City of Hope

Multidisciplinary Approaches to Cancer Symposium

Novel Targeted Therapies, Bispecific Antibodies, and CAR T-Cell Therapy in Lymphoma

Focus: Diffuse Large B-Cell Lymphoma

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Department of Hematology and HCT

City of Hope

Disclosures

- Research Support from CARGO Therapeutics, Genentech-Roche, Kite Pharma-Gilead, Janssen-JNJ & Regeneron Pharmaceuticals.
- Member of the Speakers Bureau for Kite Pharma-Gilead

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Discussing travel and caregiver logistics, and barriers to implementation of outpatient cellular therapies in a diverse geographic and socioeconomic population.*
- *Addressing financial and logistical barriers inherent to bispecific and cellular therapies to broaden access to these therapeutics, both on clinical trial and commercially.*

Recent Landscape in R/R DLBCL

First Line

- R-CHOP21
- DA-R-EPOCH
- Pola-R-CHP
- *Tafa-Len-R-CHOP [Front-MIND]
- *Glofitamab-Pola-R-CHP [SKYGLO]
- *Epocoritamab-Pola-R-CHP [EPCORE NHL-5]
- *Axicabtagene ciloleucel [ZUMA-12 & ZUMA-23]
- *Cemacabtagene ansegedleucel [ALPHA3]

Second Line

- R-chemo→ASCT
- Axicabtagene ciloleucel
- Lisocabtagene maraleucel
- *Epcor/Glofit-R-ICE→ASCT [EPCORE NHL-2 & GO43693]
- *Mosun-Pola +/- CAR-T [SUNMO & UM IIT]

ASCT Ineligible:

- Lisocabtagene maraleucel
- Polatuzumab-BR
- Tafasitamab-Lenalidomide
- *Epcor/Glofit-R-GemOx [EPCORE NHL-2 & GO41944]
- *Mosunetuzumab-Lonca [COH IIT]

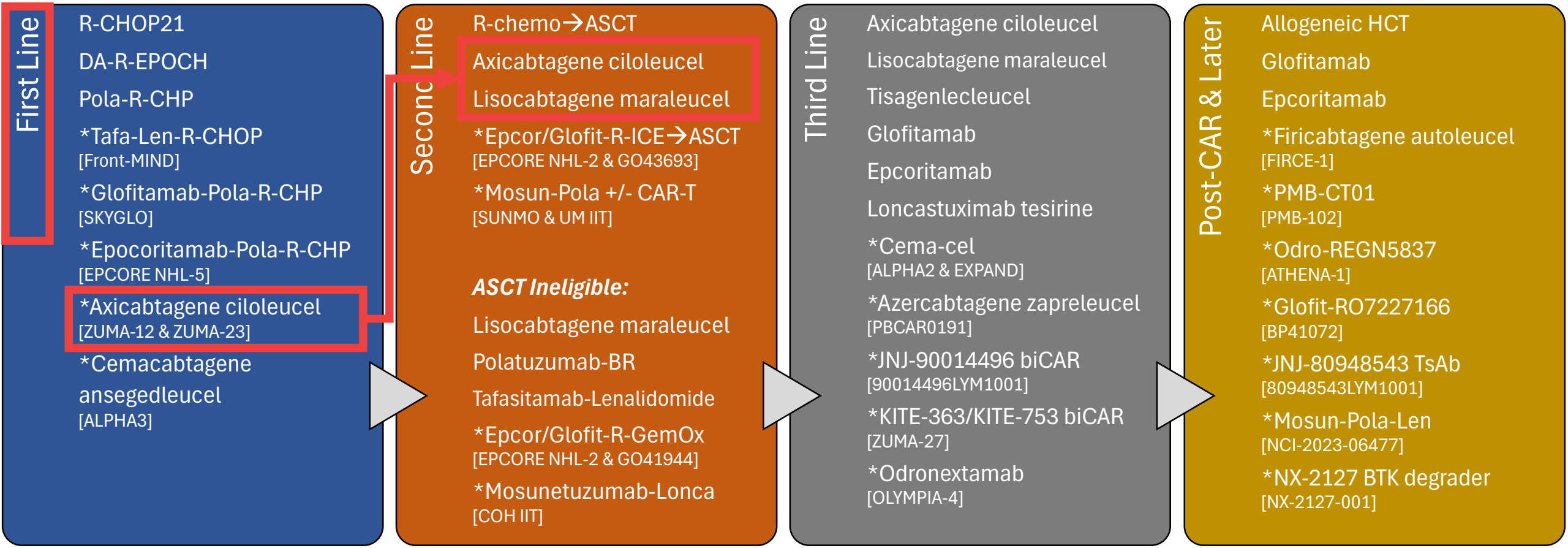
Third Line

- Axicabtagene ciloleucel
- Lisocabtagene maraleucel
- Tisagenlecleucel
- Glofitamab
- Epcoritamab
- Loncastuximab tesirine
- *Cema-cel [ALPHA2 & EXPAND]
- *Azercabtagene zapreleucel [PBCAR0191]
- *JNJ-90014496 biCAR [90014496LYM1001]
- *KITE-363/KITE-753 biCAR [ZUMA-27]
- *Odronextamab [OLYMPIA-4]

