# CAR T-cell Therapy for Patients with Lymphoma: Who Benefits

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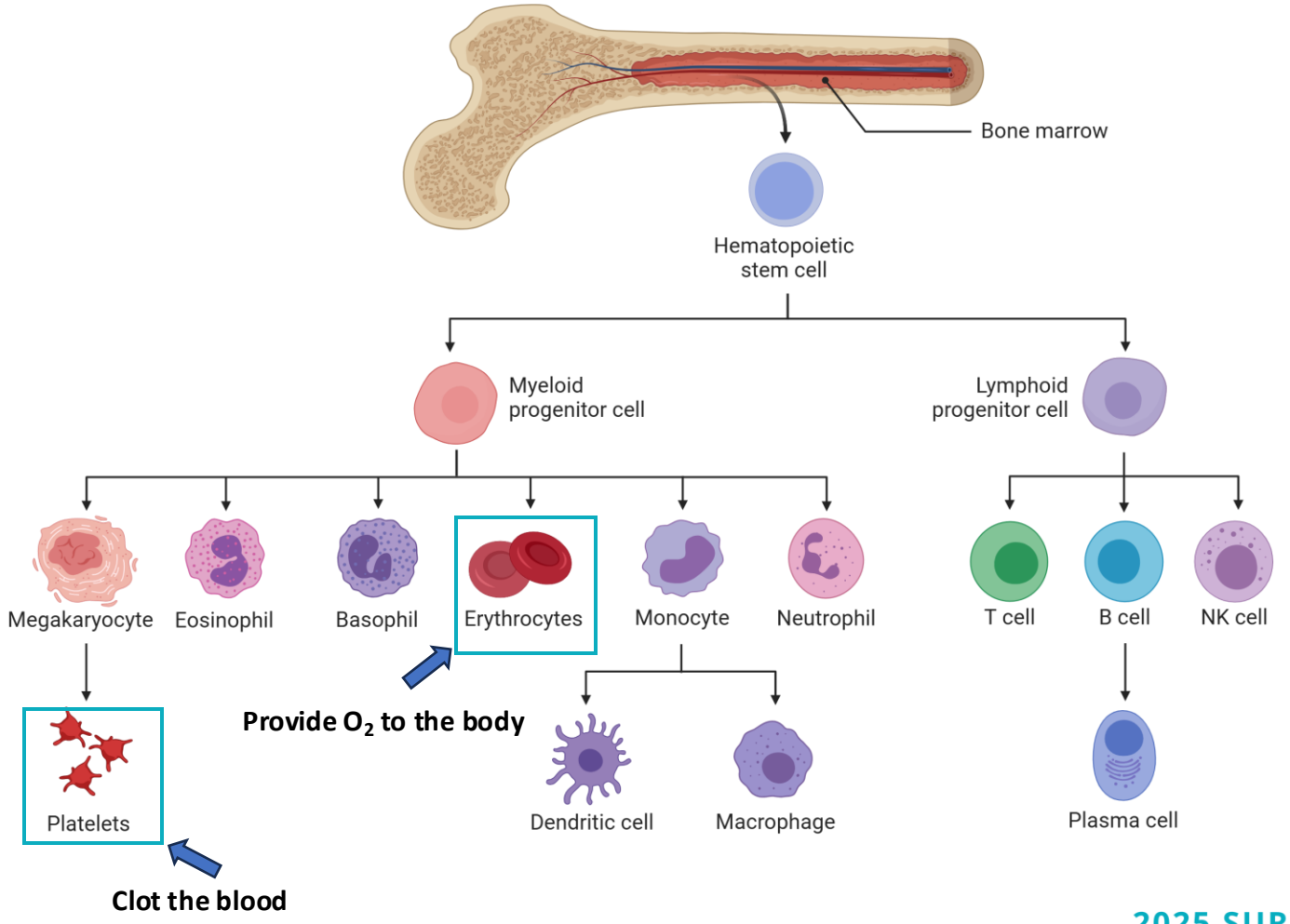
University of Miami

May 5 2025

# Agenda

- Introduction to Lymphoma
- The science of CAR T-cell therapy
- The CAR journey

# Intro to the Complete Blood Count (CBC)



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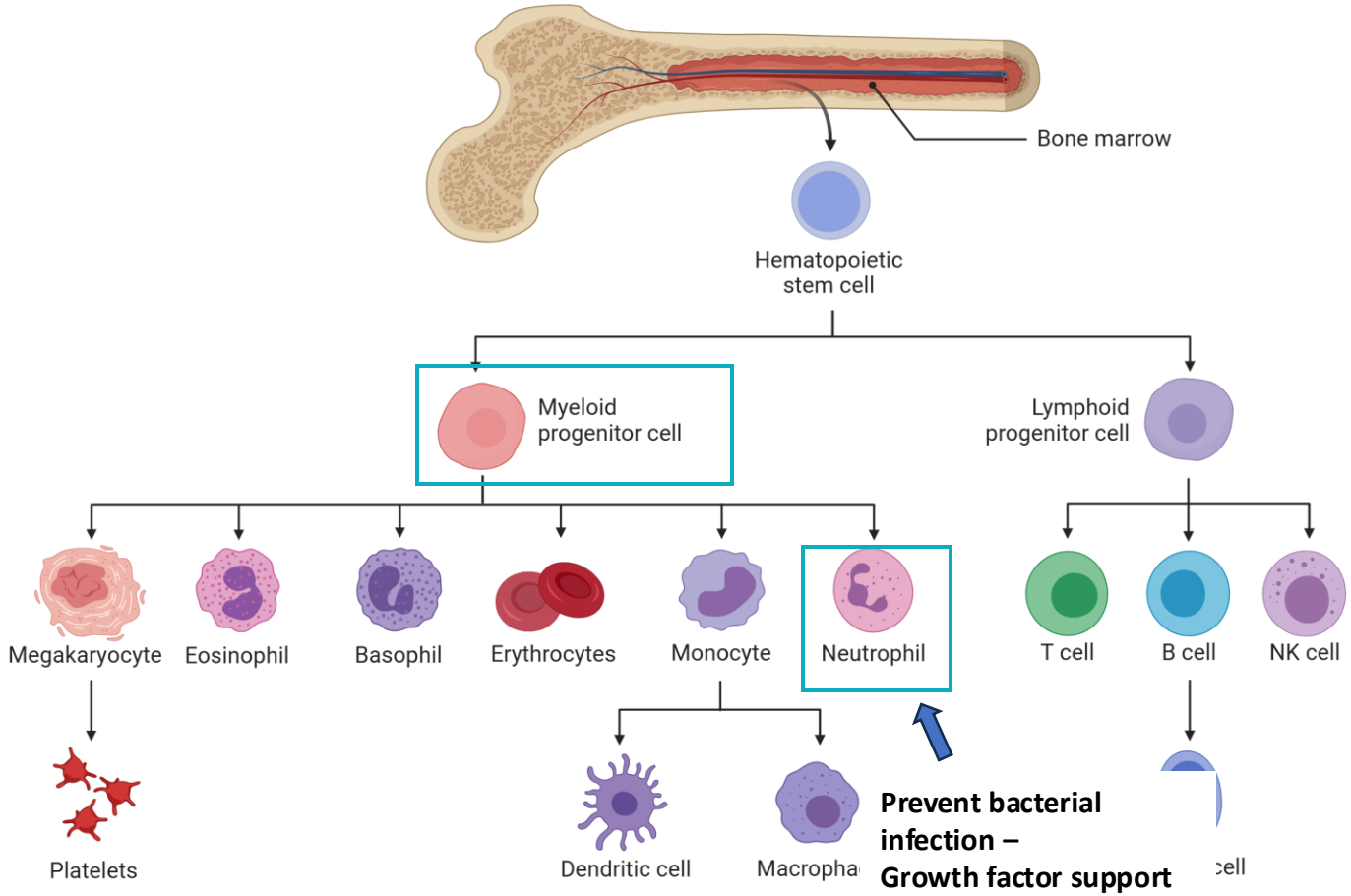
# Intro to the Complete Blood Count (CBC)



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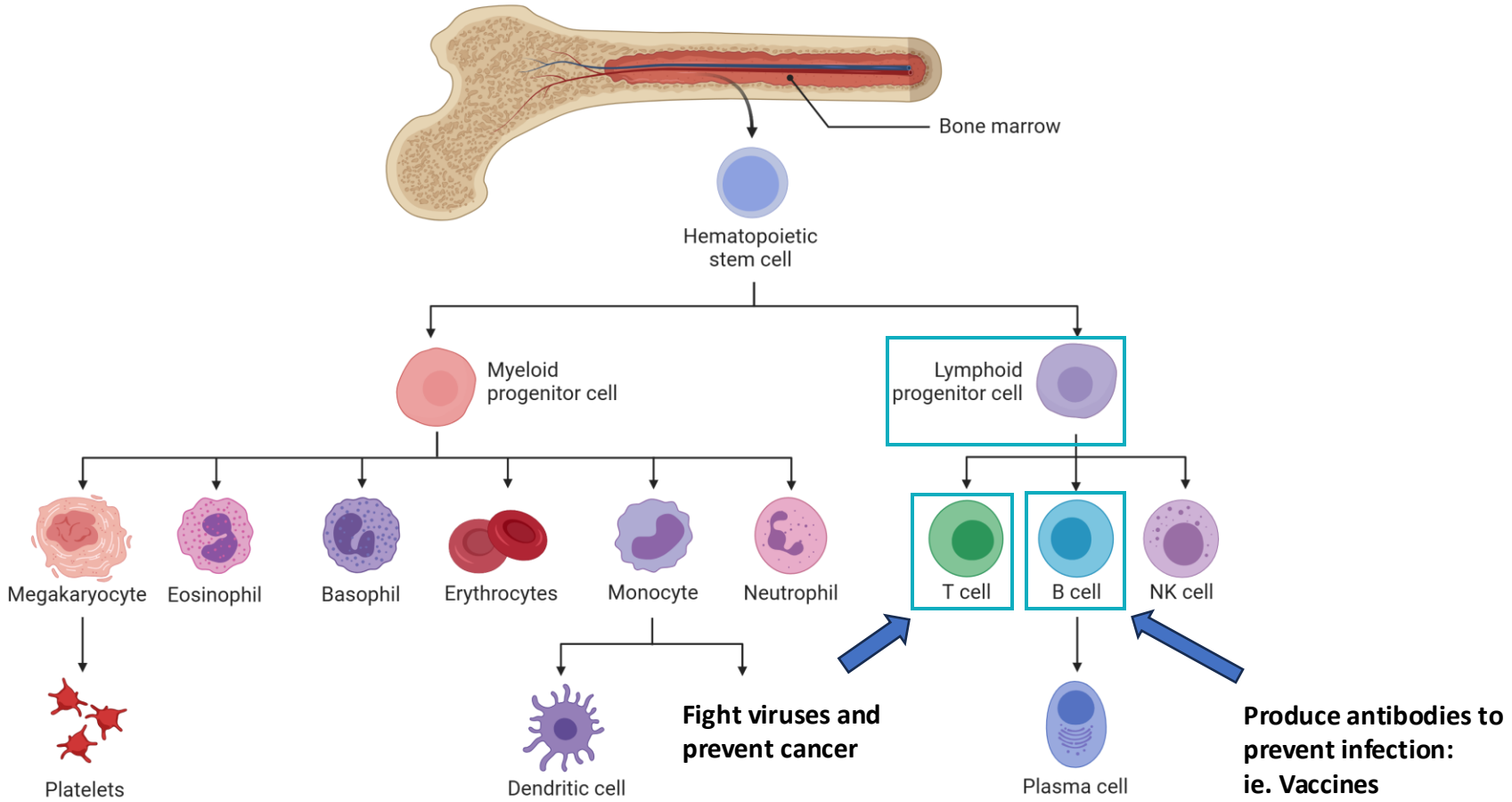
# Intro to the CBC– the Adaptive Immune System



