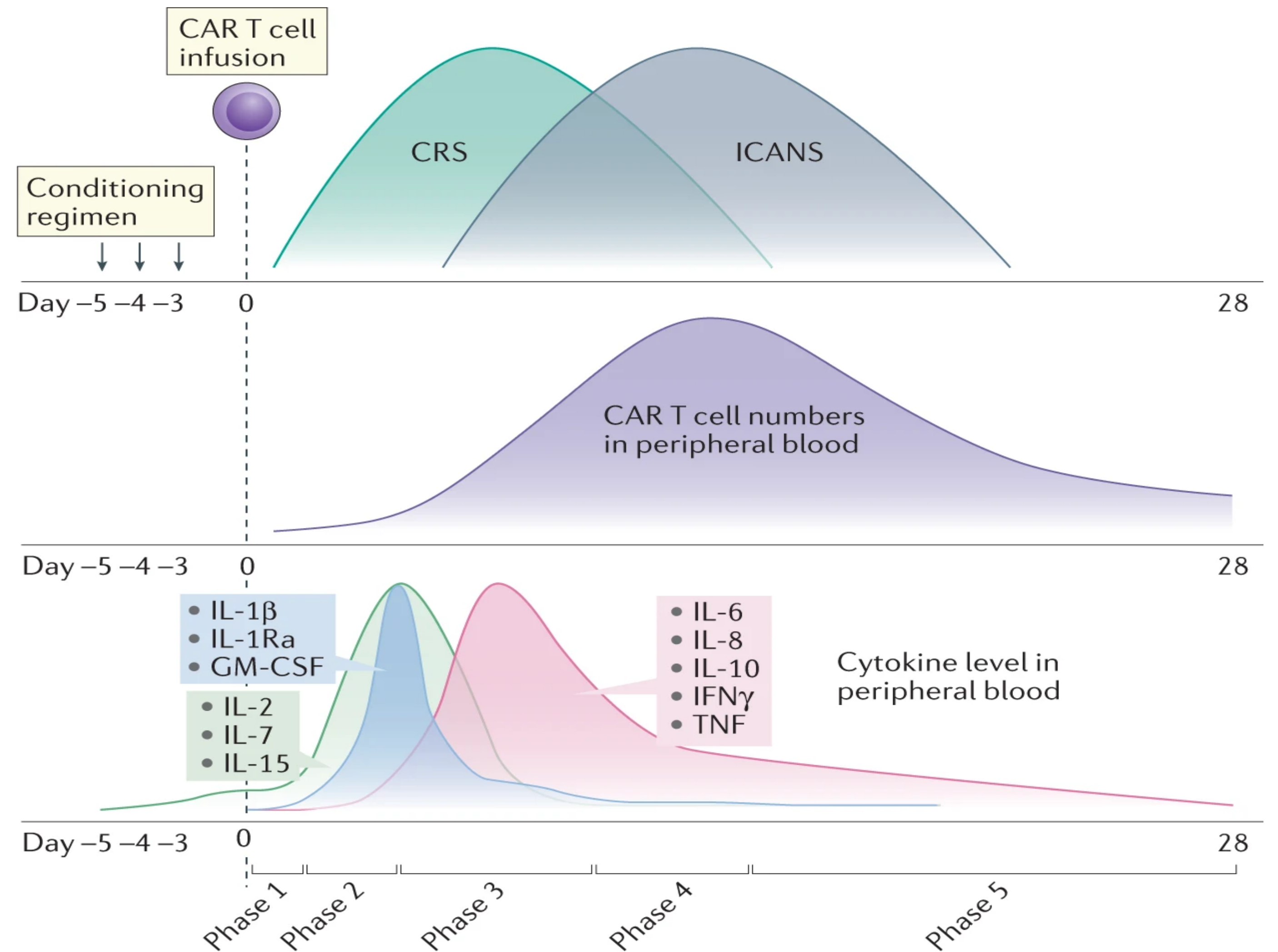
- Symptoms associated with ICANS:

- Encephalopathy
- Auditory/visual hallucinations
- Speech alterations
- Headache, fatigue, tremors
- Dysgraphia
- Clinical or subclinical seizures
- Cerebral edema with coma



