# Our Future RE-IMAGINED

DISCOVERY ▪ MANUFACTURING ▪ PATIENTS

# 34th PIA Annual Meeting

PIA

INNOVATION THAT CARES

Pharmaceutical Industry Association
Of Puerto Rico

# Cellular Therapy 2024

Cristian I. Rodríguez Arocho, MD
BMT and Cellular Therapy
Hematology Oncology

# Agenda

Introduction

Cellular Therapy Basics

FDA approved cellular therapy with indications

CART vs BITEs

# Conflict of Interest


BMS

Abbvie/Genmab

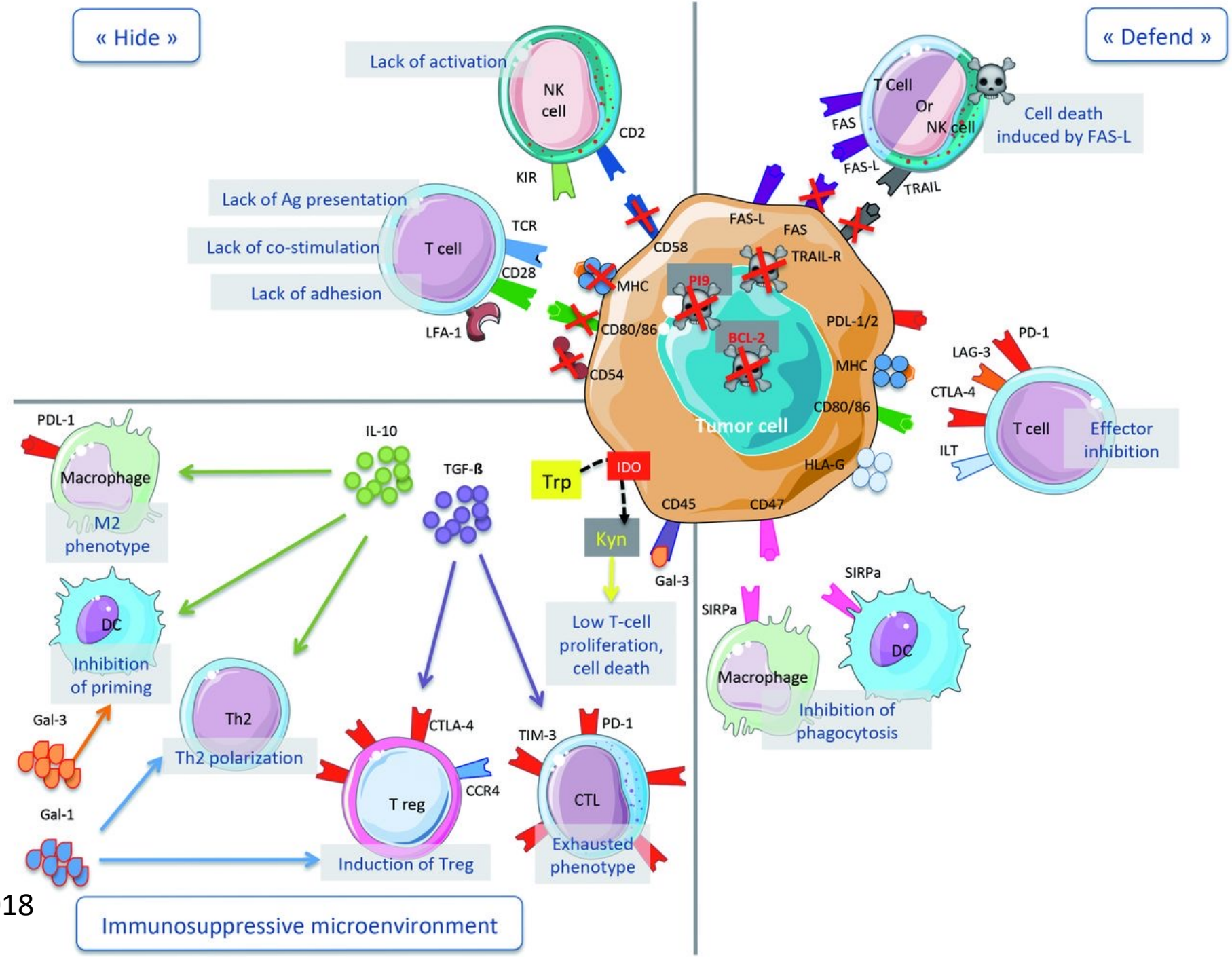
Alexion

Sofi

Genentech

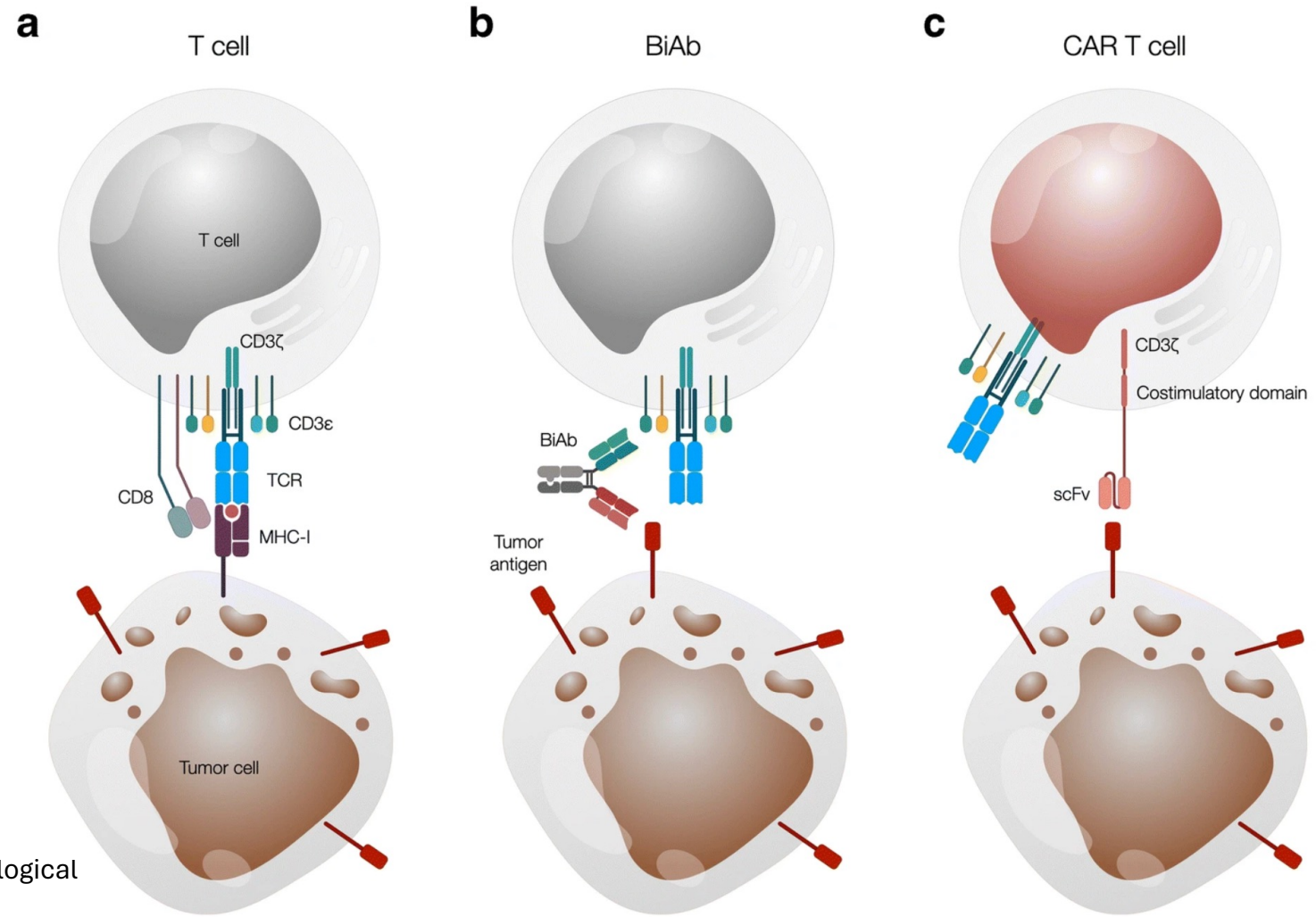
MorphoSys/Incyte

Lilly




Charette et al
Haemaologica 2018

# CART vs Bi-Specific Monoclonal Antibodies




Schwerdtfeger et al., Current Hematological Malignancy 2021

# CART CART vs Bi-Specific Monoclonal Antibodies

**CART**

One infusion

Manufacture time (2-8 weeks)