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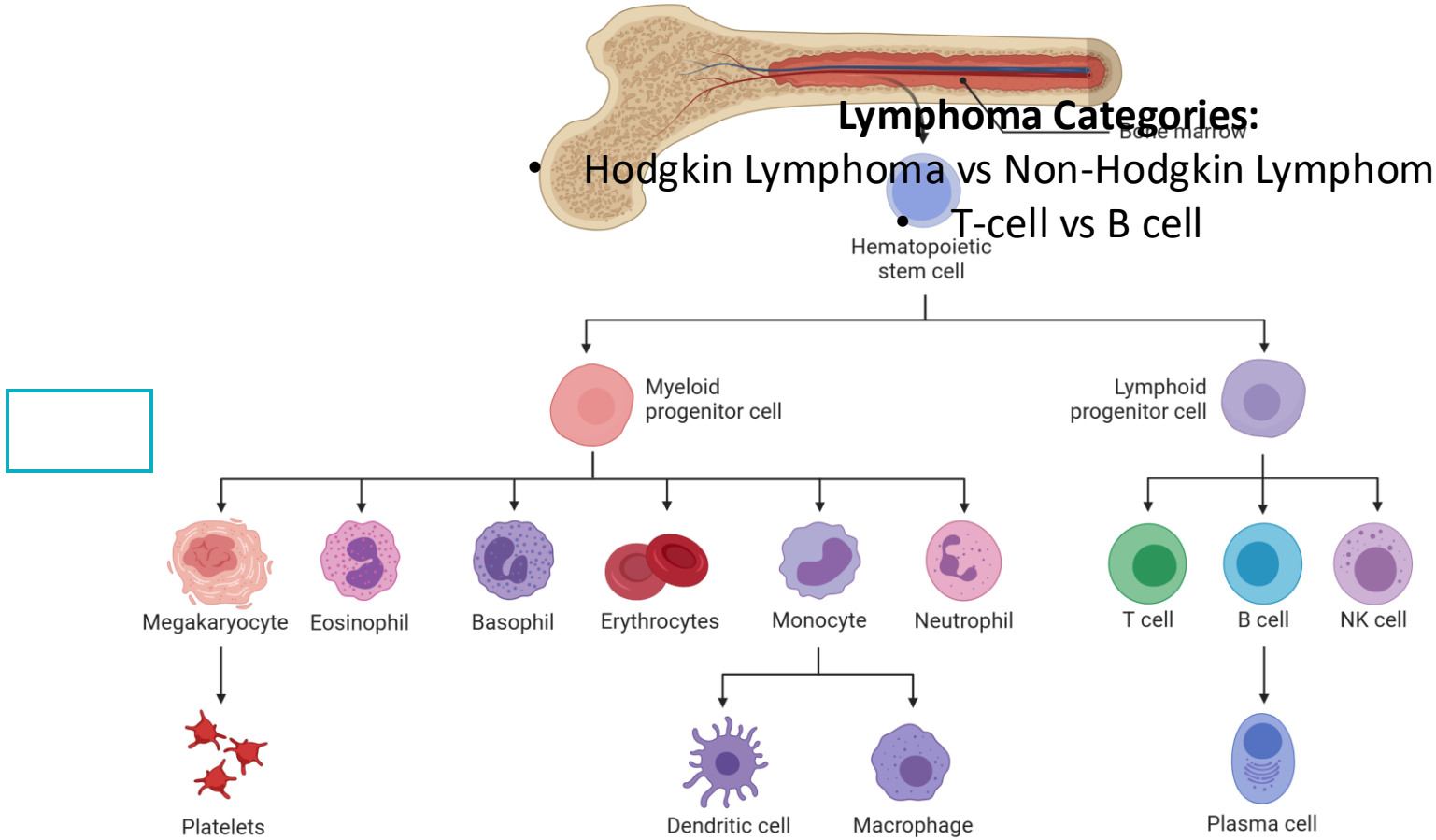
# Lymphoma is a Cancer of Immune Cells




**Lymphoma Categories:**

- Hodgkin Lymphoma vs Non-Hodgkin Lymphoma (NHL)
  - T-cell vs B cell



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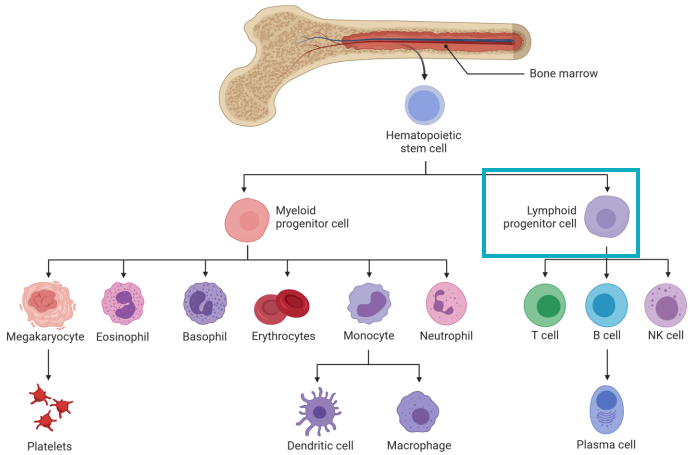
# How I Think About Lymphoma Categories




**Lymphoma Categories:**

- Hodgkin Lymphoma vs **Non-Hodgkin Lymphoma (NHL)**
- T-cell vs **B cell**

**Aggressive**

- Grows fast, life threatening
- Curable in a proportion of patients
- Ie Diffuse large B-cell lymphoma (DLBCL)

**Indolent**

- Slow growing
- Incurable
- Ie Follicular lymphoma(FL)

**Mantle cell lymphoma**

- Features of both aggressive and indolent lymphomas
- Generally considered incurable but can act very aggressively



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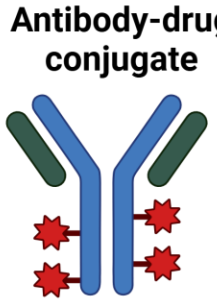
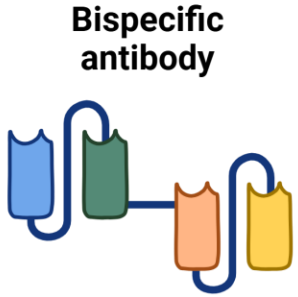
# Current Therapies Target B cell Surface Markers