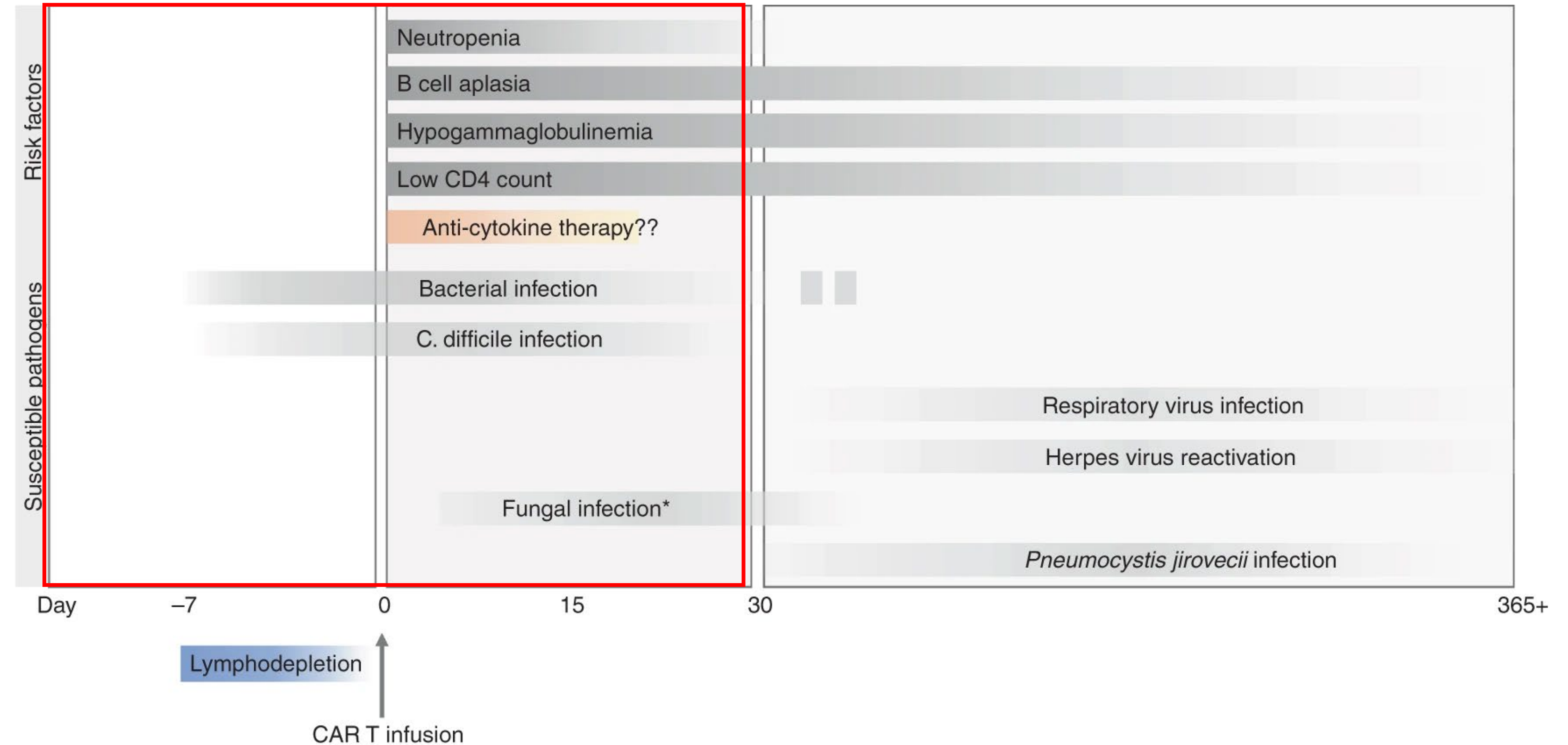
Time of Onset

- CRS:
 - Median onset: ~3 days
 - Median duration: ~7 days
- ICANS:
 - Median onset: ~7 days
 - Median duration: ~9 days
 - Late onset have been reported