$$$

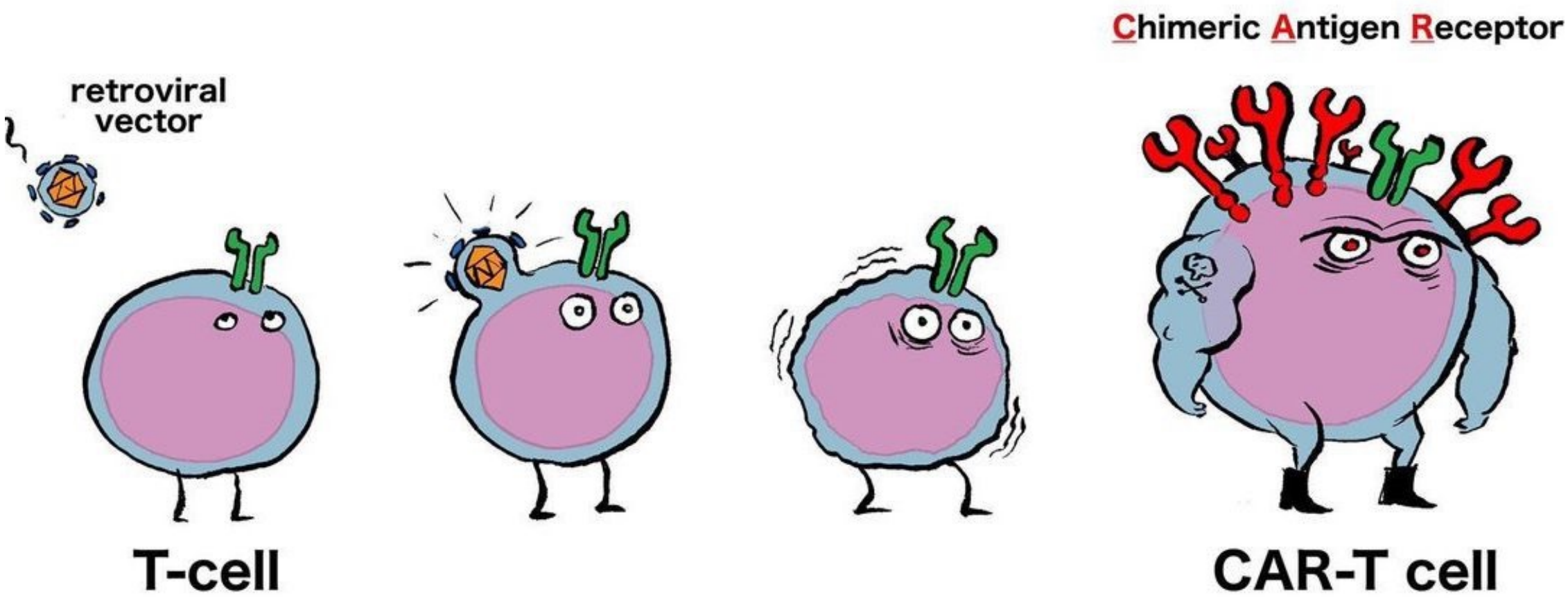
**BITEs**

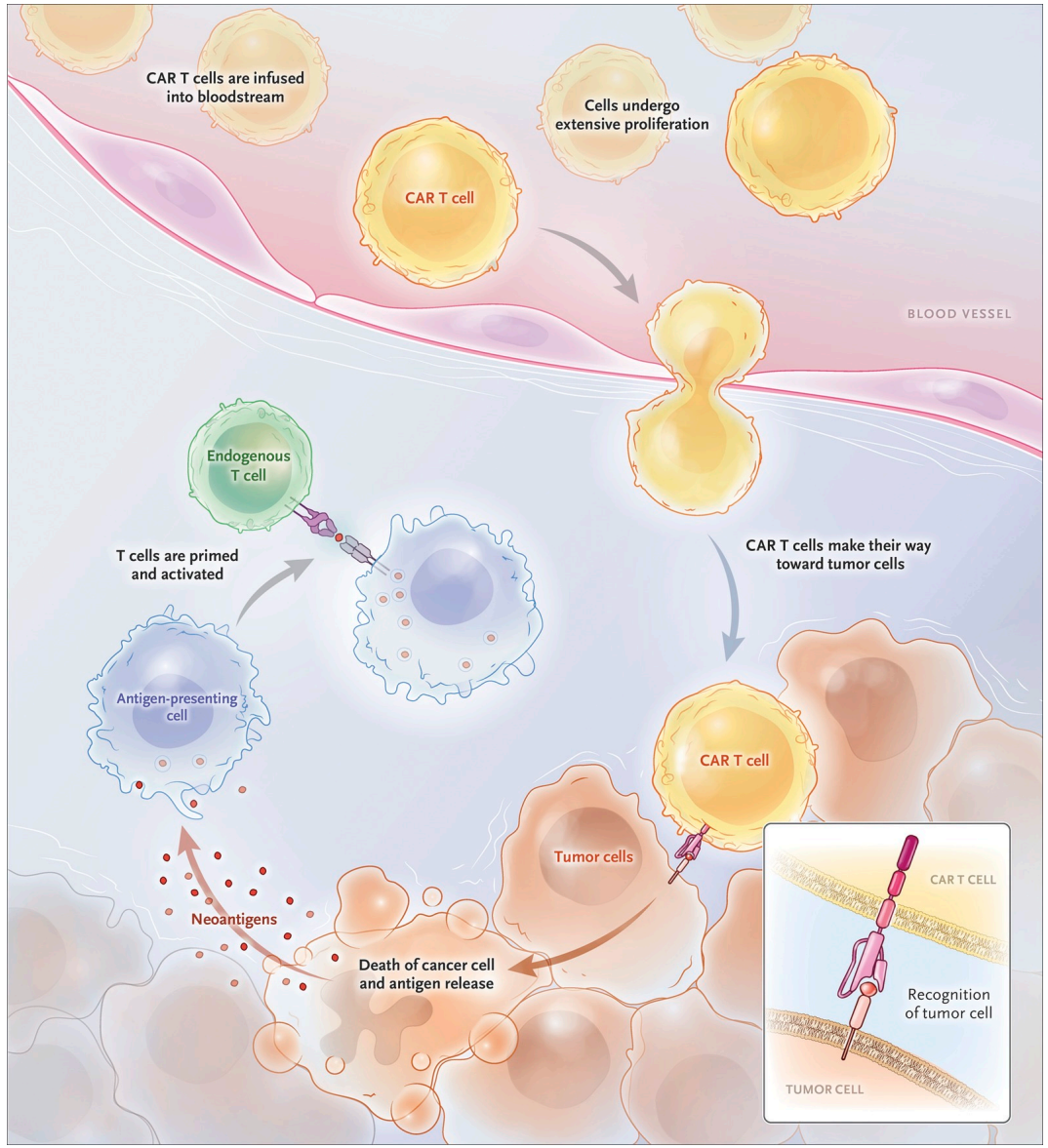
Interval therapy

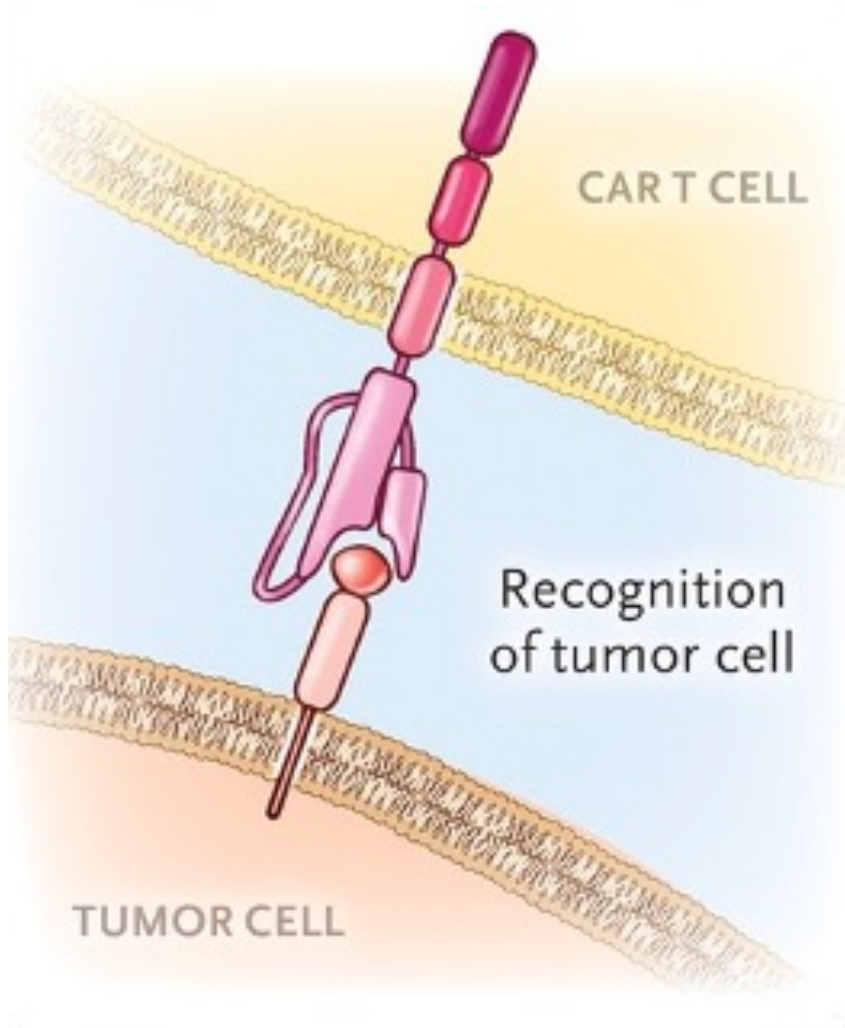
Off the shelf

$$$

# CART Therapy





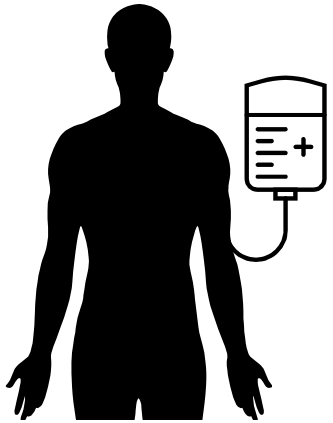




June CH, Sadelain M. N Engl J Med 2018;379:64-73

# Autologous CAR T-Cell Therapy: Underlying Principles

## Leukapheresis

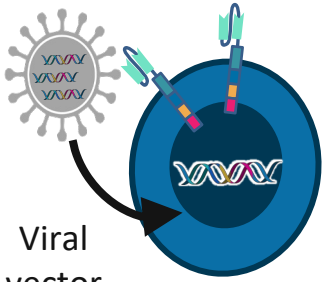
Collect patient's white blood cells

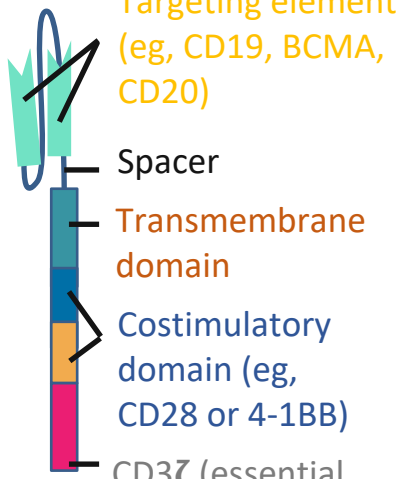


## Manufacturing

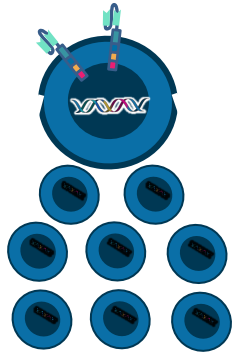
Isolate and activate T cells

Engineer T cells with CAR gene




Expand CAR T cells

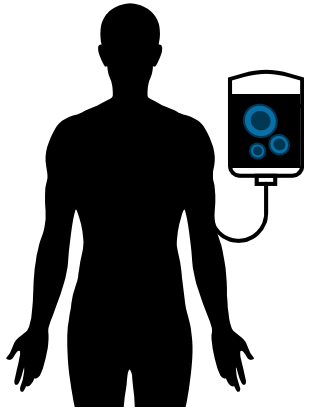


Median manufacturing time: 17-28 days

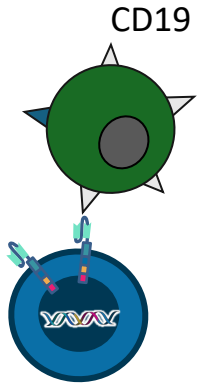
Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

## Infusion

Infuse same patient with CAR T cells



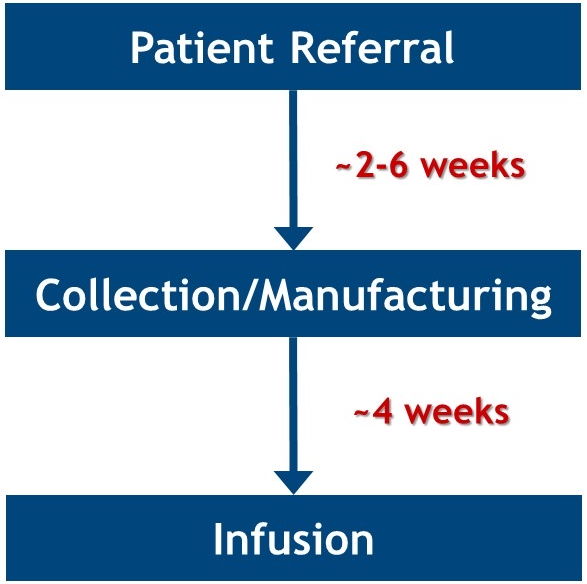
## Activity




Majors. EHA 2018. Abstr PS1156. Lim. Cell. 2017;168:724. Sadelain. Nat Rev Cancer. 2003;3:35.
Brentjens. Nat Med. 2003;9:279. Park. ASH 2015. Abstr 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

Slide credit: clinicaloptions.com

# CAR T-cell Therapy: Barriers To Timely Treatment




**PATIENT**

- ✓ Health care disparities
- ✓ Performance status
- ✓ Comorbidities

**DISEASE**

- ✓ Stage and disease tempo
- ✓ Need for bridging therapy

**ONCOLOGIST**

- ✓ Timely referral

**PAYER**

- ✓ Cost
- ✓ Timely authorization

**CENTER**

- ✓ Capacity

**Cleveland Clinic Experience***

- ✓ N=38 ref/rel large B-cell lymphoma referrals for Axi-cel (03/18 – 05/19)
- ✓ 11 (29%) did not receive Axi-cel (median survival 1 month):
  - ✓ Rapid disease progression 55%
  - ✓ Complications of prior treatment 27%
  - ✓ Manufacturing failure 1%

** A Mian et al, ASH Annual Meeting, 2019 (Blood, 134 [Suppl 1]: 4452)*

# FDA Approved CART indications

- Indications
  - Relapse/Refractory **High grade B cell lymphoma (DLBCL, PMBCL, TFL)** after 1 line of systemic therapy (primary refractory or relapsed within 12 months after fishing chemo-immunotherapy) or R/R HBCL after > 2 lines of systemic therapy
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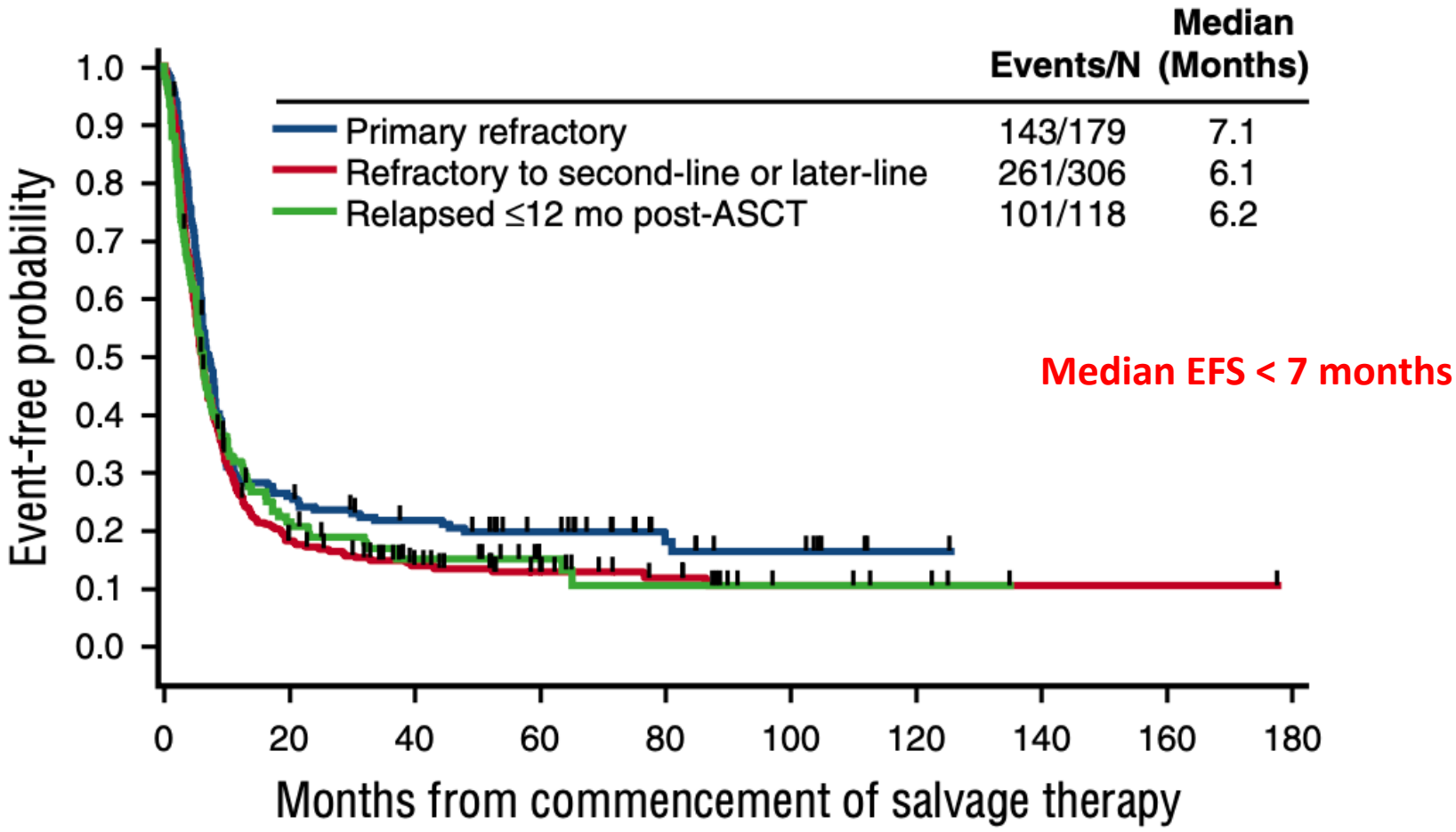
  - Relapse/Refractory **MM** after 4 lines of therapy (including IMIDs, PI and anti CD38 Abs

Alexander M, Culos K, Roddy J, et al. Chimeric Antigen Receptor T Cell Therapy: A Comprehensive Review of Clinical Efficacy, Toxicity, and Best Practices for Outpatient Administration. *Transplant Cell Ther*. 2021;27(7):558-570. doi:10.1016/j.jtct.2021.01.014