**Target labeling**
- Rituximab
- Obinutuzumab

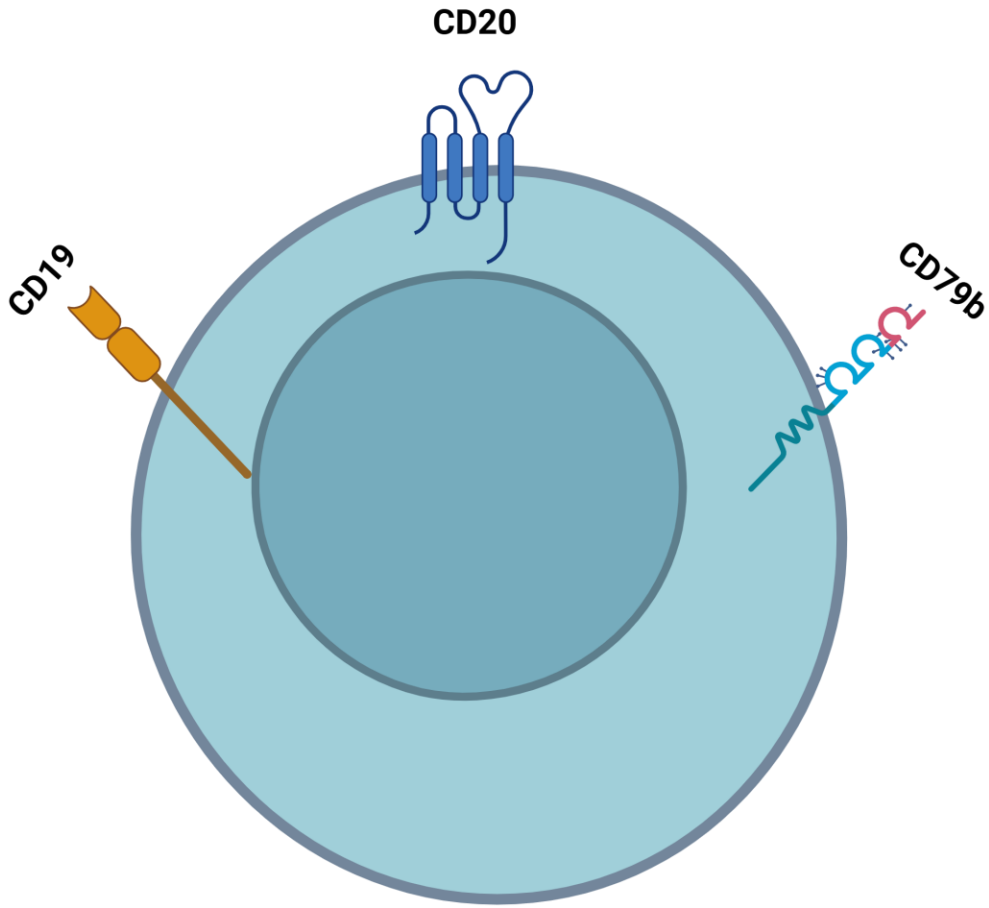

**Targeted drug delivery**
- Polatuzumab
- Loncastuximab




**Bring immune system to the cancer**
- Glofitamab
- Epcoritamab
- Mosunetuzumab




**B cell markers with approved therapies**



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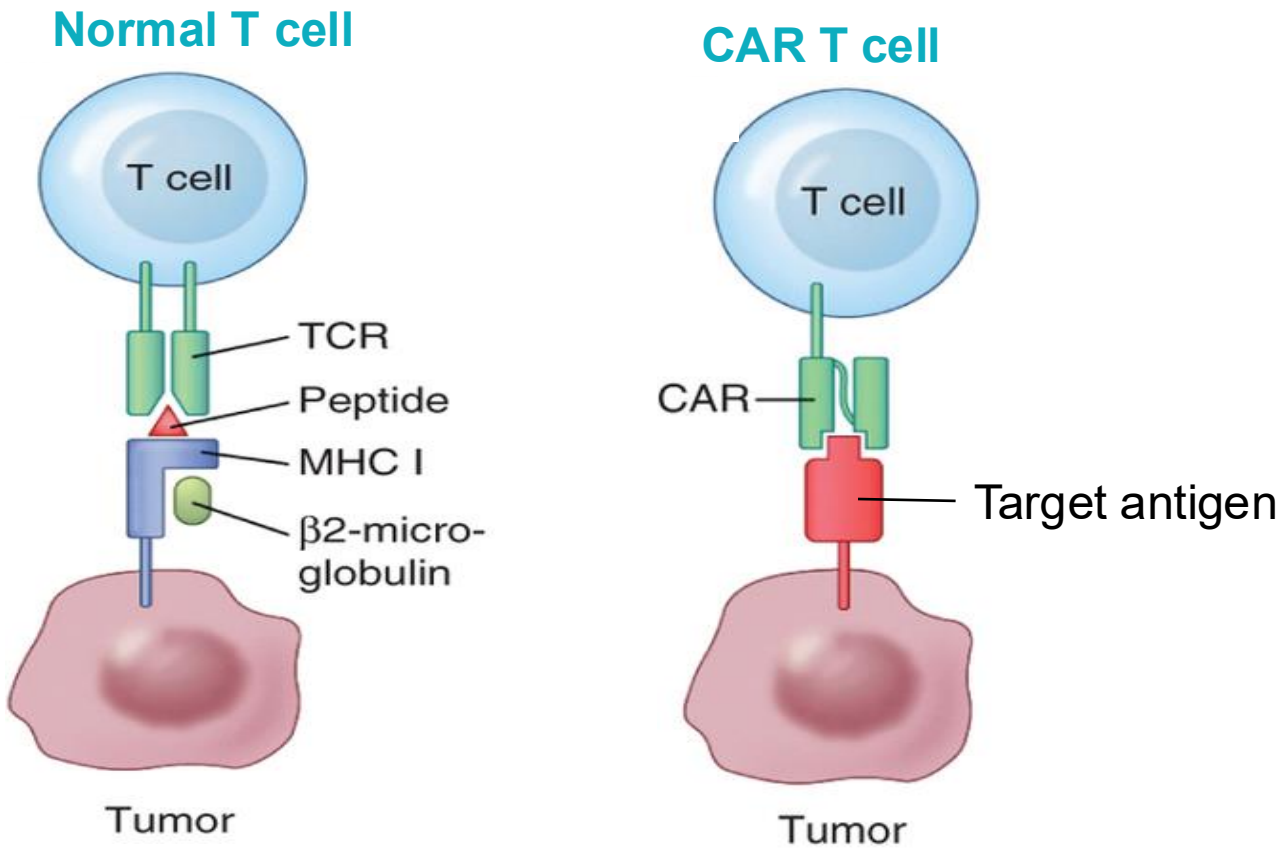
# Chimeric Antigen Receptor (CAR) Modified T cells




CAR-T benefits:

- Living cells
- Localize to tumor
- Tumor Killing
- Persist in body to prevent relapse

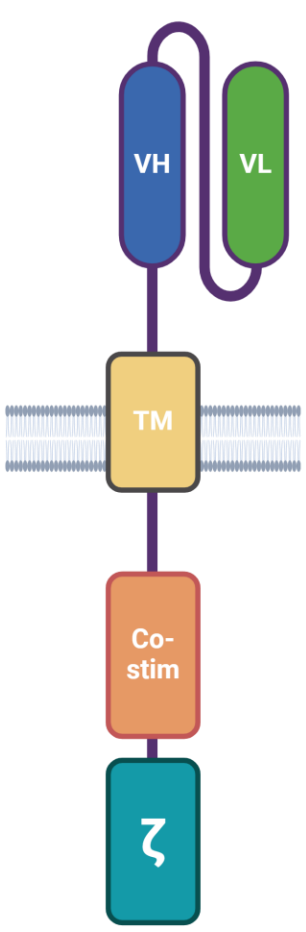


Adapted from Hinrichs & Restifo. Nat Biotech 2013

# What is a Chimeric Antigen Receptor (CAR)?

**Binds target**
B-cell fragment

**Kill switch**
T-cell fragment
The CAR “motor”




**The Chimera**



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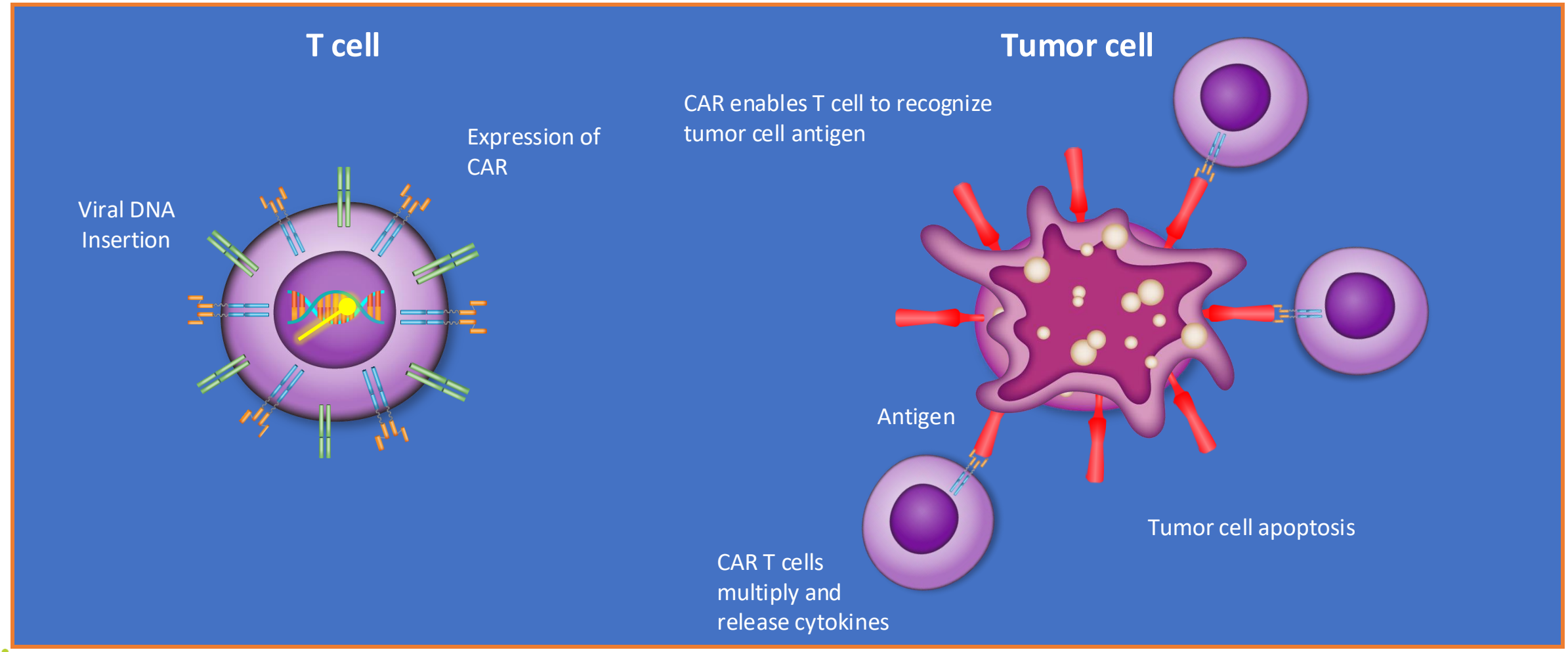
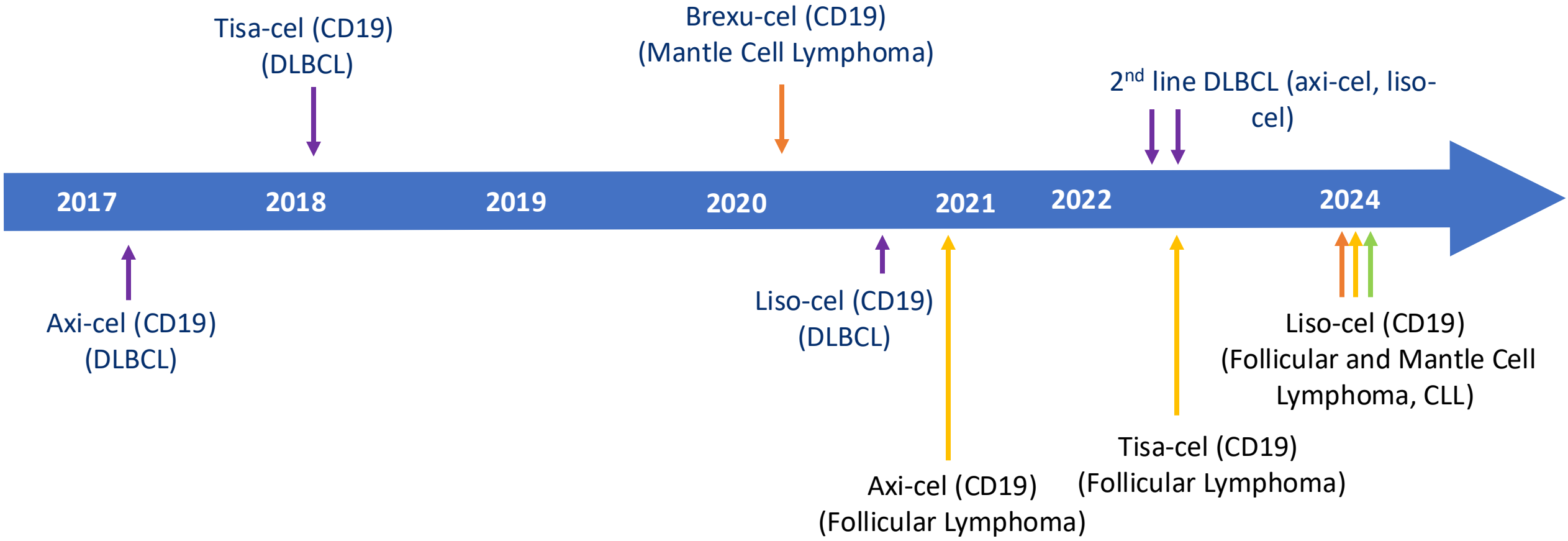
# CAR T Cells: Mechanism of Action






Courtesy of David Miklos

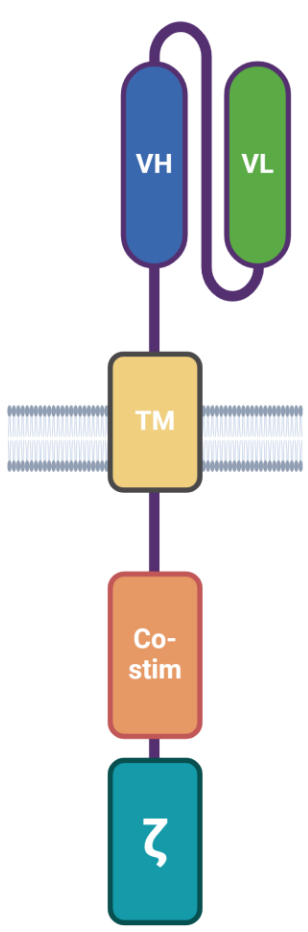
# US FDA Approvals of CAR T-cell Therapy in Lymphoma



# Approved CARs in B Cell Lymphoma

**Binds target**
B-cell fragment

**Kill switch**
T-cell fragment
The CAR "motor"




| | Axi-cel | Liso-Cel | Tiso-cel |
|---|---|---|---|
| Target | CD19 | CD19 | CD19 |
| Co-stim (CAR motor) | CD28 – fast CAR expansion, peters out | 41BB – slower onset, longer persistence | |
| Approvals | DLBCL (2nd and 3rd line)<br>FL<br>MCL | DLBCL (2nd and 3rd line)<br>FL<br>MCL | DLBCL (3rd line)<br>FL |