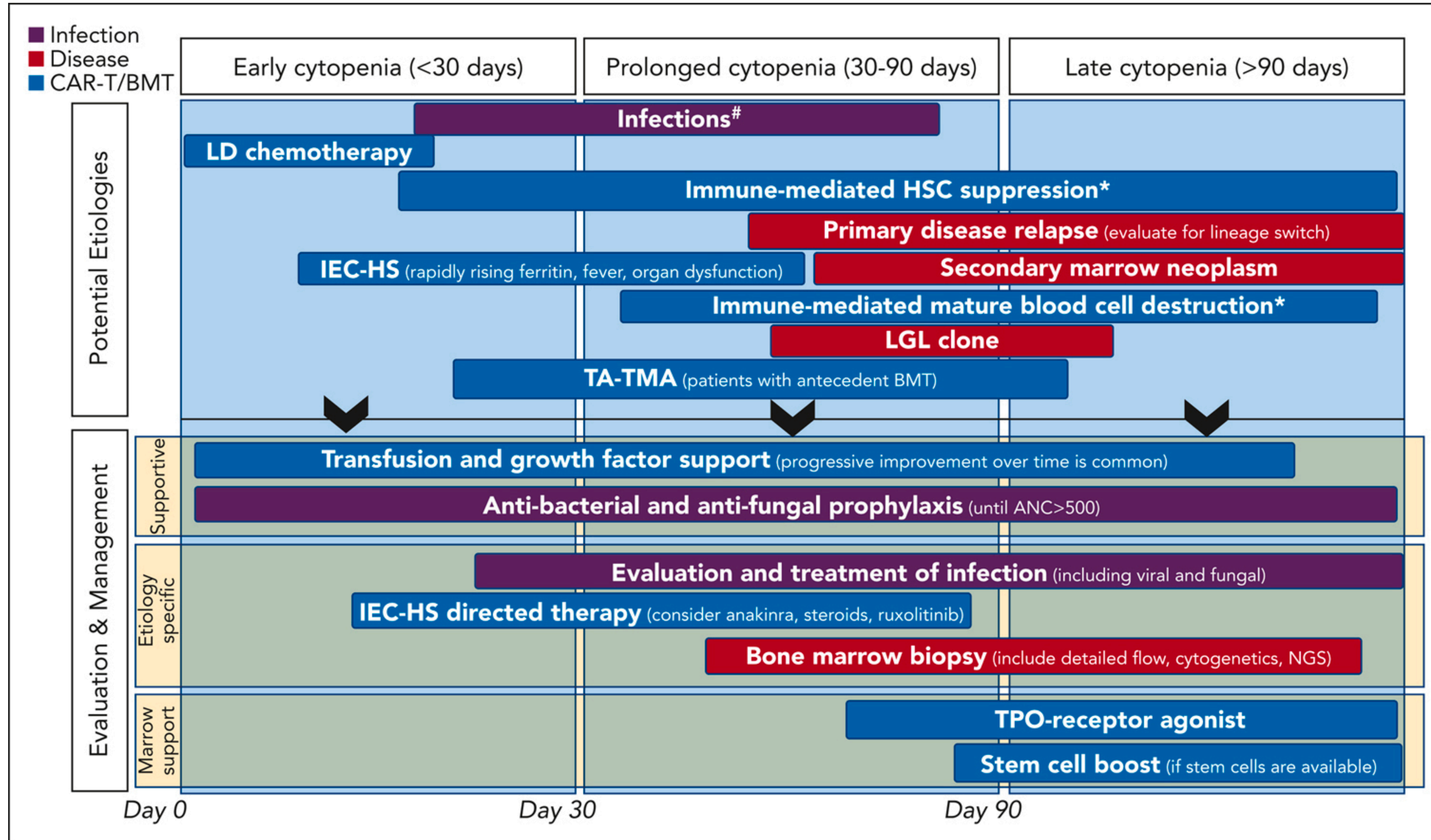


Infections

- Infection rate overall:
 - 18-56%
- Grade ≥ 3 :
 - 12-28%
- Mostly bacterial (40%) when reported
- Antimicrobial prophylaxis while neutropenic
- Cytomegalovirus (CMV):
 - 10%
 - True incidence unknown



Cytopenias



Monitoring Post-CAR T-cell Therapy

- Once weekly visits in clinic with labs prior until day 30.
- Caregiver must be present 24/7.
- Restaging at day 30, day 100, day 180, 1 year, 2 year.
- Vaccinations begin at 3-6 months.

Late Toxicities of CAR T-cell Therapy

- B cell aplasia
- Hypogammaglobulinemia
 - IVIG infusions
- Prolonged cytopenias
 - Up to 15% of patients
- Infections
 - Mostly viral (PJP and antivirals x1 year)
- Secondary malignancies