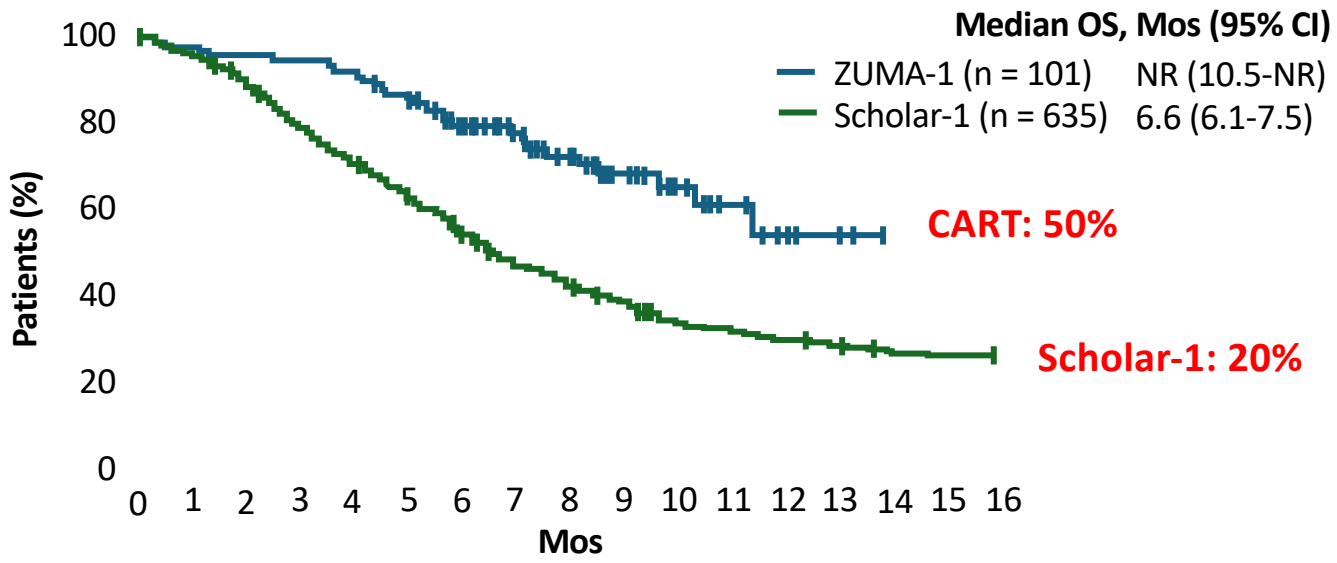
# Refractory DLBCL Scholar-1




Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood*. 2017;130(16):1800-1808. doi:10.1182/blood-2017-03-769620

# ZUMA-1 vs SCHOLAR-1: Outcomes With Axicabtagene Ciloleucel vs SOC for Refractory DLBCL

- Retrospective analysis comparing outcomes with axicabtagene ciloleucel (in ZUMA-1) vs SOC (in SCHOLAR-1*)[1]




*Retrospective analysis of 2 phase III trials and 2 observational cohorts in which patients received treatment for refractory disease after first-/second-line therapy or relapsed disease after ASCT.[2]

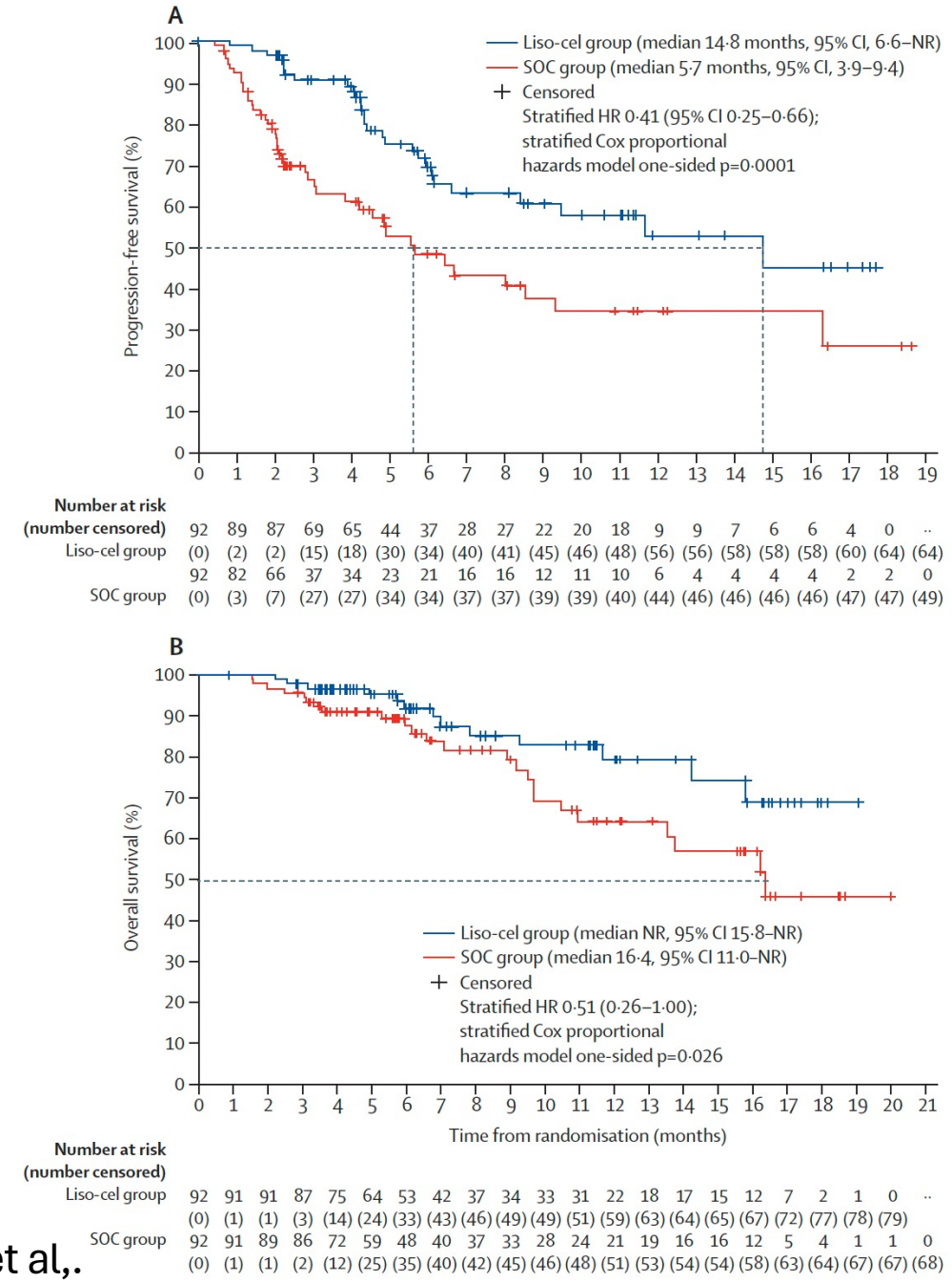
1. Neelapu. SOHO 2017. Abstr NHL-023. 2. Crump. Blood. 2017;130:1800.

Slide credit: clinicaloptions.com

# Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial

*Manali Kamdar, Scott R Solomon, Jon Arnason, Patrick B Johnston, Bertram Glass, Veronika Bachanova, Sami Ibrahimi, Stephan Mielke, Pim Mutsaers, Francisco Hernandez-Ilizaliturri, Koji Izutsu, Franck Morschhauser, Matthew Lunning, David G Maloney, Alessandro Crotta, Sandrine Montheard, Alessandro Previtali, Lara Stepan, Ken Ogasawara, Timothy Mack*, Jeremy S Abramson, for the TRANSFORM Investigators†*

# Liso-Cel




Kamdar et al,. Lancet 2022

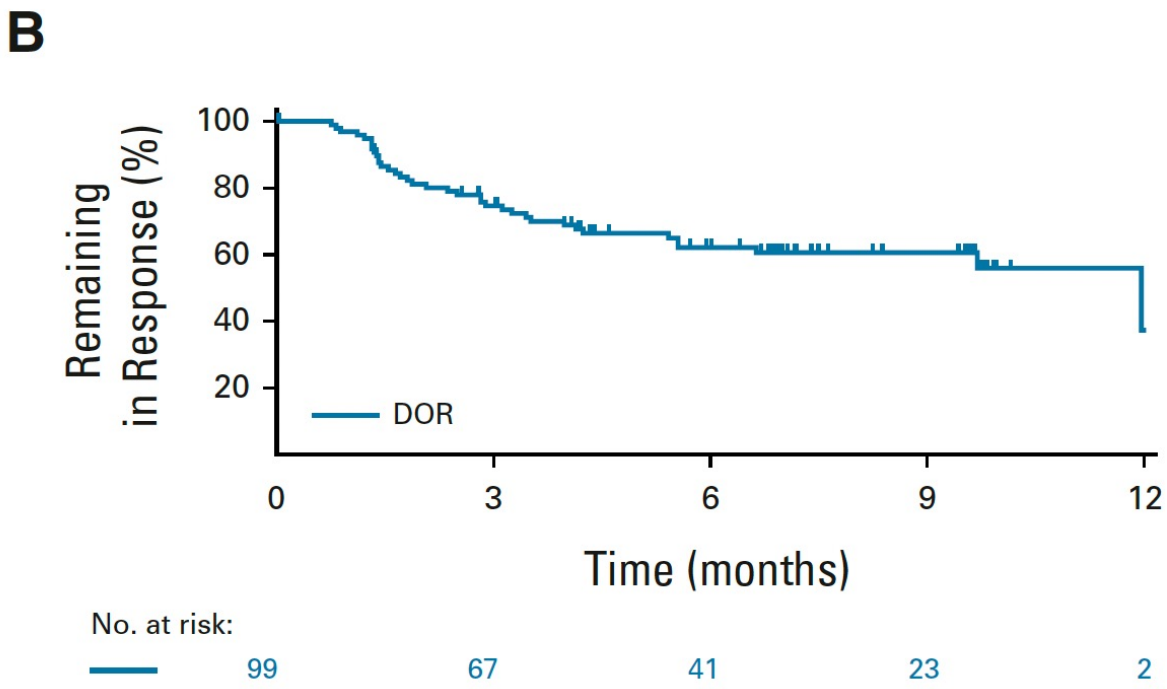
# FDA Approved CART for Large B Cell Lymphoma

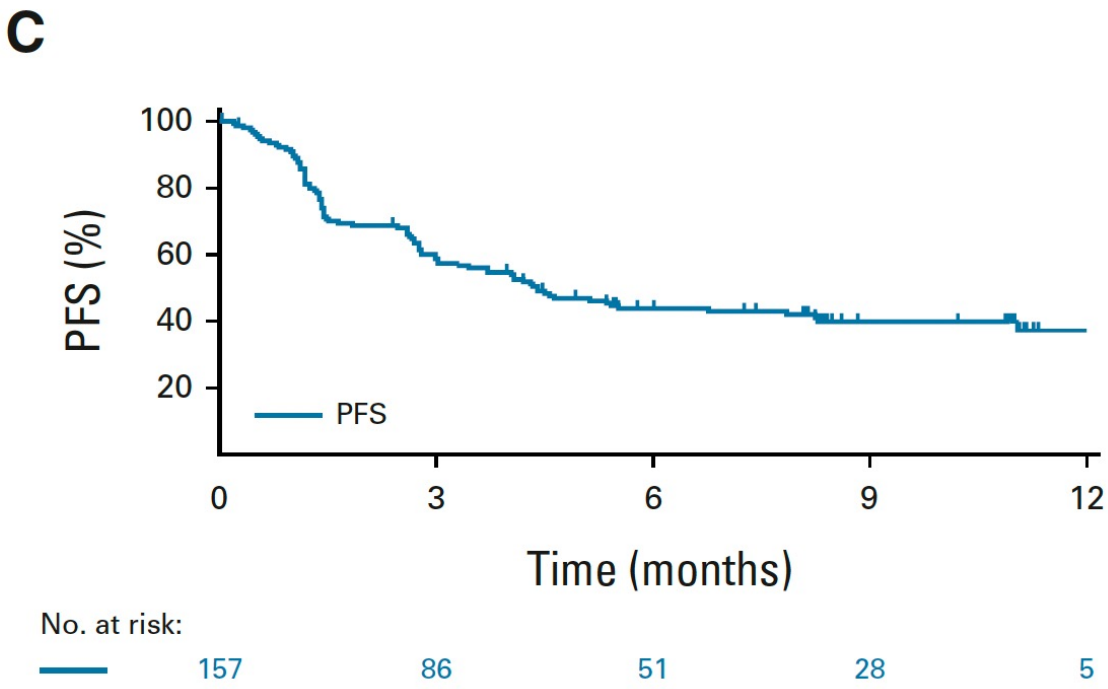
| Trial | Disease | Efficacy |
|---|---|---|
| JULIET (Tis-Cel) | Adult patients with R/R LBCL after two or more lines of systemic therapy, including DLBCL not otherwise specified (NOS), high grade B-cell lymphoma and TFL. | ORR 52%<br>CR 40%<br>Median PFS: NR<br>Median OS: 12 mo |
| ZUMA-1, ZUMA-7 (Axi-Cel) | Primary refractory LBCL that is refractory to first line chemoimmunotherapy or that relapses within 12 months of first line chemoimmunotherapy.<br><br>Adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy, including DLBCL NOS, PMBCL, high grade B-cell lymphoma, and TFL. | ORR 82%<br>CR 54%<br>Median PFS: 5.8 mo<br>Median OS: NR |
| TRANSCEND NHL 001 (Liso-Cel) | LBCL refractory to first line chemoimmunotherapy or relapse within 12 months of first line chemoimmunotherapy including DLBCL NOS, TFL, high- grade B-cell lymphoma, PMBCL, and FL grade 3B.<br><br>Relapsed or refractory LBCL disease after two or more lines of systemic therapy. | ORR 73%<br>CR 53%<br>Median PFS: 6.8 mo<br>Median OS: 21.1 mo |

# What about BITEs for R/R DLBCL?

- 3rd line **Epcoritamab** (indefinite) or **Glofitamab** (max of 12 cycles)
- **Epcoritamab** (until disease progression or unacceptable toxicity)
  - ORR of 63% with CR rate of 39% (phase I/II trial)
  - FDA approved (5/2023) after 2 lines of systemic therapy
- **Glofitamab** + Obinutuzumab
  - ORR of 56% with CR of 43% (phase I/II trial)
  - FDA approved (6/2023) after 2 lines of systemic therapy