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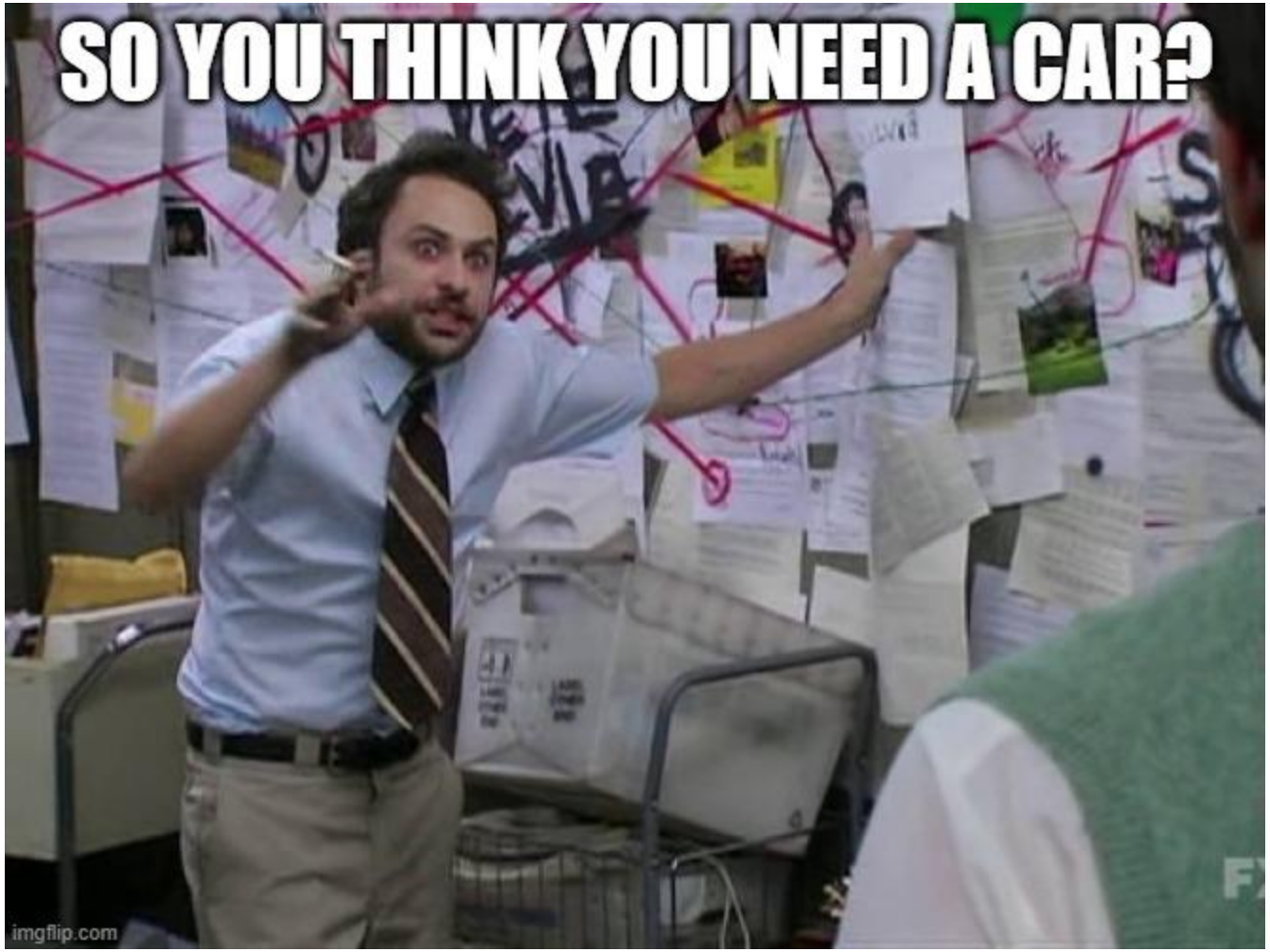
# When Am I Eligible for CAR-T: Follow the Roadmap

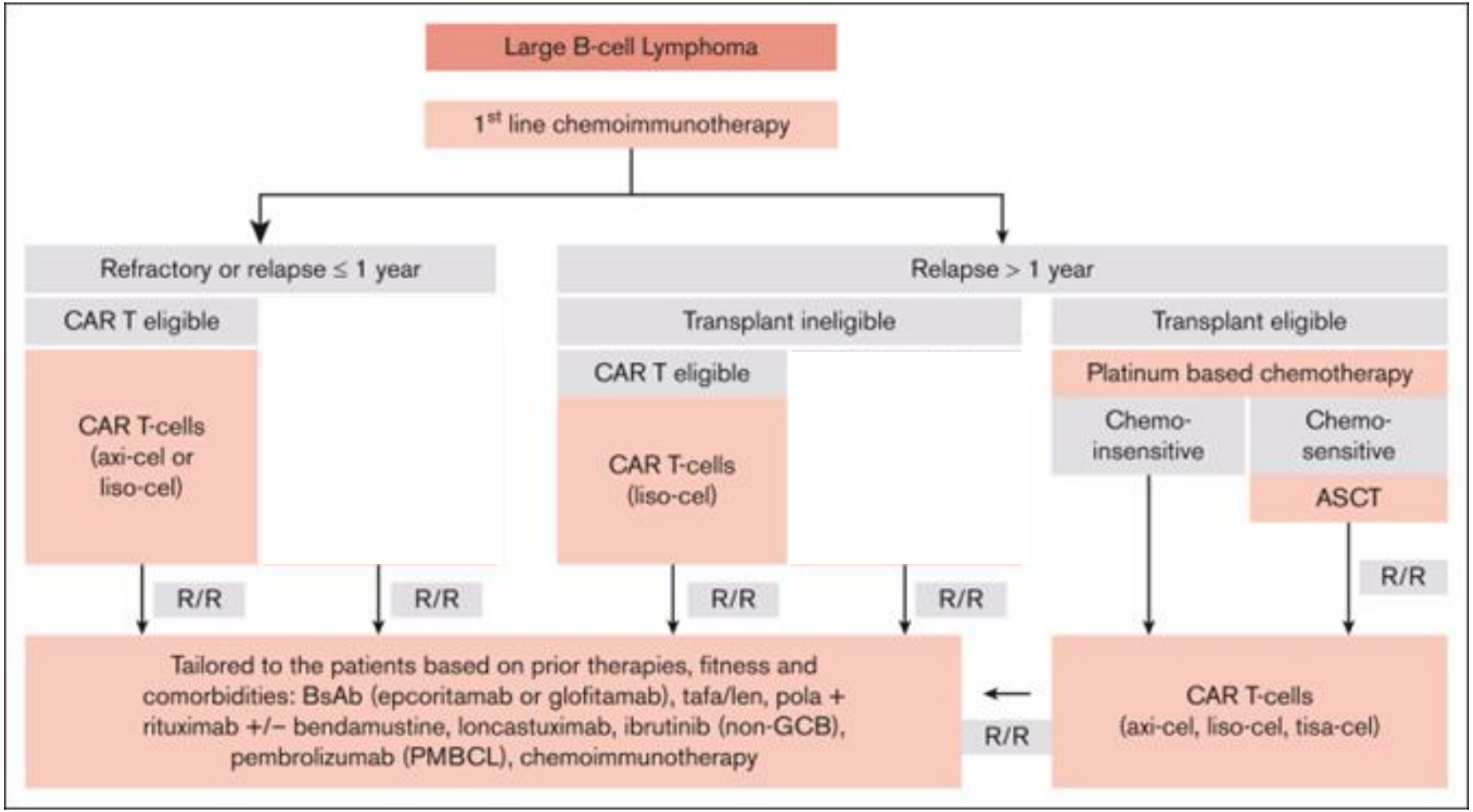





https://imgflip.com/memegenerator/92084495/Charlie-Conspiracy-Always-Sunny-in-Philadelphia. Accessed March 26,2025

# When Am I Eligible for CAR-T: Diffuse Large B-cell Lymphoma (DLBCL)

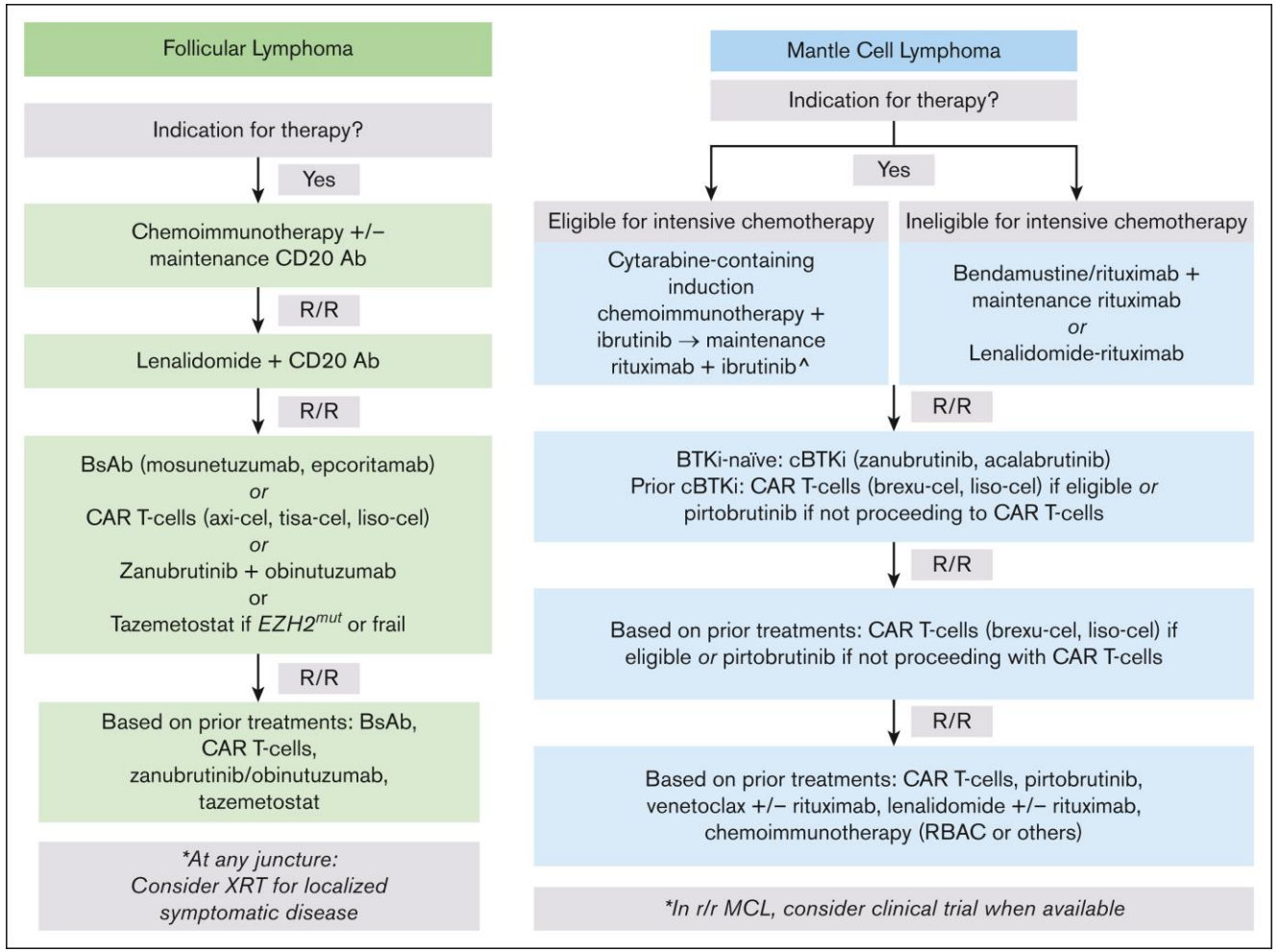
- 2nd line if lymphoma did not go into remission after chemo or returned in 1 year
- If relapse greater than one year, if eligible for auto transplant, can receive further chemo and reserve CAR-T for 3rd line