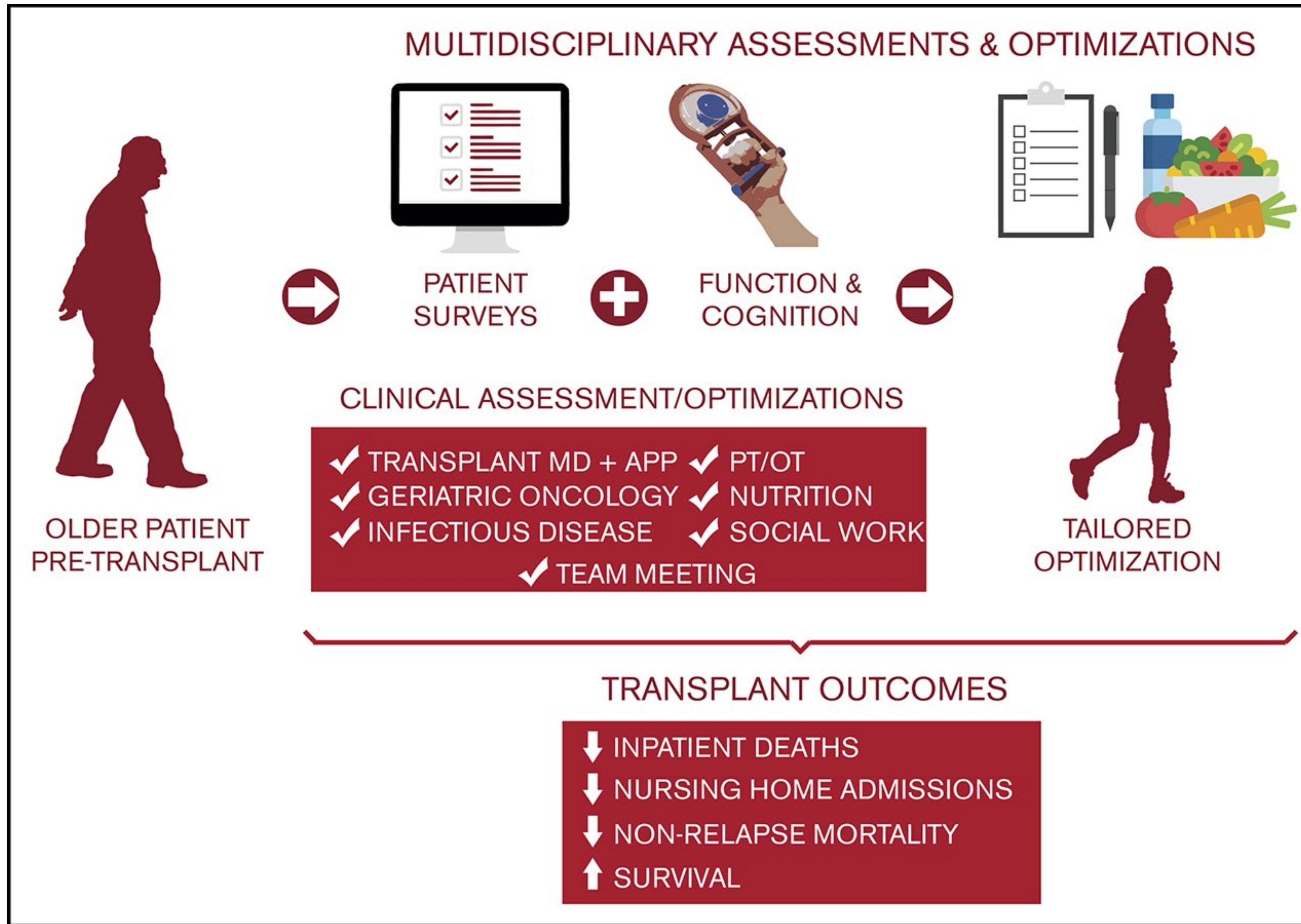
Secondary Malignancies

- 22 cases of secondary T-cell lymphomas reported to the FDA
 - In 3 cases, CAR transgene detected in the malignant clone
- Projected 5-year incidence 15.2% for a solid tumor and 2.3% for a hematologic malignancy
- For autologous stem cell transplant, risk for secondary cancer is approximately 15%.

1. Cappell et al, JCO, 2020
2. Chong et al, NEJM, 2021
3. Zhao et al, J. Hema. Onc, 2022
4. Cordeiro et al, BBMT, 2020
5. Verdun and Marks, NEJM, 2024
6. Ghildardi et al., Nature Med, 2024

Coping with CAR T-cell Therapy

Multi-Disciplinary Clinic



Multi-Disciplinary Clinic at OMC

- Transplant/Cell Therapy team
 - Physician
 - Nurse practitioner (Juliette Folse, NP)
 - Pharmacist (Breanne Peyton-Thomas, PharmD)
- Transplant Infectious Disease physician (Sonya Trinh, MD)
- Palliative Care physician (Tommy Morel, MD)
- Dietician
- Social Worker
- Future additions:
 - Physical therapy and occupational therapy
 - Integrative Oncology



Thank you!

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