# Epcoritamab for R/R HBCL




Hutchings et al,.
The Lancet 2021

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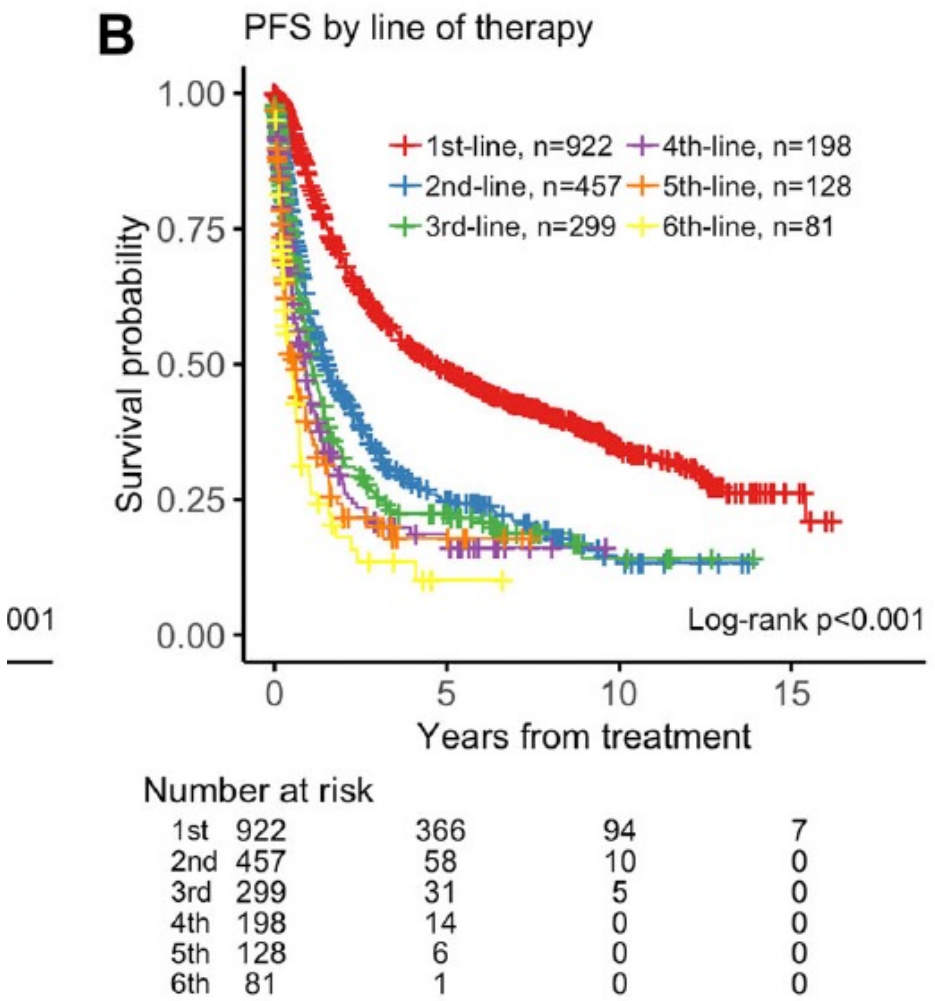
# Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups

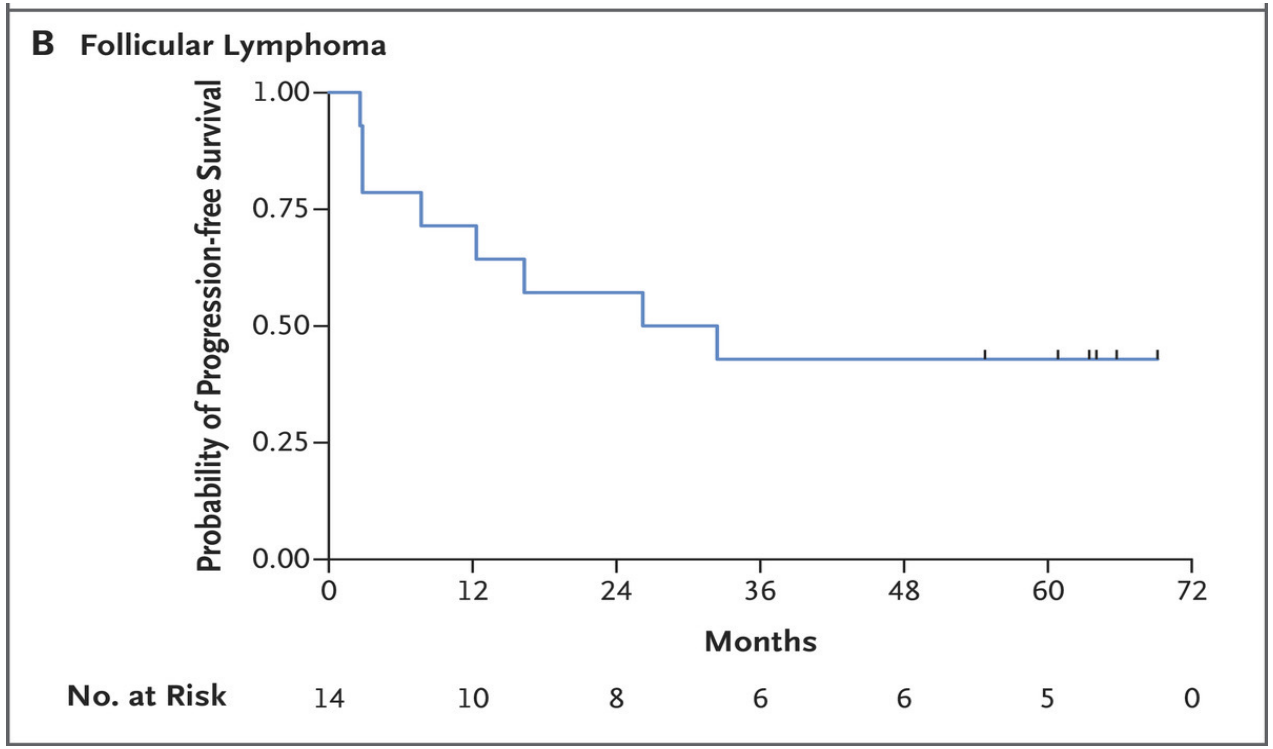



**PFS 3rd line 1.07 years**
**PFS 4th line 0.9 years**
**PFS 5th line 0.55 years**

Batlevi CL, Sha F, Alperovich A, et al. Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups. *Blood Cancer J*. 2020;10(7):74. doi:10.1038/s41408-020-00340-z

# 5-year outcomes for R/R FL with CAR T Cell Therapy

ZUMA 5




FL: POD24; **median lines of therapy: 3**

FL: 71% having a complete response. **At 5 years, 43% of patients (95% CI, 18 to 66) were progression-free**
mDOR: NR

**EA Chong et al. N Engl J Med 2021;384:673-674.**

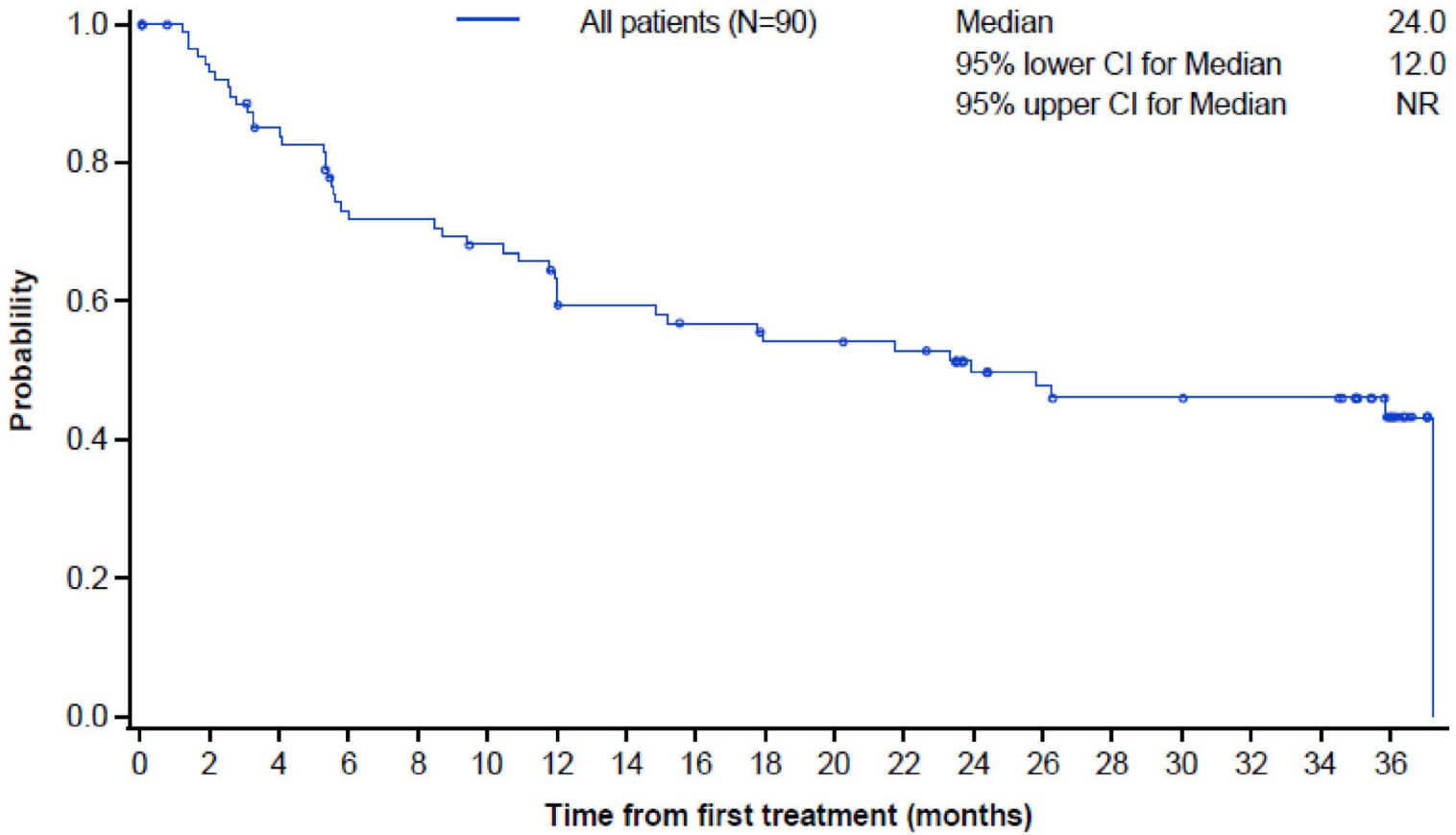
# FDA Approved CART for Follicular Lymphoma

| Trial | Disease | Efficacy |
|---|---|---|
| ZUMA-5 (Axi-Cel) | Adult patients with R/R FL after two or more lines of systemic therapy. | ORR 92% for FL, 85% for MZL<br>CR 80% FL, 60% MZL<br>Median PFS: NR<br>Median OS: NR |
| ELARA (Tis-Cel) | Adult patients with R/R FL after two or more lines of systemic therapy. | ORR 86% for FL,<br>CR 68%<br>mPFS: 37 mo<br>36 mo PFS: 53%<br>mDOR: NR<br>mOS: NR |

# What about BITEs for R/R FL?

- Mosunetuzumab (**8 to 17 cycles**). Phase II study
  - ORR was 80% with 60% CR

**Figure.** Progression-free survival (investigator-assessed) with mosunetuzumab




| | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients remaining at risk | 90 | 81 | 72 | 60 | 59 | 55 | 47 | 46 | 43 | 40 | 40 | 38 | 30 | 27 | 25 | 25 | 24 | 24 | 13 |
| Patients with an event | 0 | 6 | 13 | 23 | 24 | 27 | 34 | 34 | 36 | 38 | 38 | 39 | 41 | 42 | 43 | 43 | 43 | 43 | 44 |

CI, confidence interval; NR, not reached.

Schuster et al., Blood 2023

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# Relapse ALL

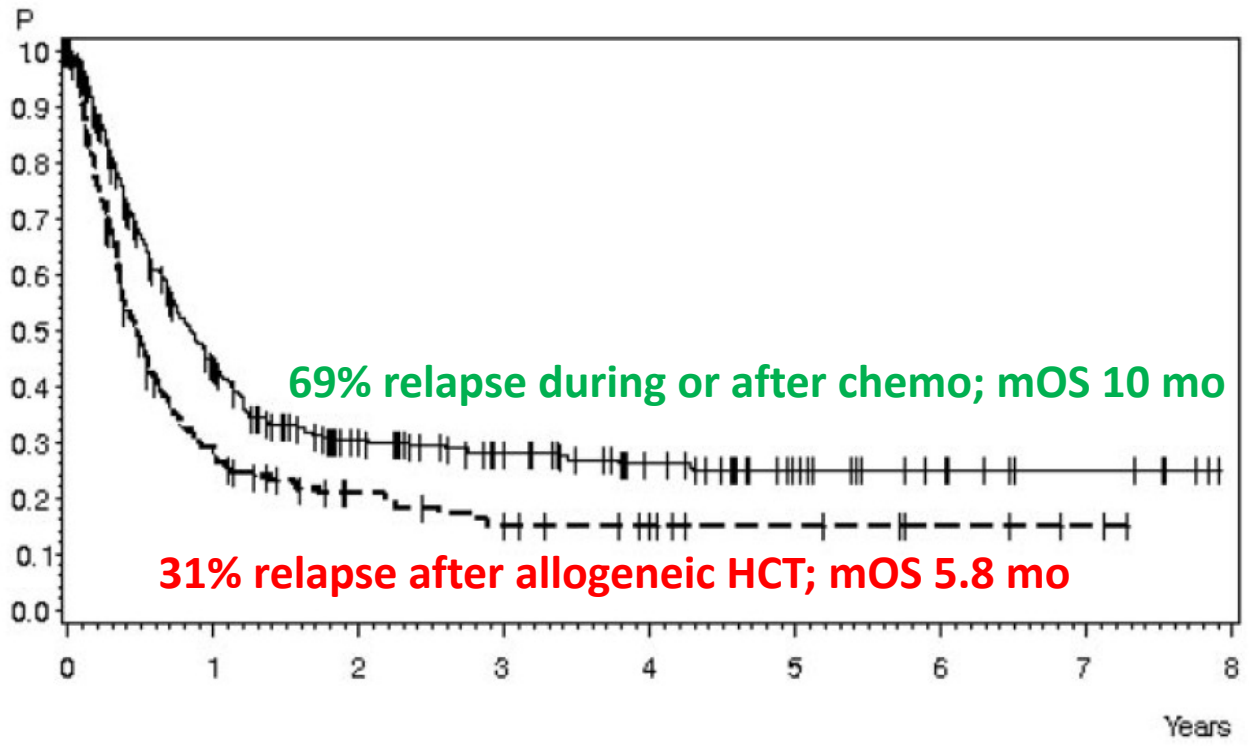



**Figure 1. Survival in patients with relapsed ALL according to first-line therapy.** Relapse during or after chemotherapy, n = 378 (solid line), 28% ± 3% after 3 years, 25% ± 3% after 5 years; median 10 months; relapse after SCT, n = 169 (dashed line), 15% ± 3% after 3 and 5 years, median 5.8 months ($P < .0001$).