Haydu and Abramson, Bld Adv 2024

# When Am I Eligible for CAR-T: Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL)

- In Mantle Cell Lymphoma, patients eligible in 2nd line if BTK exposed
- In Follicular Lymphoma, patients are eligible in 3rd line
- In indolent lymphomas, CAR-T is not felt to be curative



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# Logistics of CAR-T

**Outpatient**

1. Leukapheresis

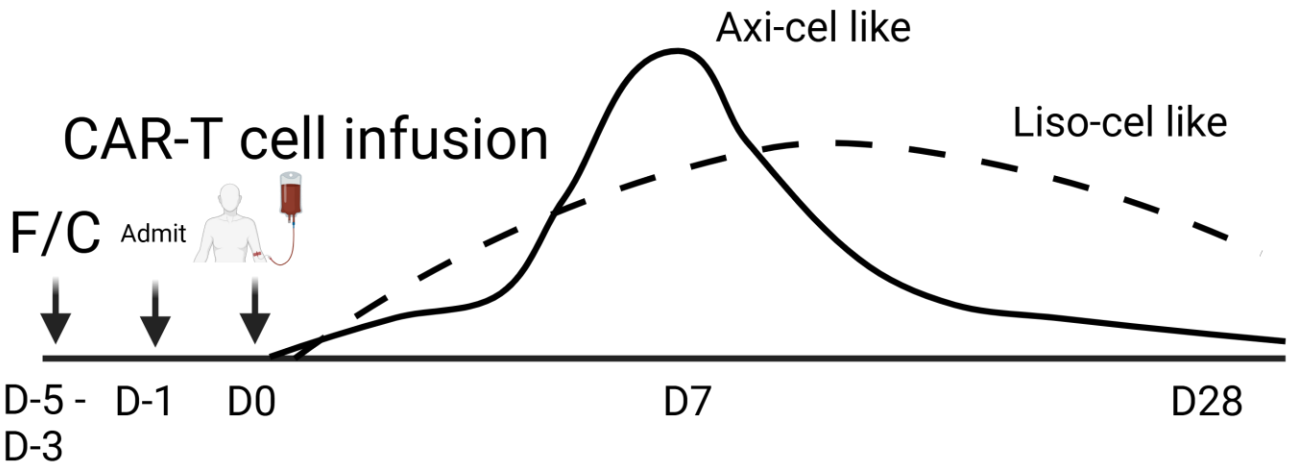
1 day – 4-6 hrs
May require a central line procedure

2. Manufacturing

3-4 weeks
May require bridging chemo for disease control

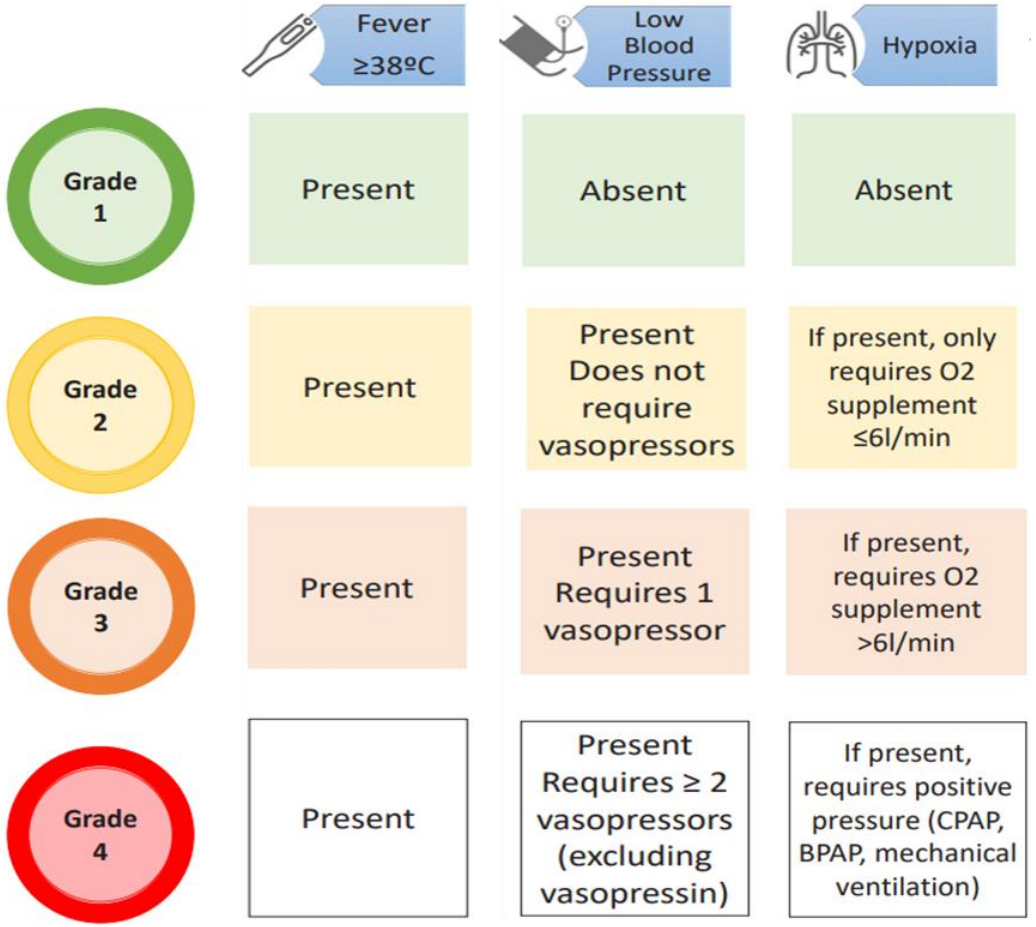
**Outpatient/ Inpatient**

3. CAR-T cell infusion



# Early Toxicities of CAR-T: Cytokine Release Syndrome (CRS)

- "Worst flu of your life"
- 2 primary effects: fever and low blood pressure
- Most patients experience a fever
- Rate of severe CRS is <5%



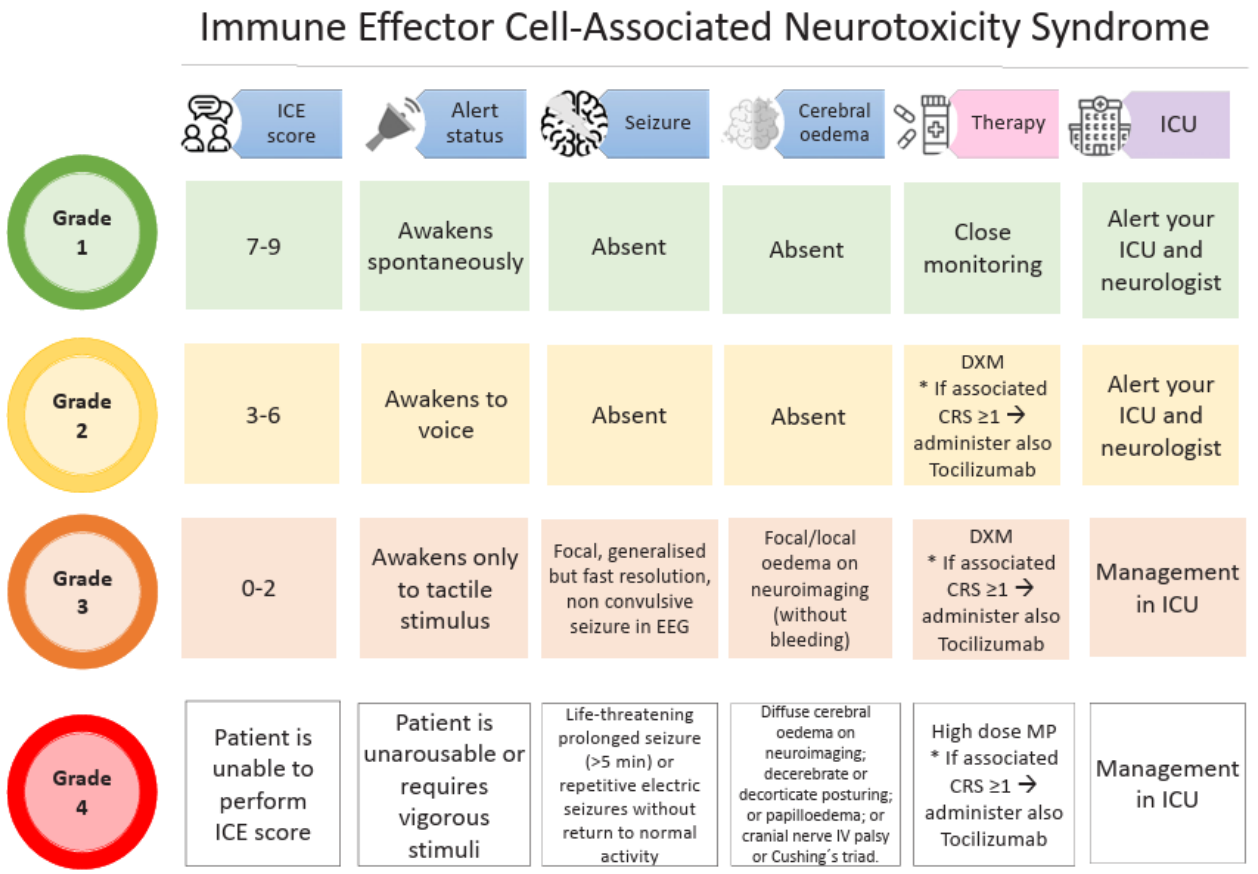

- ❖ Vasopressor = blood pressure supporting medicine
- ❖ Hypoxia = low blood oxygen



Adapted from Yáñez L, Alarcón A, Sánchez-Escamilla M, Perales MA. *ESMO Open*. 2020;4(Suppl 4):e000746.

# Early Toxicities of CAR-T: Neurotoxicity

- Grade 1 = confusion
- Grade 2 = word-finding difficulty (not a stroke)
- Grade 3 = hard to wake up or seizure or “lights on nobody home”
- Grade 4 = coma or brain swelling

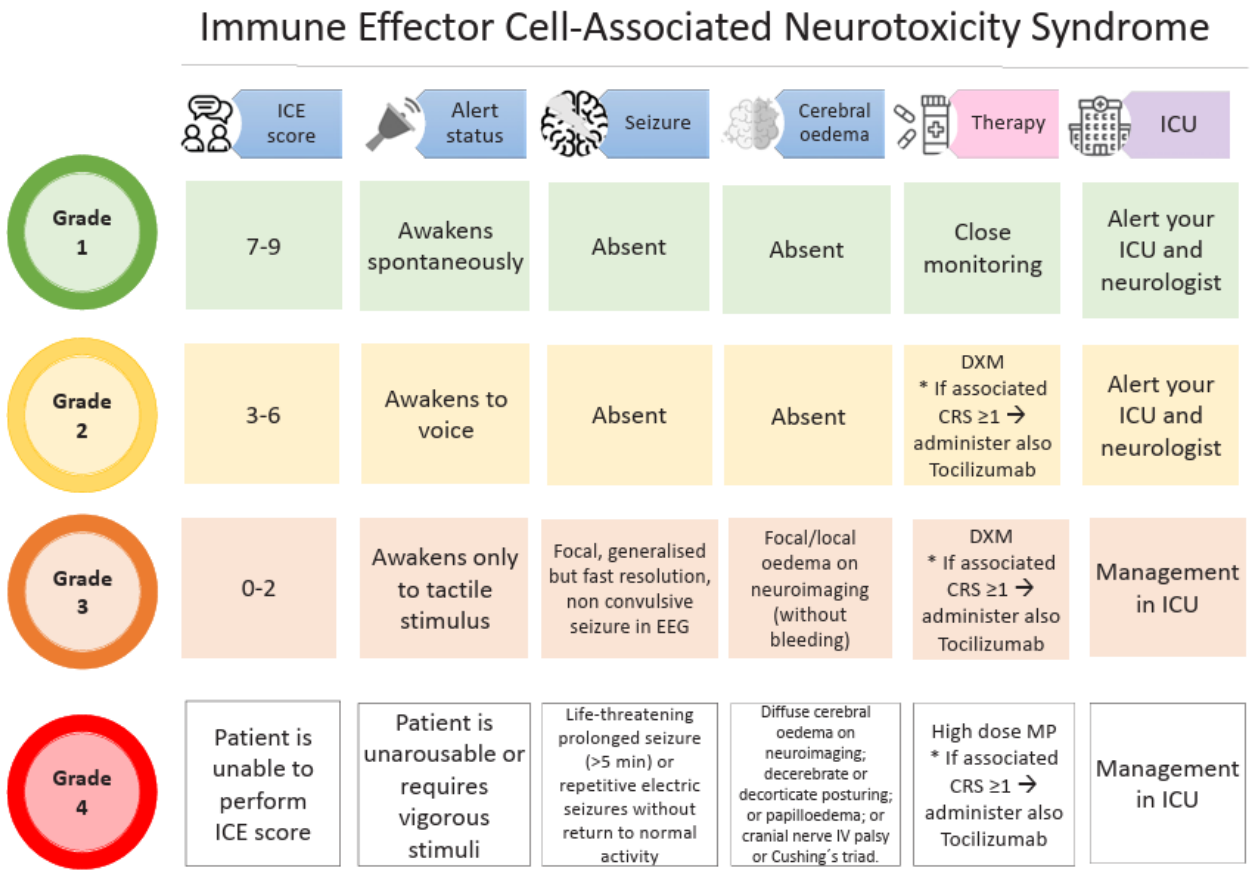





Adapted from Yáñez L, Alarcón A, Sánchez-Escamilla M, Perales MA. *ESMO Open*. 2020;4(Suppl 4):e000746.

# Early Toxicities of CAR-T: Onset of Neurotoxicity

- Onset after cytokine release syndrome
- Typically, short-lived
- Not permanent
- Older patients or those with mild cognitive impairment pre-CAR may have a more prolonged recovery

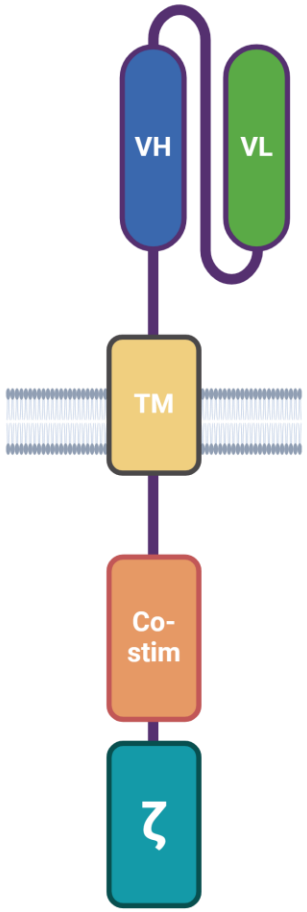





Adapted from Yáñez L, Alarcón A, Sánchez-Escamilla M, Perales MA. *ESMO Open*. 2020;4(Suppl 4):e000746.

# Rates of Cytokine Release Syndrome and Neurotoxicity

| | Axi-cel (Yescarta)<br>Brexu-cel (Tecartus) |
|---|---|
| CAR motor | CD28 |
| CRS | ~90%<br><5% severe |
| Neurotox | ~60%<br>25% severe |

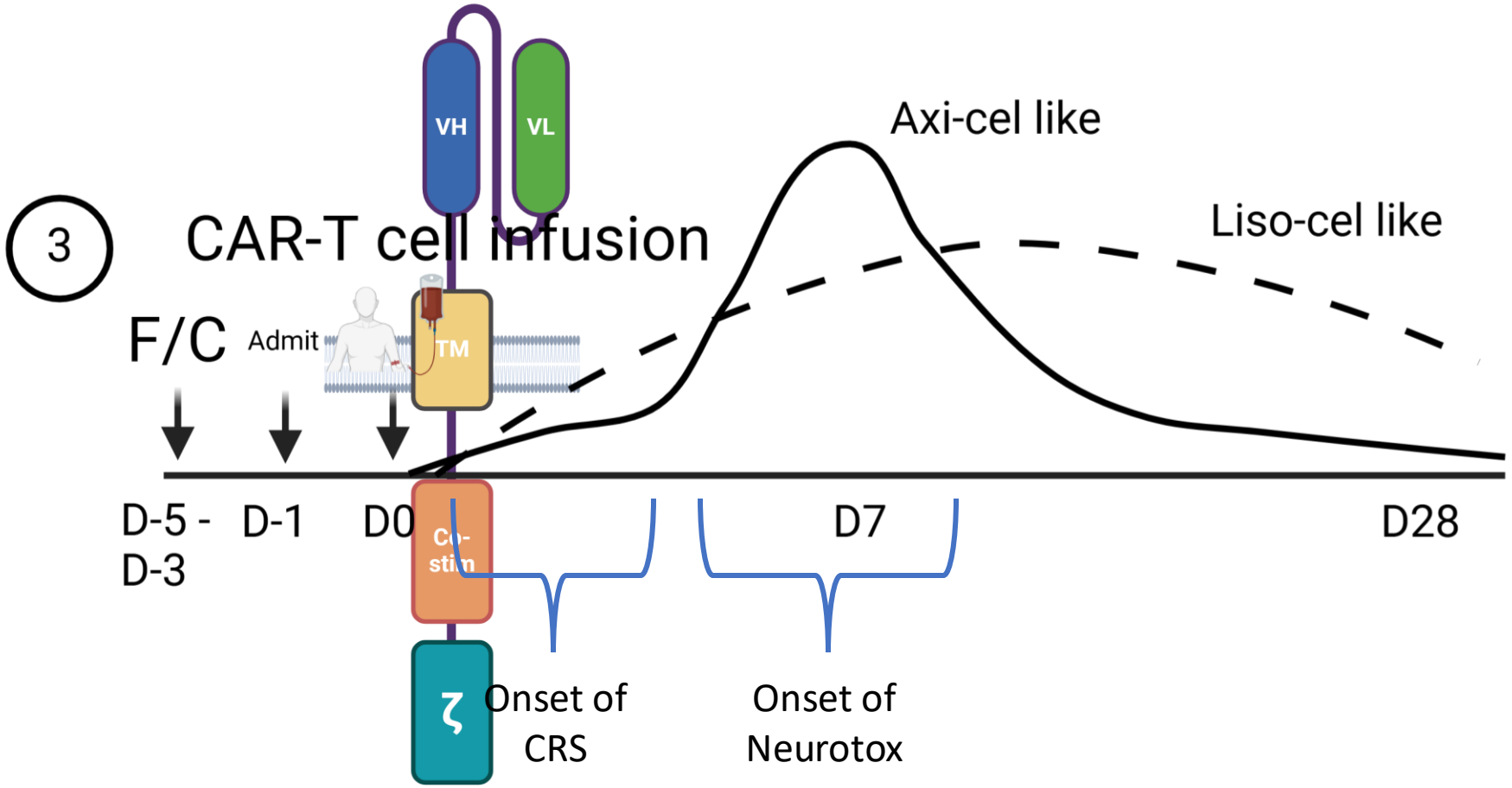



| | Liso-cel (Breyanzi)<br>Tisa-cel (Kymriah) |
|---|---|
| CAR motor | 41BB |
| CRS | ~75%<br><5% severe |
| Neurotox | ~10-30%<br>5-10% severe |



Neelapu, NEJM 2017; Schuster NEJM 2018, Abramson Lancet 2020

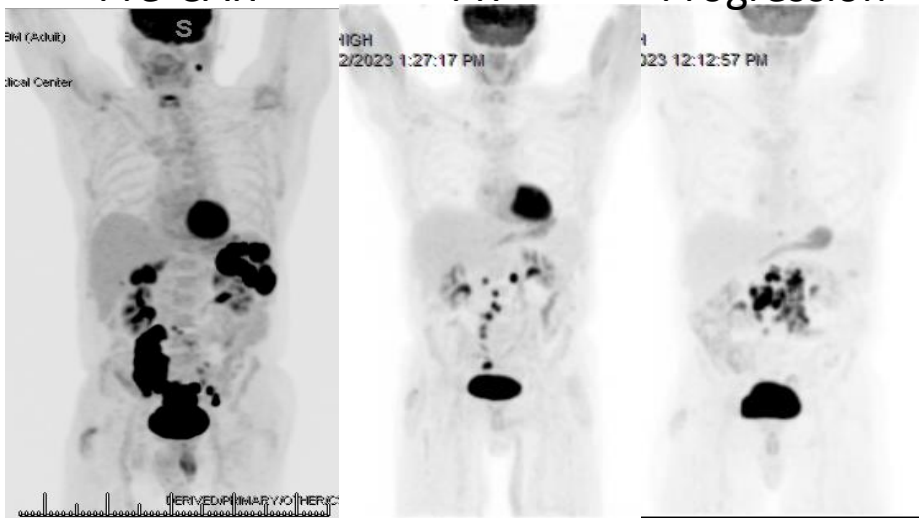
# Onset of Cytokine Release Syndrome (CRS) and Neurotoxicity