N= 547
**CR after 1st salvage 42%**
**CR after 2nd salvage 33%**
**CR after SCT 25%**
mOS at relapse 8.4 mo
**3 years survival 24%**

Gökbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood*. 2012;120(10):2032-2041. doi:10.1182/blood-2011-12-399287

# Relapse ALL pos-allogeneic HCT

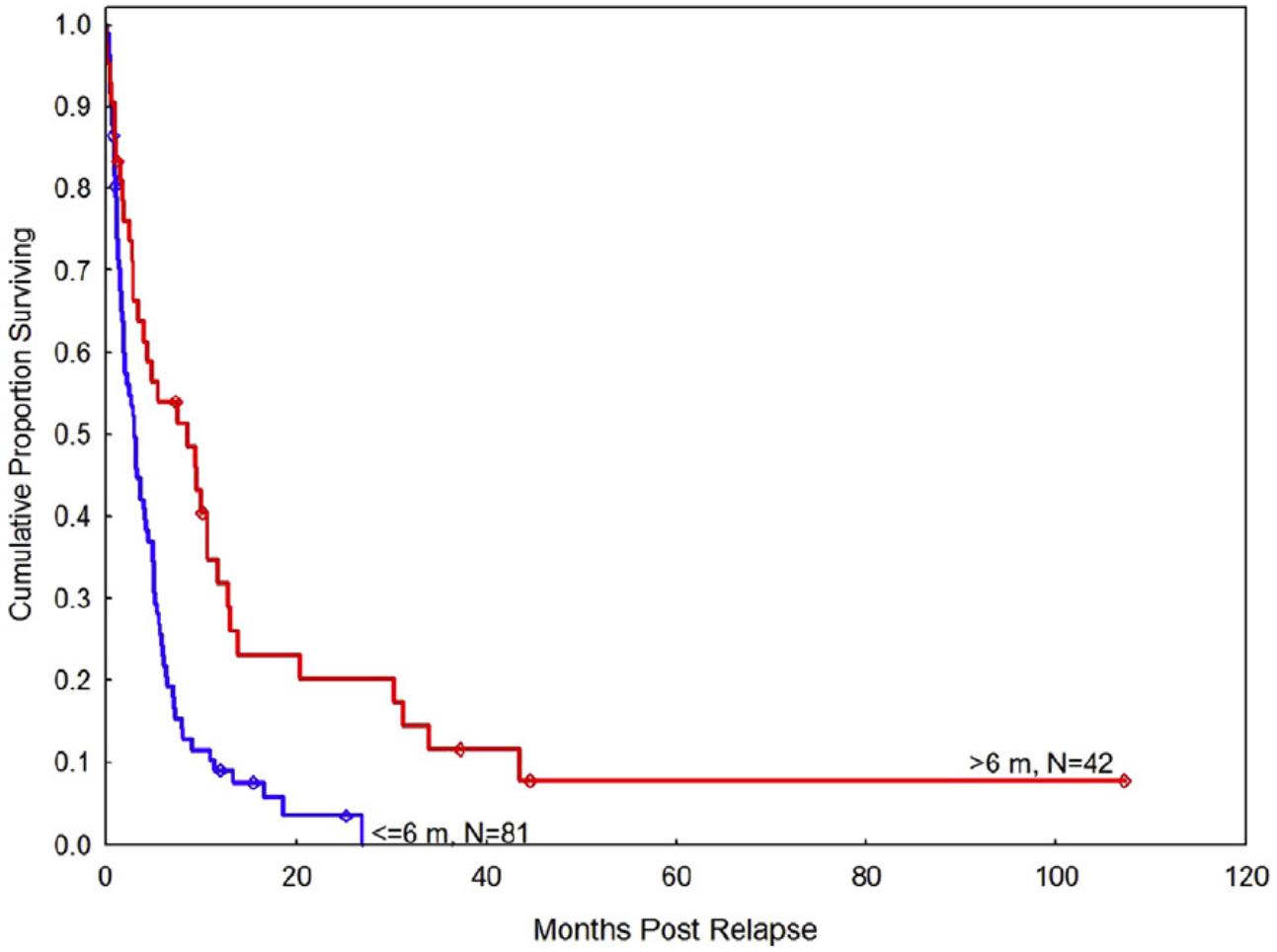
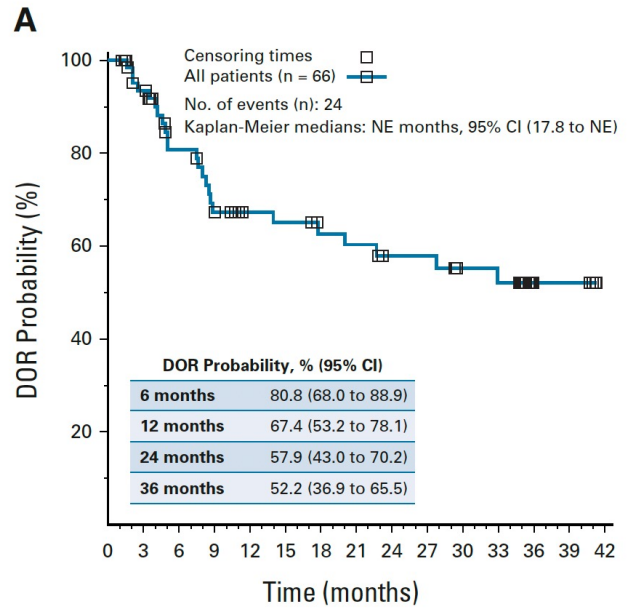
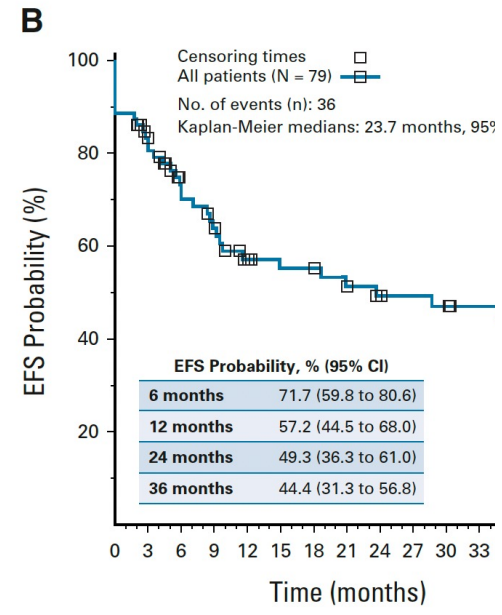


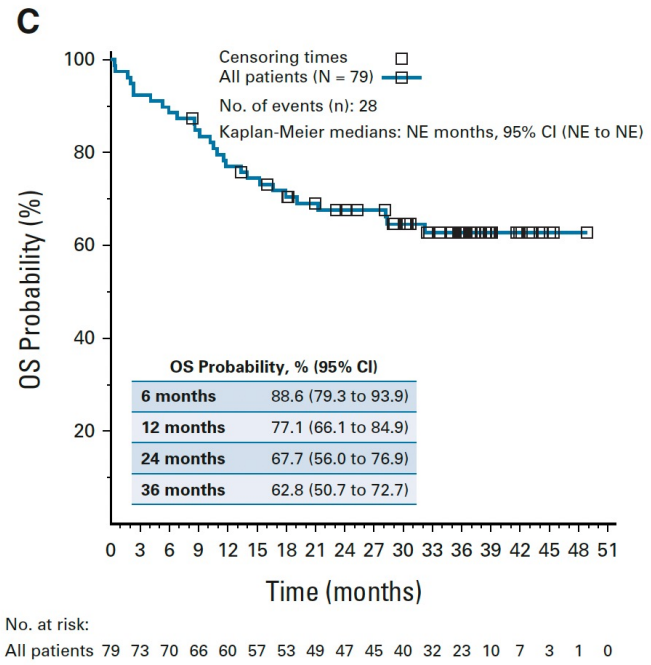

**Figure 1.** Comparison of OS between patients who relapsed within 6 months of HSCT and those who relapsed after 6 months.

Poon LM, Hamdi A, Saliba R, et al. Outcomes of Adults with Acute Lymphoblastic Leukemia Relapsing after Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2013;19(7):1059-1064. doi:10.1016/j.bbmt.2013.04.014

# Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial




Laetsch et al,. ASCO 2022

# Brexu-Cel for R/R B-ALL in adults

**Table. Efficacy Results in Pooled Analysis of Phase 1 and 2 (N=78) by Independent Review**

| Subgroup | N | CR/CRi Rate (95% CI) | Median DOR (95% CI) | Median OS (95% CI) |
|---|---|---|---|---|
| **Lines of prior therapy** | | | | |
| 1 | 15 | 87% (60-98) | 4.9 months (1.8-NE) | NR (7.6-NE) |
| ≥2 | 63 | 70% (57-81) | 20.0 months (10.3-NE) | 25.4 months (15.9-NE) |
| **Prior blinatumomab** | | | | |
| Yes | 38 | 63% (46-78) | 14.6 months (9.6-NE) | 15.9 months (8.3-25.4) |
| No | 40 | 83% (67-93) | 18.6 months (5.2-NE) | 47.0 months (18.6-NE) |
| **Prior SCT** | | | | |
| Yes | 29 | 76% (56-90) | 14.6 months (8.7-23.6) | 25.4 months (14.2-NE) |
| No | 49 | 71% (57-83) | NR (5.2-NE) | 47.0 months (10.9-NE) |

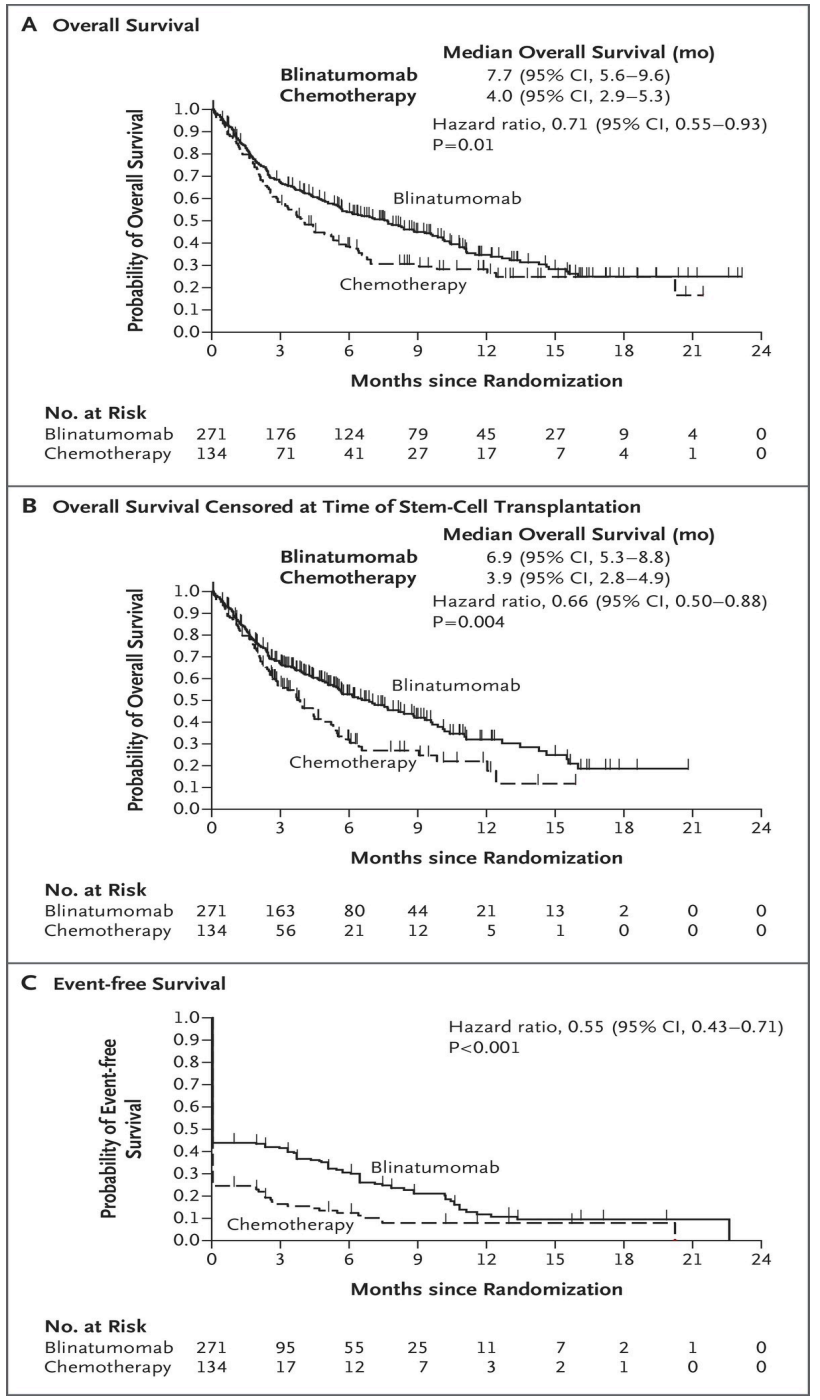
CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; OS, overall survival; NE, not estimable; NR, not reached; SCT, stem cell transplant.