# Efficacy of CAR-T: Response

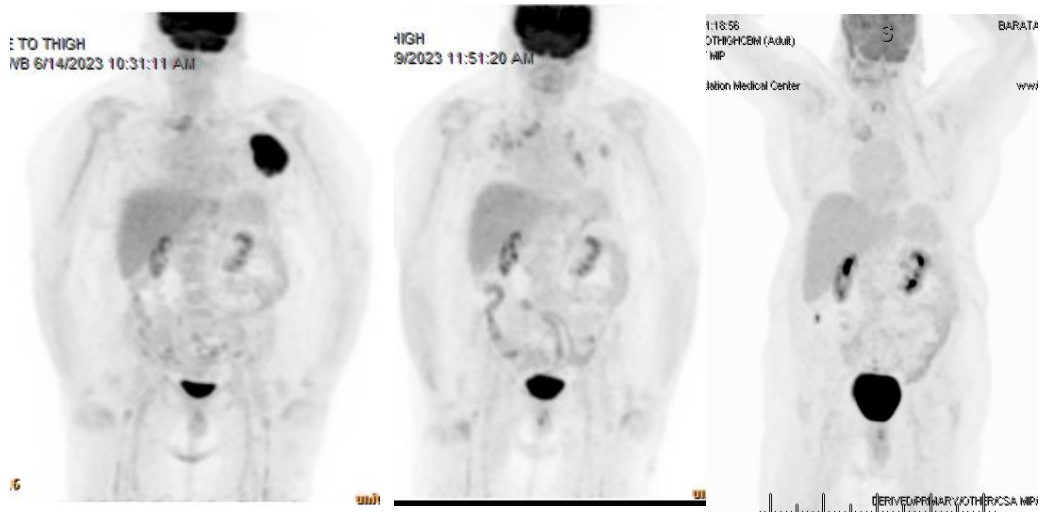
- Partial Response – tumor shrinks by >50%

Pre-CAR PR Progression



- Complete Response – no detectable tumor on scan

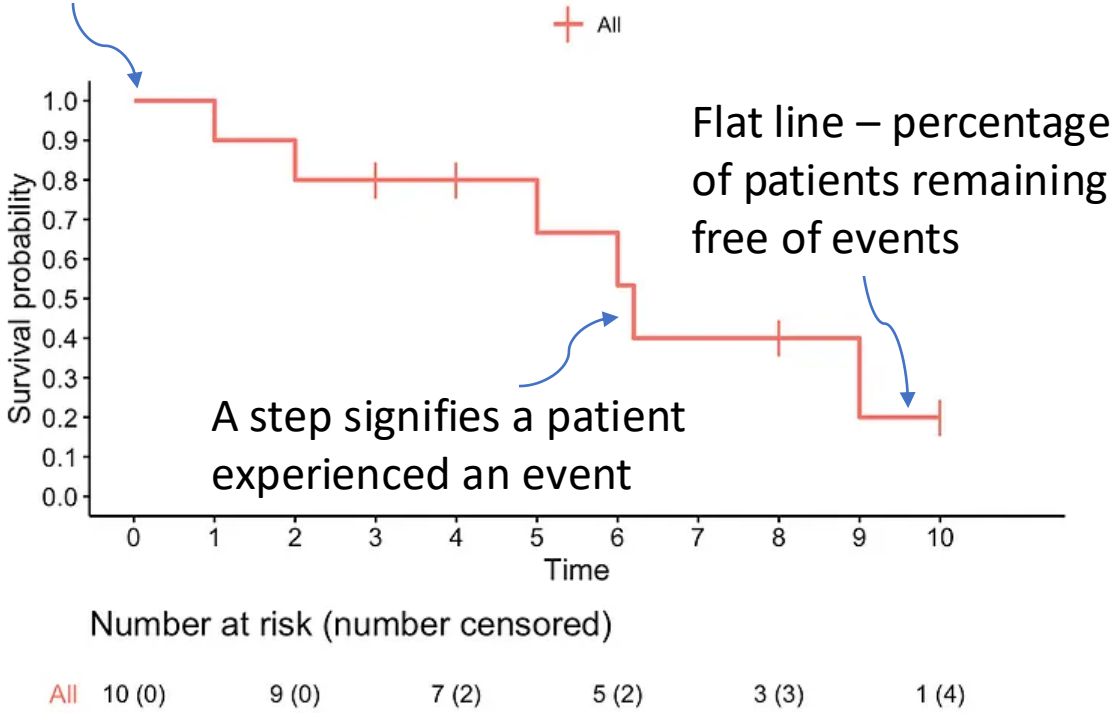
Pre-CAR CR Ongoing CR



# Efficacy of CAR-T: Survival

- Oncologists rely on Kaplan Meier curves to interpret effectiveness of a treatment over time
  - Overall Survival – is the patient alive or dead?
  - Progression-free survival – is the patient alive and in remission?

100% of patients are alive and without an event (ie death when OS, death or relapse if PFS



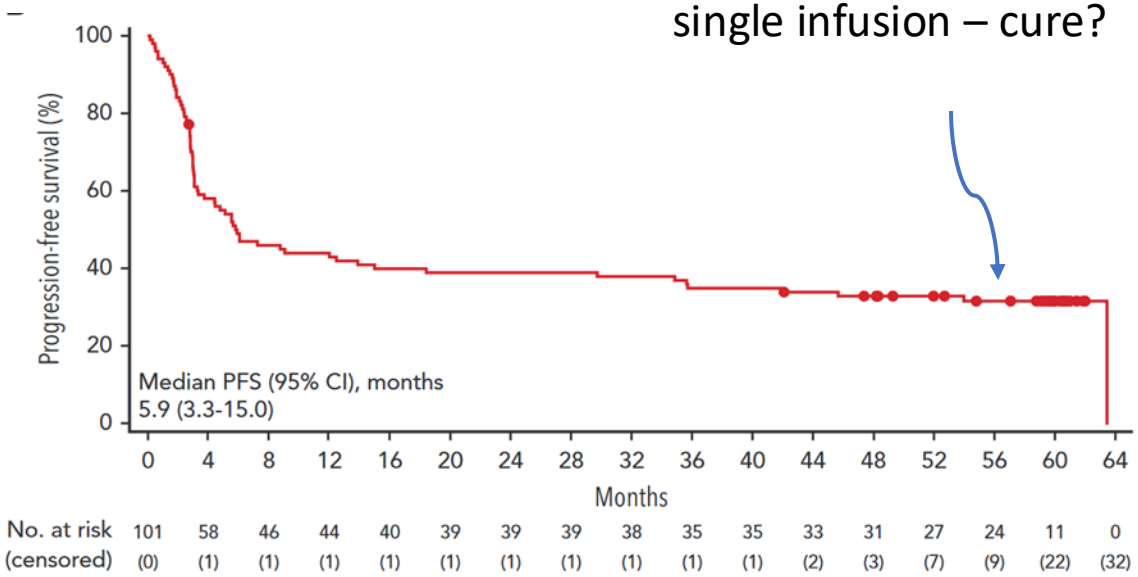



https://medium.com/towards-data-science/kaplan-meier-curves-c5768e349479. Accessed March 13,2025

# CAR-T Has High Response Rates, Durability Occurs in a Proportion of Patients

| | Diffuse Large B-cell Lymphoma | Follicular Lymphoma | Mantle Cell Lymphoma |
|---|---|---|---|
| Complete Remission | 50-60% | 75-90% | ~60% |
| Progression-free Survival | ~30-40% @ 5 yrs | ~50% @5 yrs | ~20-40%@ 4yrs |
| Overall Survival | ~50% @ 5 yrs | ~70% @ 5 yrs | 35—50% @ 4 yrs |

5 year remission after single infusion – cure?

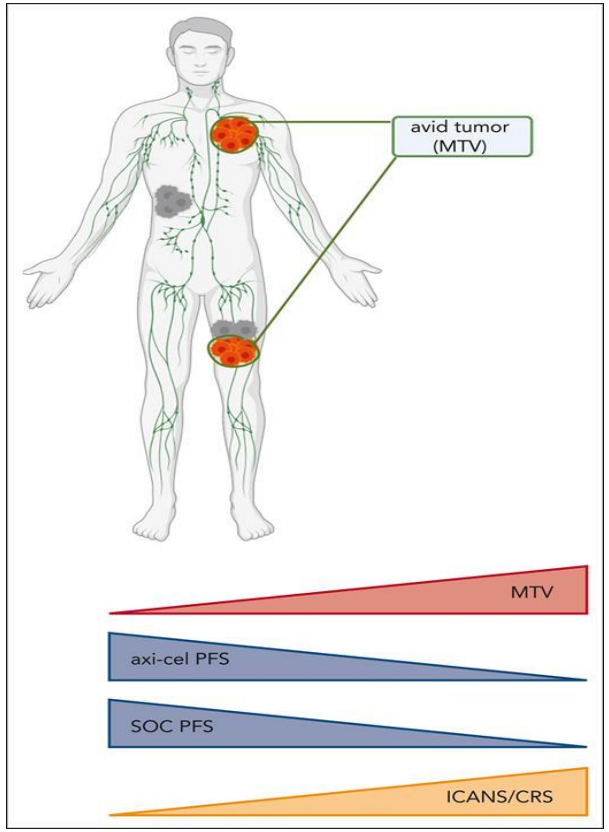


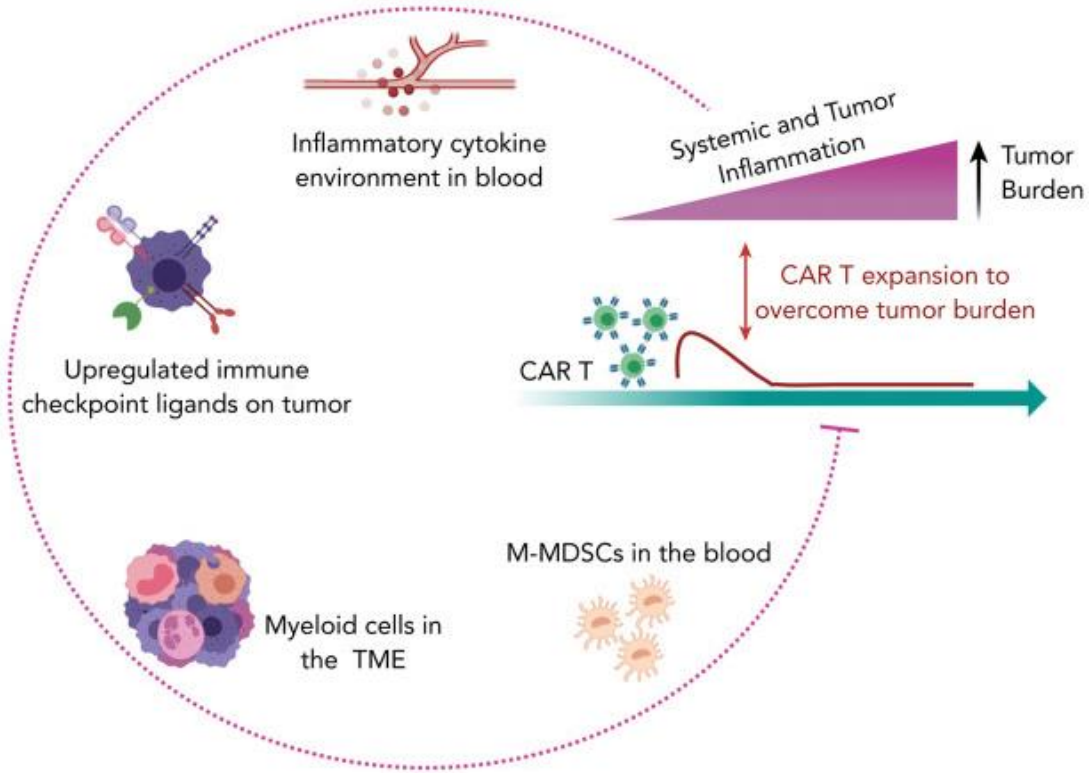

- DLBCL example of potential of CAR-T – does this apply to FL and MCL?