Shah et al ASTCT 2023

# FDA Approved CART for B-ALL

| Trial | Disease | Efficacy |
|---|---|---|
| ELIANA (Tis-Cel) | Patients up to 25 years of age with B-ALL that is refractory or in second or later relapse. | ORR 81%<br>CR 60% Cri 21%<br>EFS 73% (6mo) 50% (12 mo)<br>OS 90% (6mo) 76% (12 mo) |
| ZUMA 3 (Brexu-Cel) | Adult patients with R/R B-ALL | ORR 83%<br>CR 82%<br>Median OS: NR after $\geq$ 1 line and 25.4 mo after $\geq$ 2 lines |

# What about BITEs for R/R B-ALL?




Kantarjian H et al. N Engl J Med 2017

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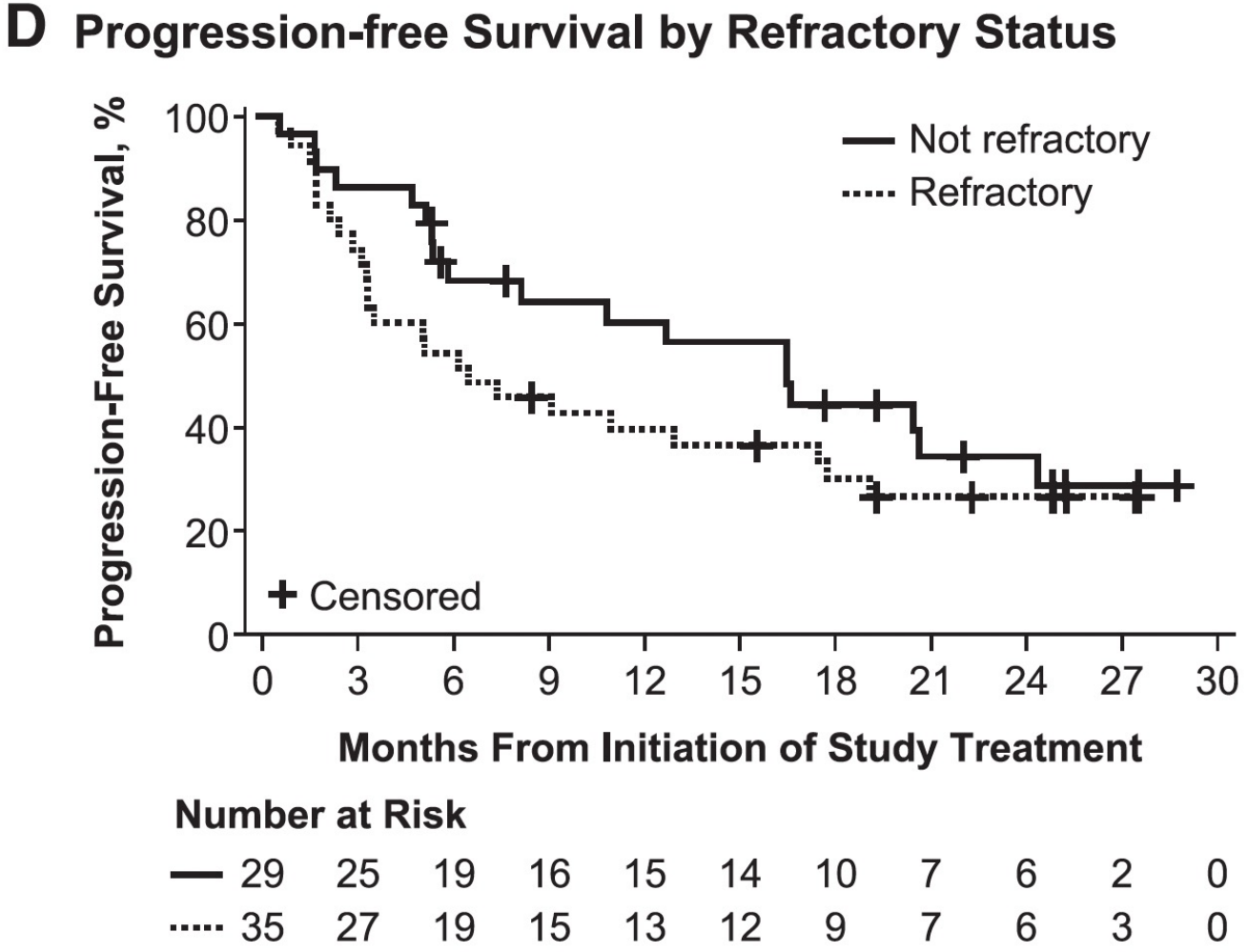
# Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results



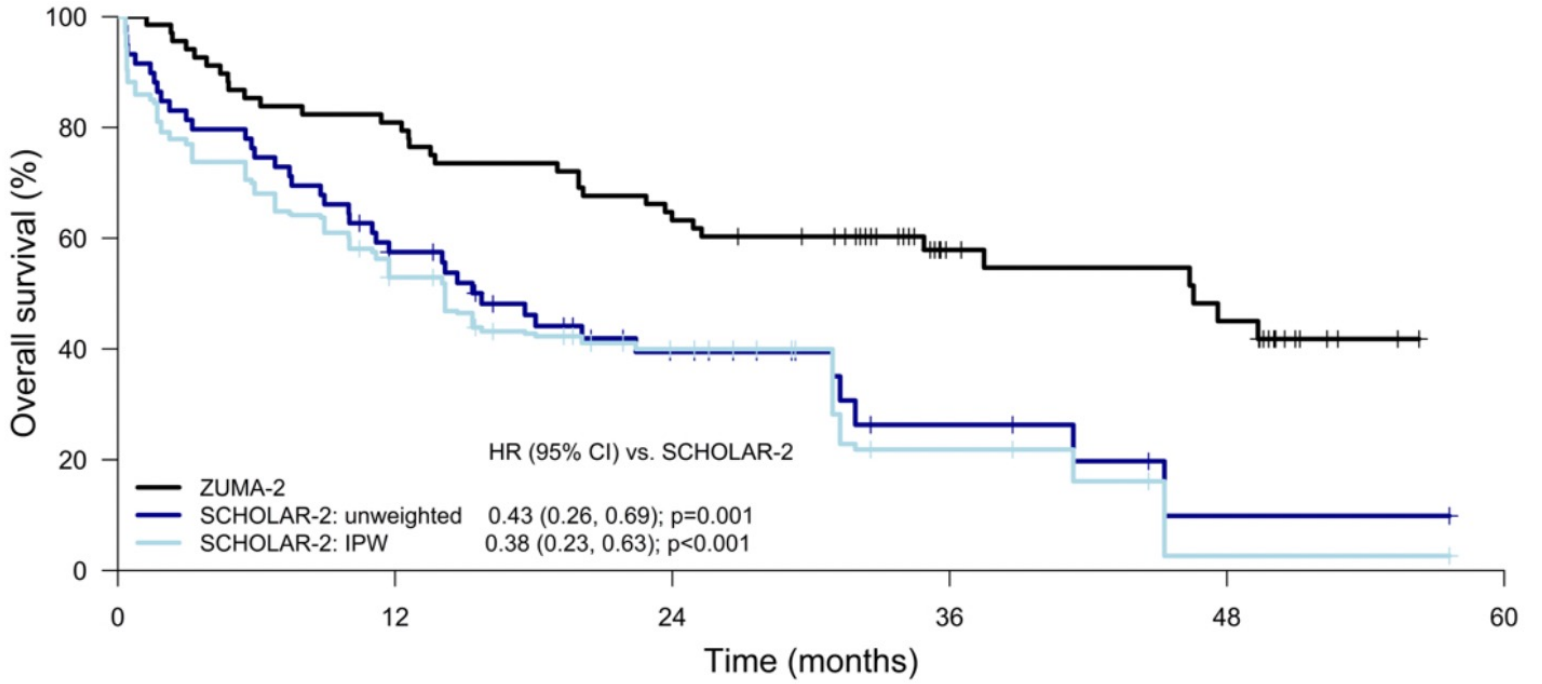

ORR 67%
CR 23%
24-month PFS 31%
mDOR 17.5 mo
**mOS for refractory:13 mo**
**mPFS for refractory: 6.6 mo**

Wang ML, Blum KA, Martin P, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. *Blood*. 2015;126(6):739-745. doi:10.1182/blood-2015-03-635326

# A Comparison of Overall Survival with Brexucabtagene Autoleucel (Brexu-cel) CAR T-Cell Therapy (ZUMA-2) and Standard of Care (SCHOLAR-2) in Patients with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Previously Treated with a Covalent Bruton Tyrosine Kinase Inhibitor (BTKi)

**Figure 1: Kaplan-Meier curves of overall survival in ZUMA-2 (brexu-cel) and SCHOLAR-2 (standard of care); IPW base-case analysis**

Median OS was 46.6 months (95% CI: 24.9–not reached) with brexu-cel and 15.7 months (95% CI: 10.0–30.9) with SOC.




| Number at risk (number censored) | | | | | | |
|---|---|---|---|---|---|---|
| ZUMA-2 | 68 (0) | 55 (0) | 43 (0) | 19 (21) | 14 (22) | 0 (35) |
| SCHOLAR-2: unweighted | 59 (0) | 32 (2) | 15 (10) | 5 (17) | 1 (19) | 0 (20) |
| SCHOLAR-2: IPW | 59 (0) | 30 (1) | 15 (9) | 4 (16) | 0 (18) | 0 (19) |

Hess et al. ASH 2022

# FDA Approved CART for Mantle Cell Lymphoma

| Trial | Disease | Efficacy |
|---|---|---|
| ZUMA 2 (Brexu-Cel) | Adult patients with R/R MCL after 2 lines of systemic therapy including a BTKi. | ORR 85%<br>CR 59%<br>Median PFS: NR<br>Median OS: NR |

# What about BITEs for R/R MCL

Under investigation

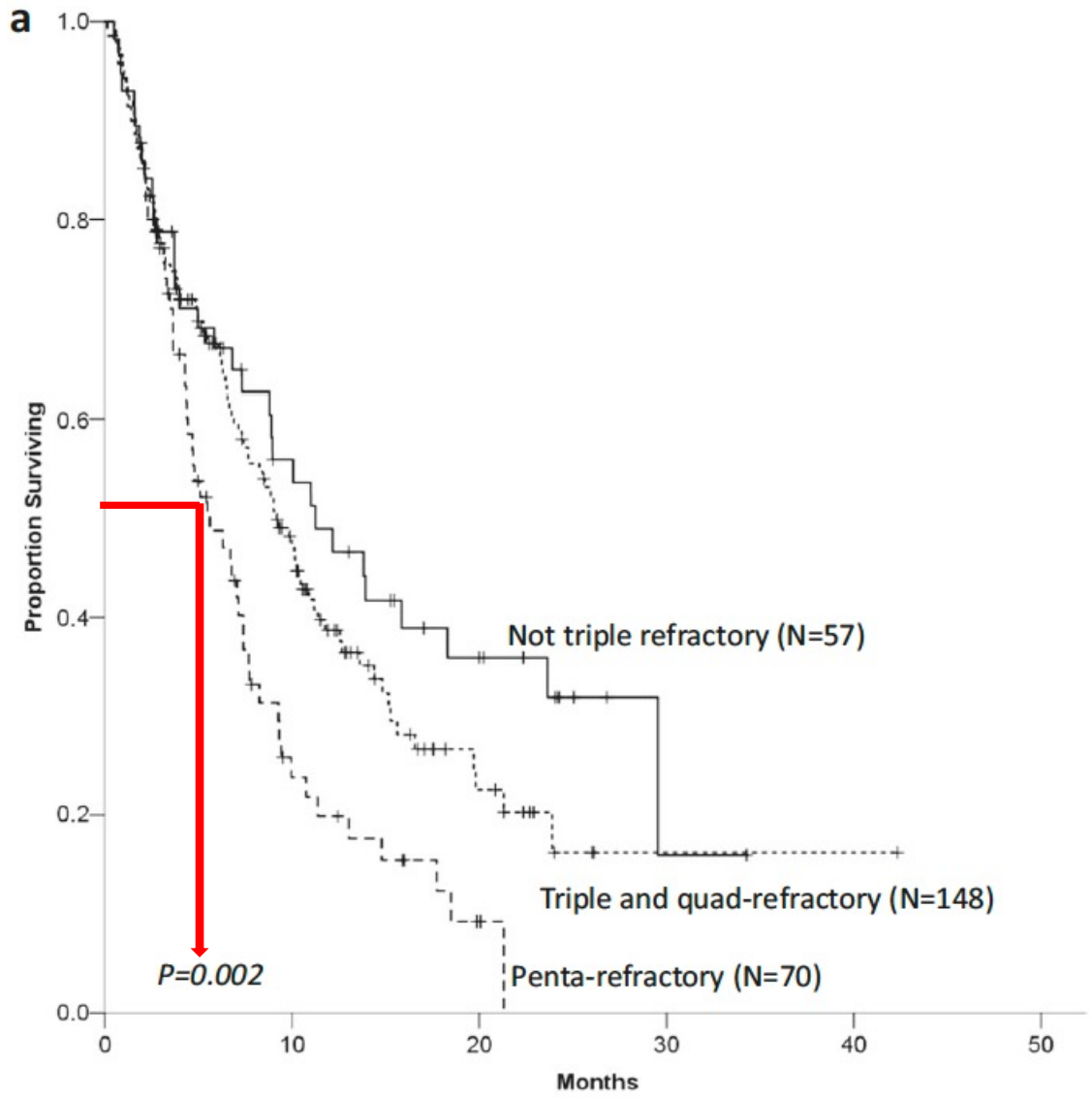
# FDA Approved CART indications

- Indications
  - Relapse/Refractory **High grade B cell lymphoma (DLBCL, PMBCL, TFL)** after 1 line of systemic therapy (primary refractory or relapsed within 12 months after fishing chemo-immunotherapy) or R/R HBCL after > 2 lines of systemic therapy
  - Relapse/Refractory **FL** after 2 lines of systemic therapy
  - Relapse/Refractory **B-ALL** refractory or in second or later relapse
  - Relapse/Refractory **MCL** after 2 lines of systemic therapy
  - Relapse/Refractory **MM** after 4 lines of therapy (including IMIDs, PI and anti CD38 Abs

Alexander M, Culos K, Roddy J, et al. Chimeric Antigen Receptor T Cell Therapy: A Comprehensive Review of Clinical Efficacy, Toxicity, and Best Practices for Outpatient Administration. *Transplant Cell Ther*. 2021;27(7):558-570. doi:10.1016/j.jtct.2021.01.014

# Refractory MM

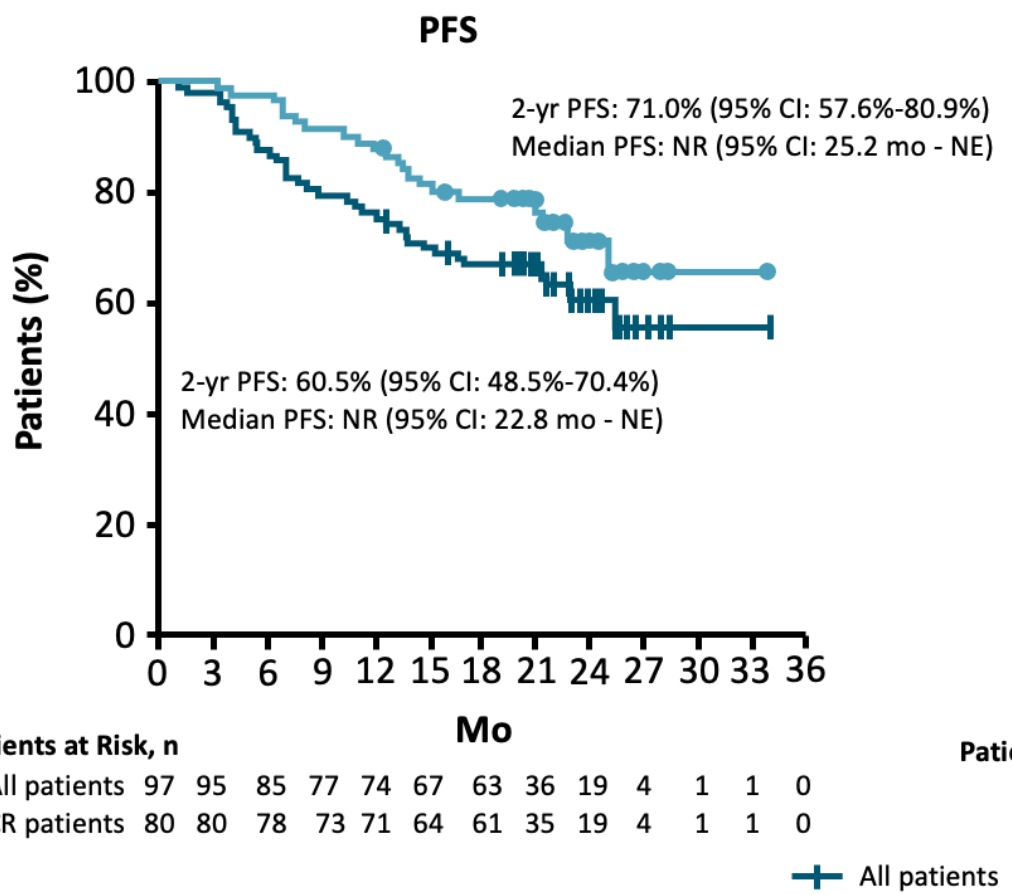
**OS of MM patients refractory to CD38 MoAB**

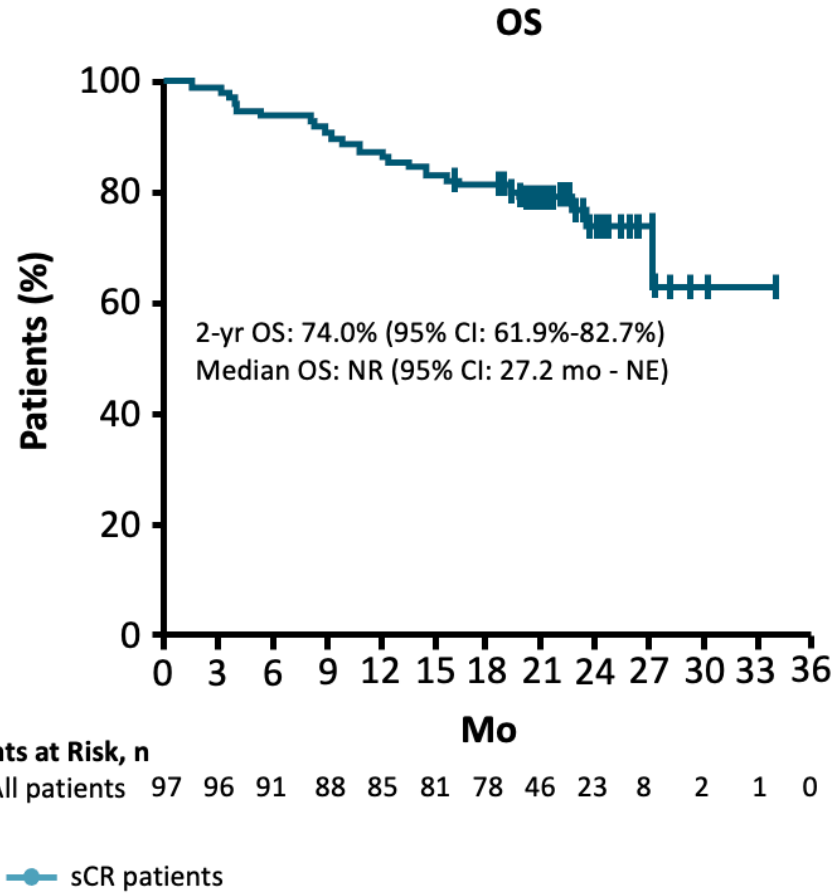



Gandhi UH, et al. *Leukemia*.

# CARTITUDE-1: PFS and OS With Ciltacabtagene Autoleucel For R/R MM

**3 or more previous lines of therapy**

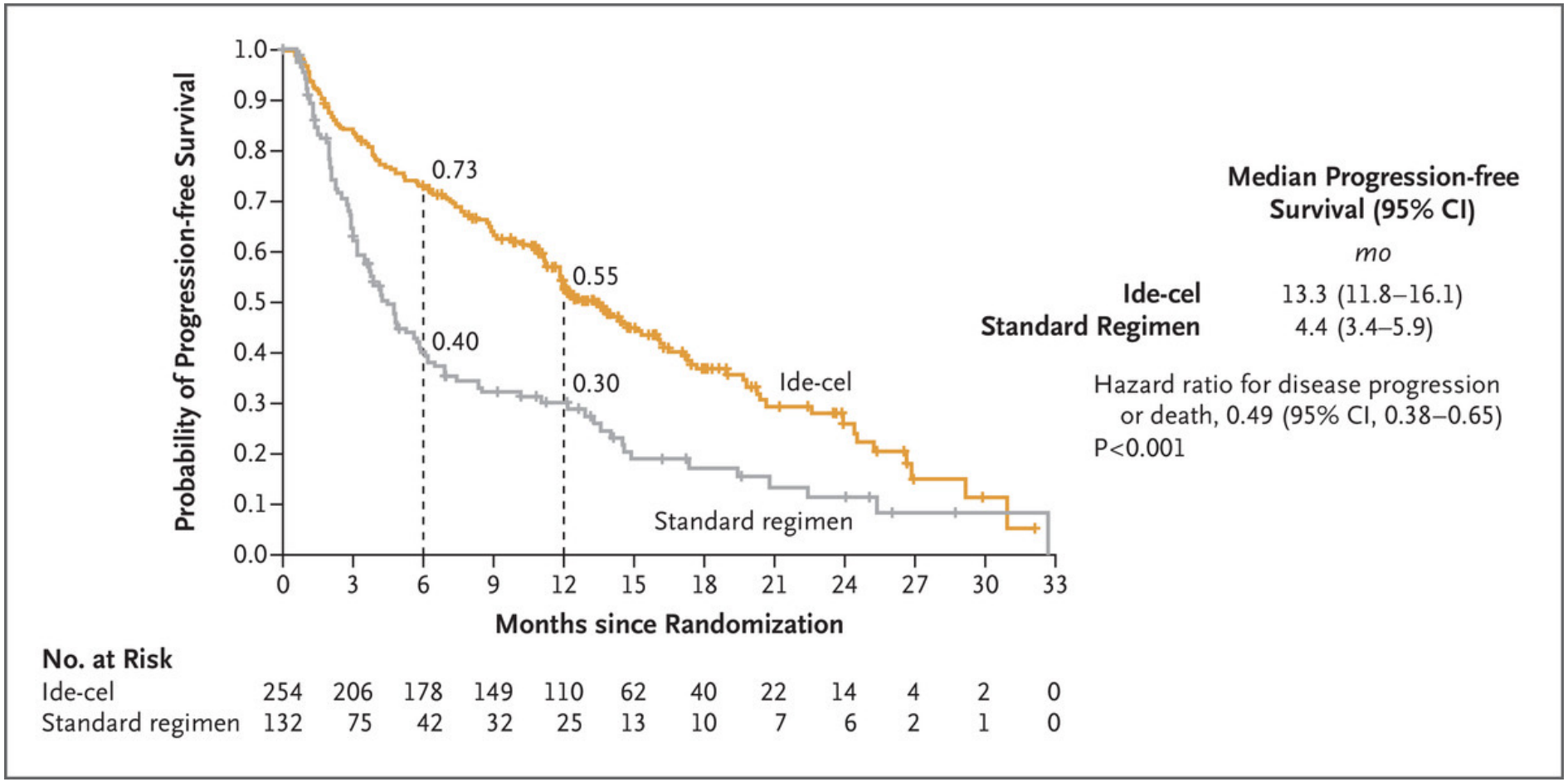



All patients  sCR patients

# Ide-cel or Standard Regimens in Relapsed and Refractory Multiple Myeloma

Phase 3 trial involving adults with relapsed and refractory multiple myeloma who had received **two to four regimens**




Rodriguez-Otero et al. NEJM 2023

# FDA Approved CART Cell for Multiple Myeloma

| Trial | Disease | Efficacy |
|---|---|---|
| CARTITUDE-1 (Cilta-Cel) | Adult patients with R/R multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody | ORR 97%<br>sCR 67% (MRD negative)<br>Median PFS: NR<br>Median OS: NR |
| KarMMa (Ide-Cel) | Adult patients with R/R multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody | ORR 73%<br>CR 33% of which 79% achieved MRD negativity<br>Median PFS: 8.8 mo<br>Median OS: 19.4 mo |

# What about BITEs for R/R MM

Teclistamab (BCMA target)

Elranatamab (BCMA target)

Talquetamab (GPRC5D target)