Neelapu, NEJM 2017; Schuster NEJM 2018, Abramson Lancet 2020; Neelapu, Blood 2023; Wang JCO 2023; Wang JCO 2024; Morchauser Nat Med 2024; Jacobson Lancet Onc 2022

# High Tumor Burden and Inflammation Impact CAR Effectiveness



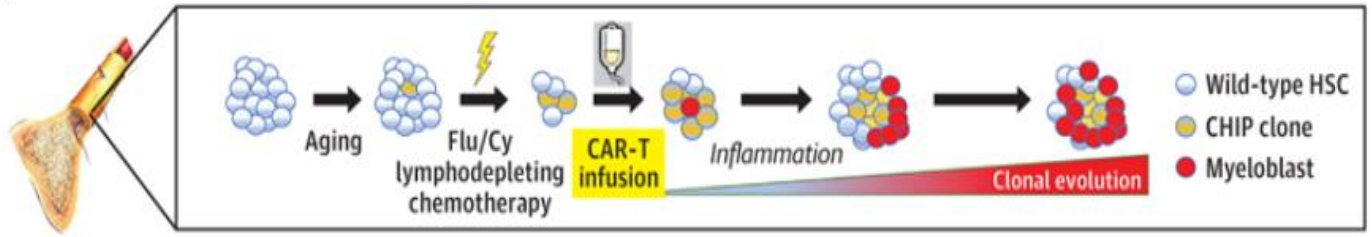



Darnell, Blood 2024; Jain Blood 2021

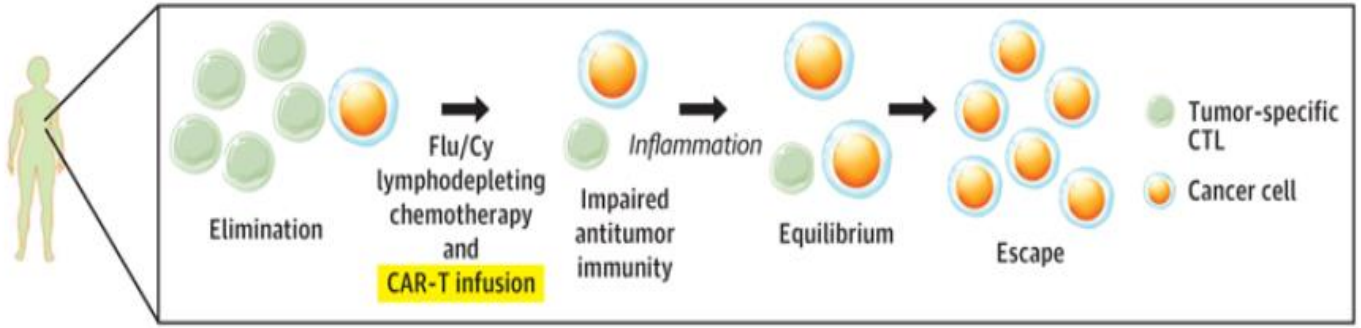
# Late Toxicities of CAR-T: Second Cancers

- CAR-T cell expansion causes significant inflammation as well as a weakened immune system
- This can lead to outgrowth of blood and solid cancers
- Blood cancer is more common and occurs in ~5% of patients

B Blood cancer development post CAR-T



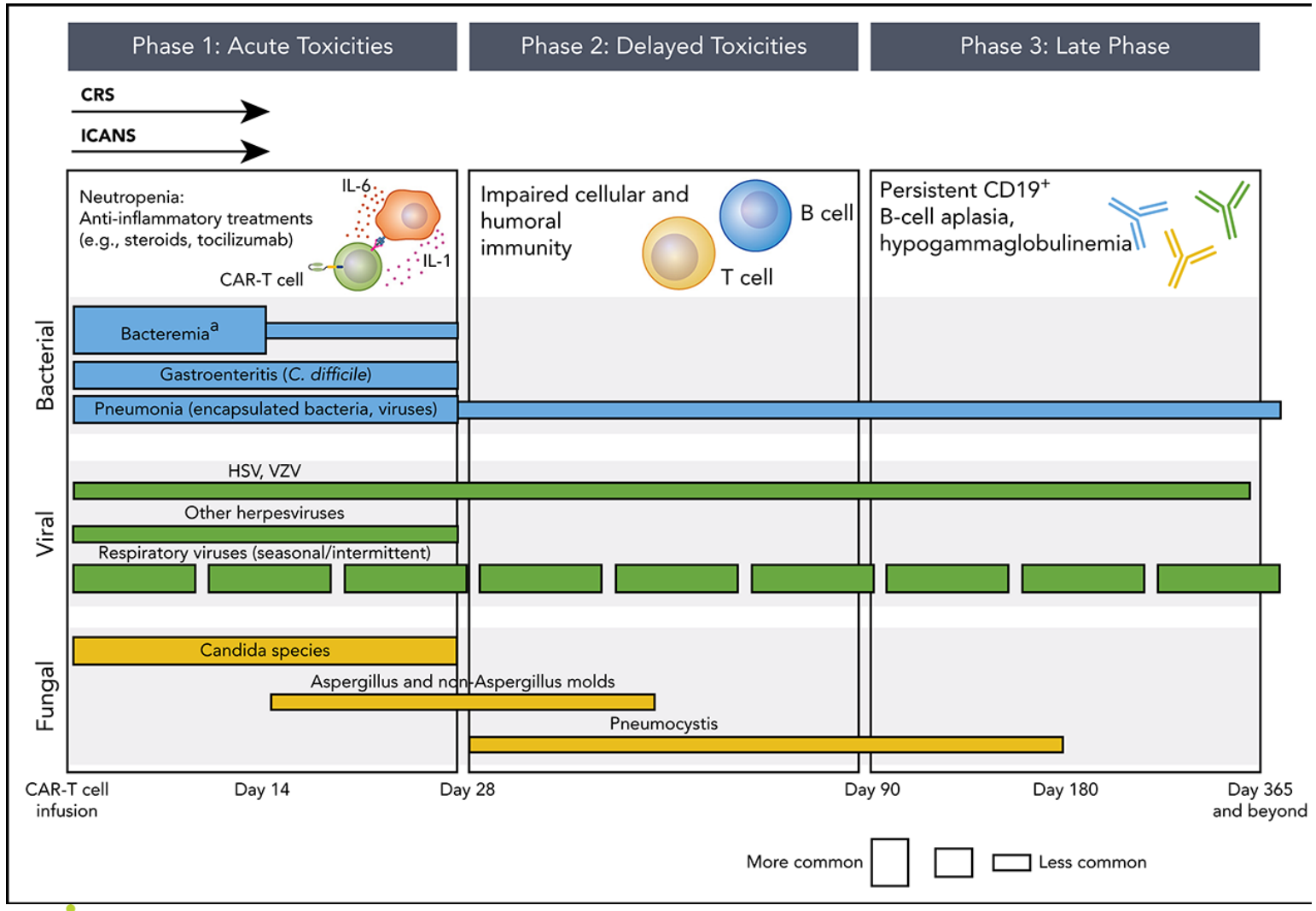

C Solid tumor development post CAR-T

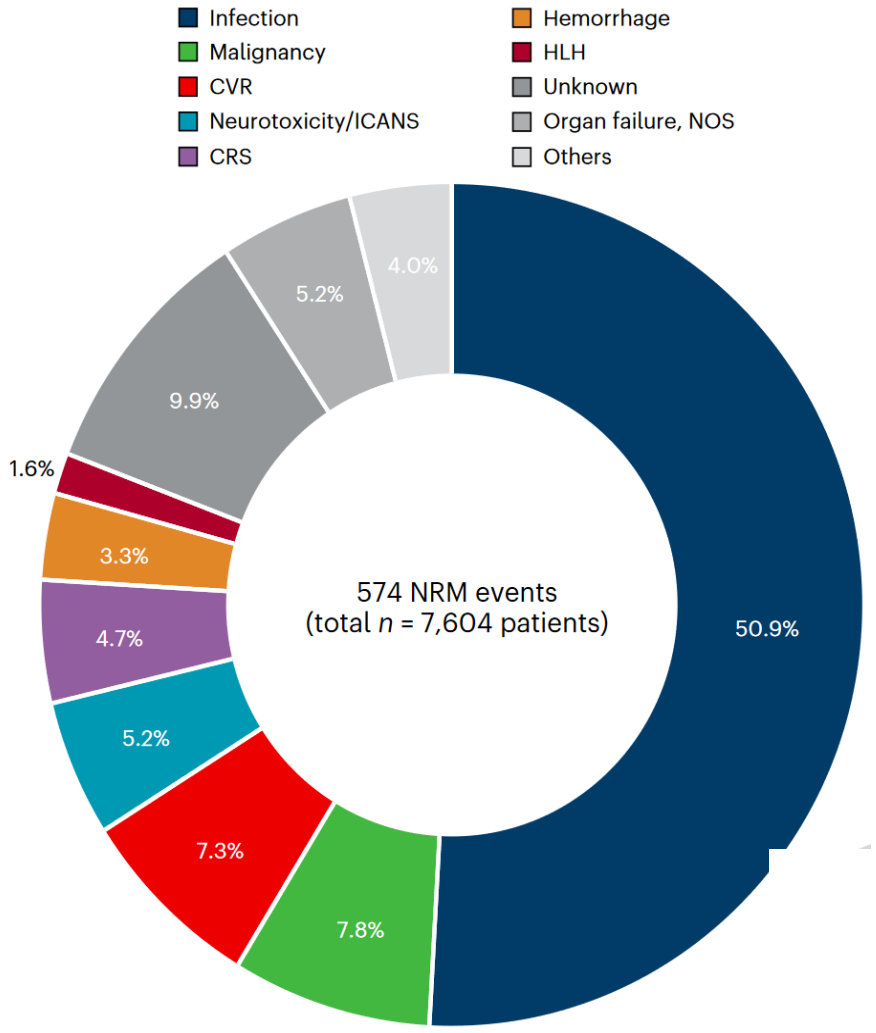





Patel, Jama Onc 2025

# Late Toxicities of CAR-T: Infection






Hill, Blood 2021;Cordos dos Santos Nat Med 2024

# What If I Relapse After CAR-T?

**DLBCL**

- Glofitamab
- Epcoritamab
- Loncastuximab tesirine
- Pola-BR
- Mosunetuzumab-Pola
- Clinical trials

**Mantle Cell Lymphoma**

- Glofitamab
- Ventoclax-based
- Pirtobrutinib
- Chemotherapy
- Clinical trials

**Follicular Lymphoma**

- Glofitamab
- Mosunetuzumab
- Zanubrutinib-Obinutzumab
- Tamezostat
- Loncastuximab
- Clinical trials



Haydu and Abramson, Bld Adv 2024

# Summary

- CAR-T has gained approval in both aggressive (DLBCL) and indolent lymphomas (MCL, FL).
- 5-year follow-up shows a proportion of patients will have durable remissions, suggestive of a potential cure.
- CAR-T remains an involved logistical process both before and after treatment – a good support system is important to make the process smooth
- Longer-term toxicities are increasingly recognized and an active area of research to allow people to enjoy remissions induced by CAR-T
- The treatment paradigm in lymphoma is changing rapidly, and when CAR-T is used may be different in the coming years. As a powerful modality, CAR-T will likely remain a mainstay of treatment