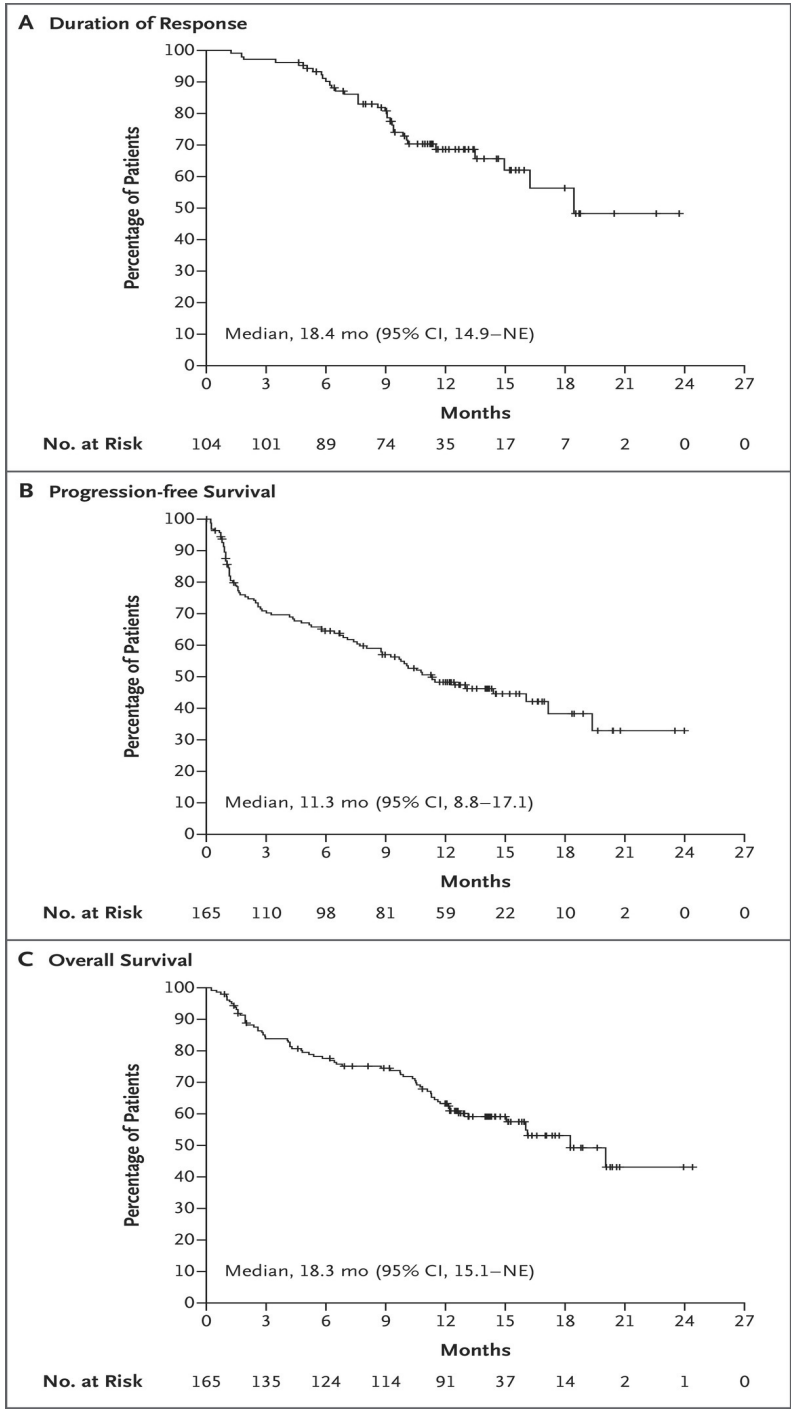
# BCMA BITEs

- **Teclistamab**
- ORR 63%
- CR 43%
- mDOR 24 months
- mDOR for CR not achieved

- **Elranatamab**
- ORR 61%
- CR 35%
- DOR: pending longer follow up

# Teclistamab

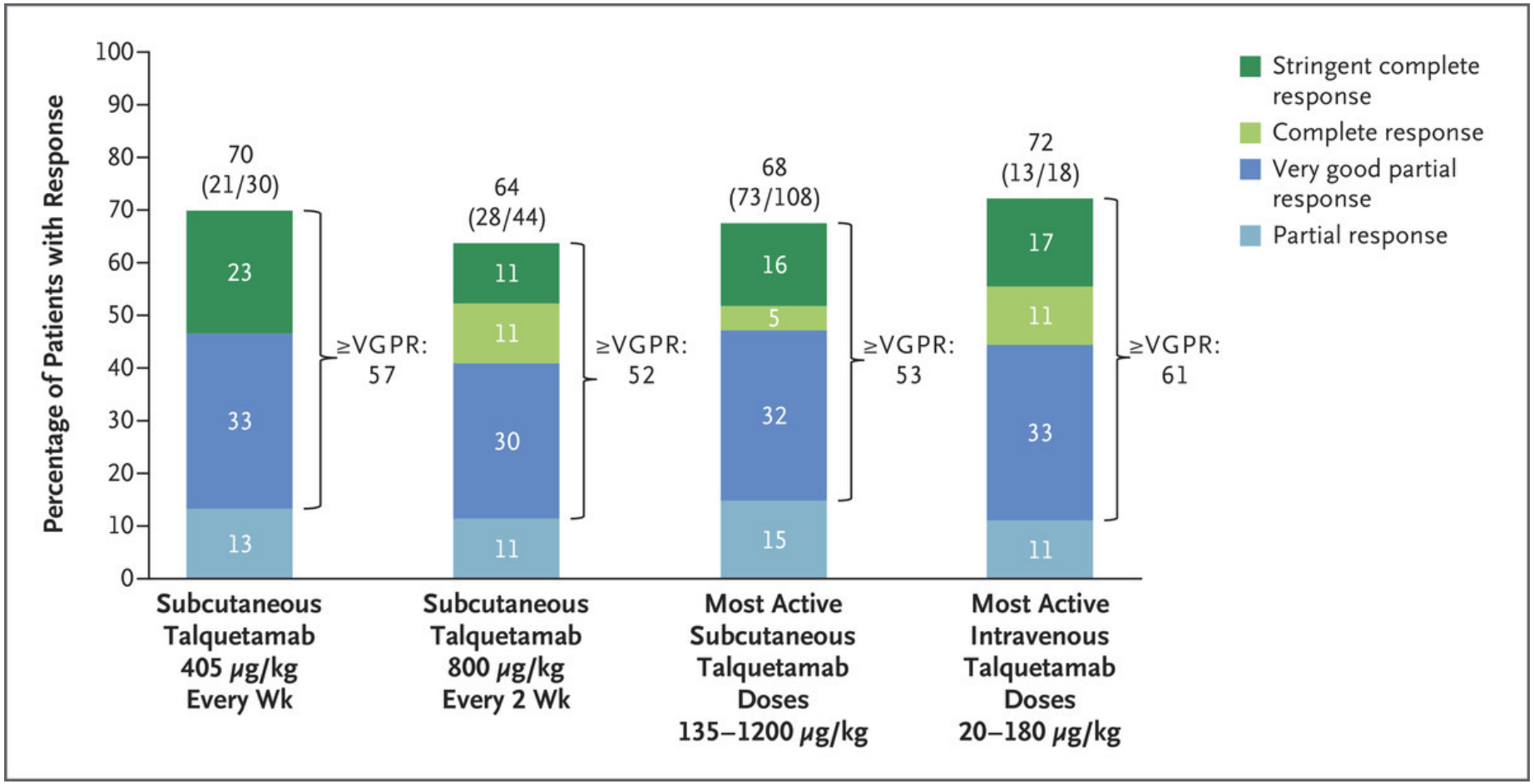
Median 5 lines of therapy




P Moreau et al. N Engl J Med. 2022

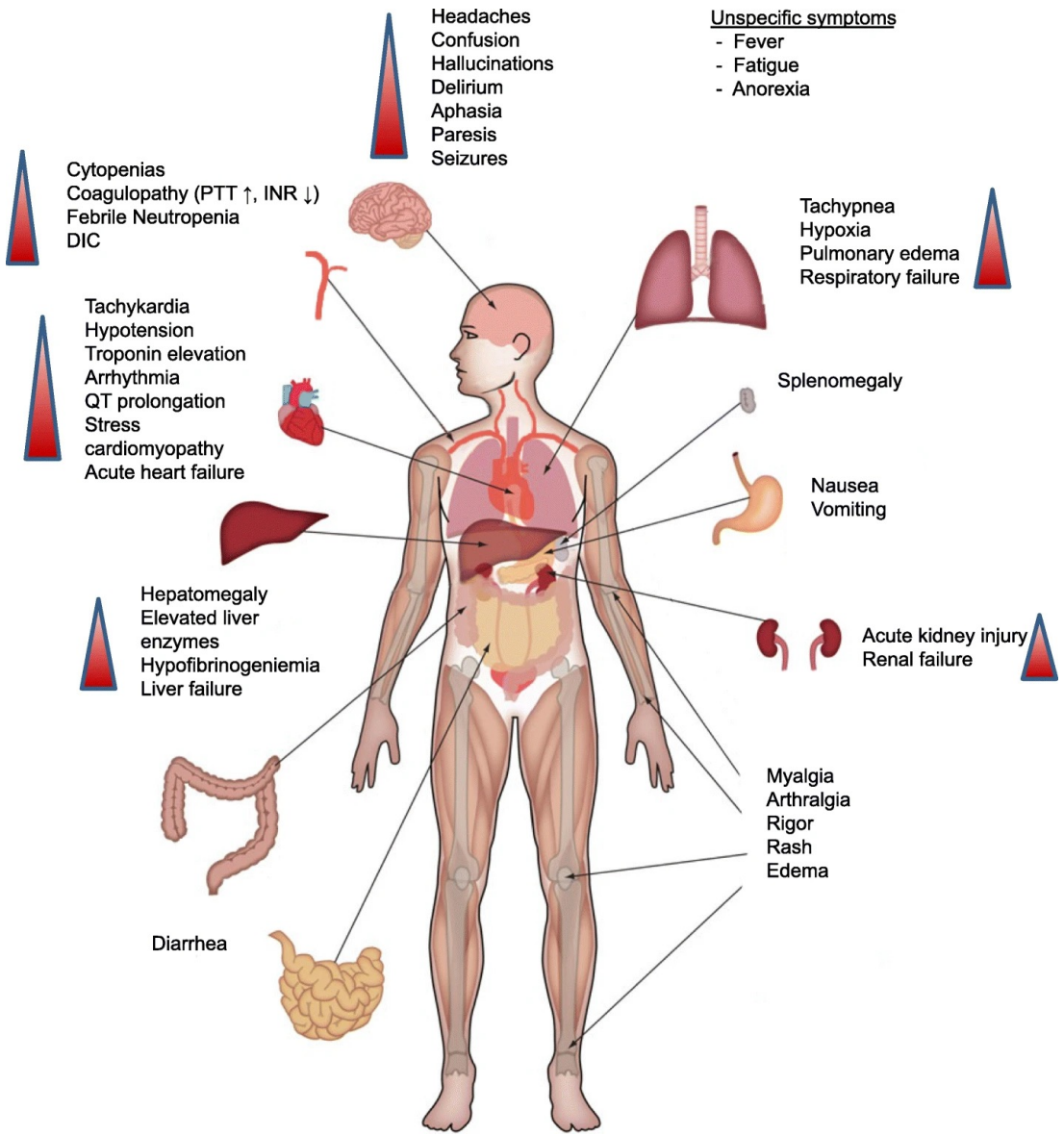
# Talquetamab  bispecific antibody against CD3 and GPRC5D

Median 6 lines of therapy

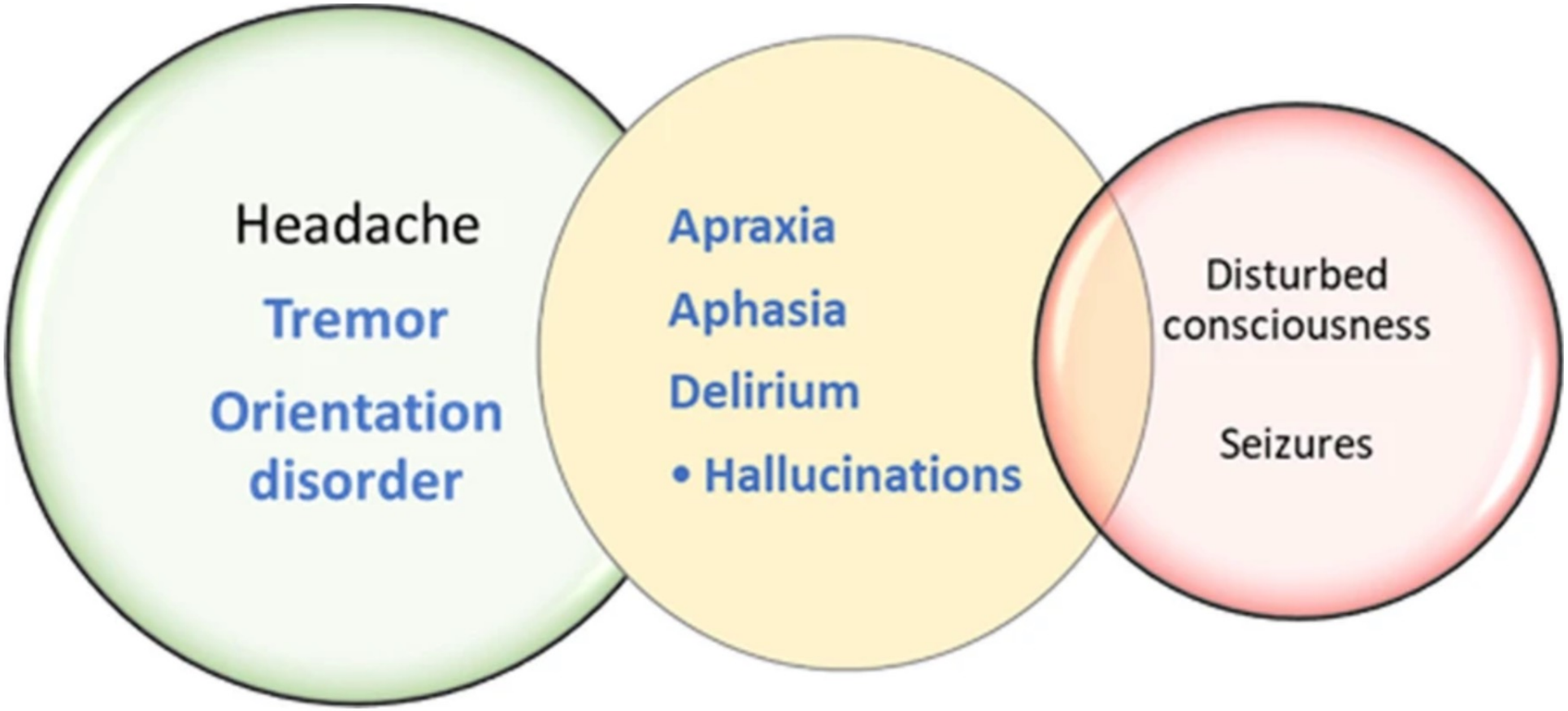


# CRS

“**Supraphysiologic** response following **any immune** therapy that results in the activation or engagement of **endogenous  or infused T cells and/or other immune effector cells**.” Immune efector cell associated neurotoxicity should be excluded from the definition of CRS.


Headaches
Confusion
Hallucinations
Delirium
Aphasia
Paresis
Seizures
Unspecific symptoms
- Fever
- Fatigue
- Anorexia
Cytopenias
Coagulopathy (PTT ↑, INR ↓)
Febrile Neutropenia
DIC
Tachypnea
Hypoxia
Pulmonary edema
Respiratory failure
Tachykardia
Hypotension
Troponin elevation
Arrhythmia
QT prolongation
Stress cardiomyopathy
Acute heart failure
Splenomegaly
Nausea
Vomiting
Hepatomegaly
Elevated liver enzymes
Hypofibrinogeniemia
Liver failure
Acute kidney injury
Renal failure
Myalgia
Arthralgia
Rigor
Rash
Edema
Diarrhea

# Neurotoxicity



# Mortality

**Table 2. Incidence and types of CD19 CAR-T cell therapy-related fatalities from systematic review and meta-analysis.**

| Variable | CD-19 Car-T (n=890) | Kymriah (n=201) | Yescarta (n=209) | P* |
|---|---|---|---|---|
| Deaths, No. (%) | 33 (3.71%) | 7 (3.48%) | 9 (4.31%) | 0.667 |
| Type of fatal toxic effect | | | | |
| CRS | 10 (30.30%) | 0 | 2 (22.22%) | 0.499 |
| Nervous system disorders | 6 (18.18%) | 1 (14.29%) | 1 (11.11%) | 1 |
| Infections and infestations | 4 (12.12%) | 1 (14.29%) | 0 | 0.49 |
| Blood and lymphatic system disorders | 3 (9.09%) | 2 (28.57%) | 1 (11.11%) | 0.617 |
| Cardiac disorders | 2 (6.06%) | 1 (14.29%) | 1 (11.11%) | 1 |
| Respiratory, thoracic and mediastinal disorders | 2 (6.06%) | 0 | 2 (22.22%) | 0.499 |
| Gastrointestinal disorders | 2 (6.06%) | 0 | 0 | NA |
| Hepatobiliary disorders | 1 (3.03%) | 1 (14.29%) | 0 | 1 |
| unknown cause | 3 (9.09%) | 1 (14.29%) | 2 (22.22%) | 1 |

* Fatal toxic effects rates of Kymriah and Yescarta were compared using $\chi 2$ testing.

Ide-Cel ~1%
Cilta-Cel ~6%

Cai C, Tang D, Han Y, et al. A comprehensive analysis of the fatal toxic effects associated with CD19 CAR-T cell therapy. *Aging*. 2020;12(18):18741-18753. doi:10.18632/aging.104058

# Future Directions

- Cellular therapy for T cell malignancies
- Cellular therapy for Solid tumor
- Dual target CARs
- Allogeneic CARs

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