Post-CAR & Later

- Allogeneic HCT
- Glofitamab
- Epcoritamab
- *Firicabtagene autoleucel [FIRCE-1]
- *PMB-CT01 [PMB-102]
- *Odro-REGN5837 [ATHENA-1]
- *Glofit-RO7227166 [BP41072]
- *JNJ-80948543 TsAb [80948543LYM1001]
- *Mosun-Pola-Len [NCI-2023-06477]
- *NX-2127 BTK degrader [NX-2127-001]

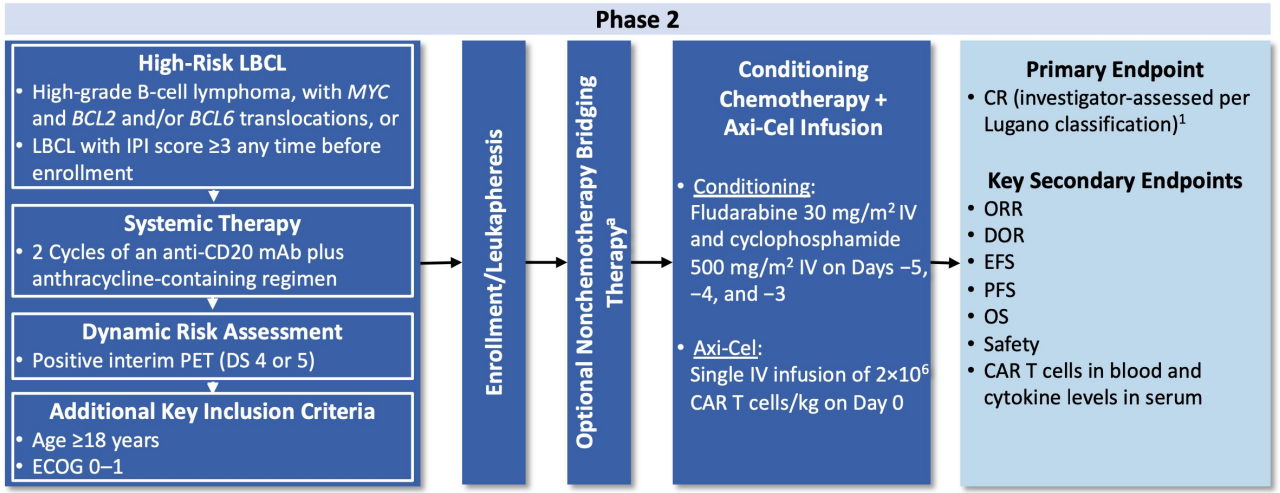
Recent Landscape in R/R DLBCL

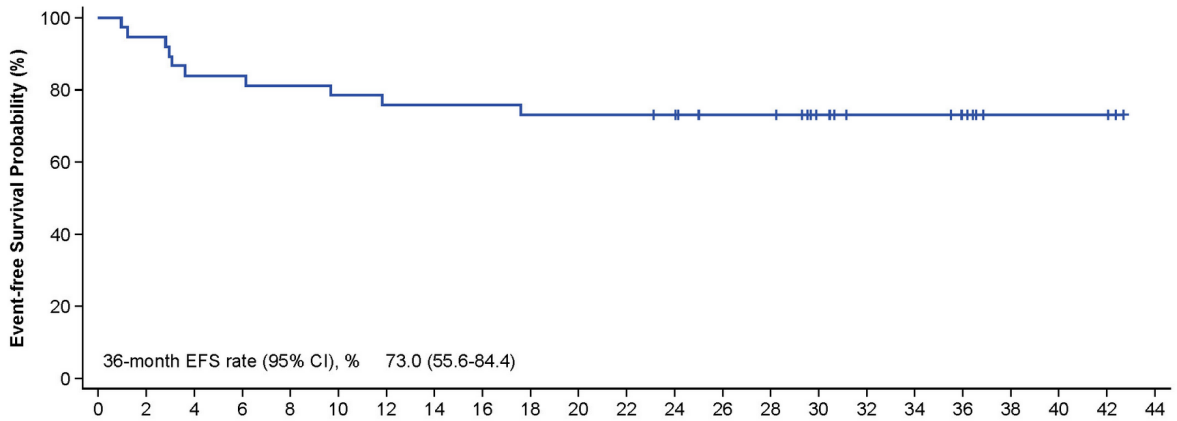


*Ongoing clinical trial

Earlier CAR: CD19-CAR T first line experience

- **Key Outcomes:**
  - N=40 treated; 40% Double- or triple-hit, 78% IPI ≥3; 45% primary refractory
  - 100% had successful CAR-T product manufacturing at 2E06 CAR+ cell/kg dose
  - ORR 89%, CRR 78%
  - 3-year EFS 73%, PFS 75%, OS 81%
  - 3 (8%) Gr ≥ 3 CRS; median duration 6 days; 63% received tocilizumab, 35% received steroids
  - 7 (18%) Gr ≥ 3 ICANS; median duration 7 days; 33% received steroids
  - 1 death due to COVID-19 (350 days post-CAR-T)
- Now in multicenter phase 3 trial (ZUMA-23)



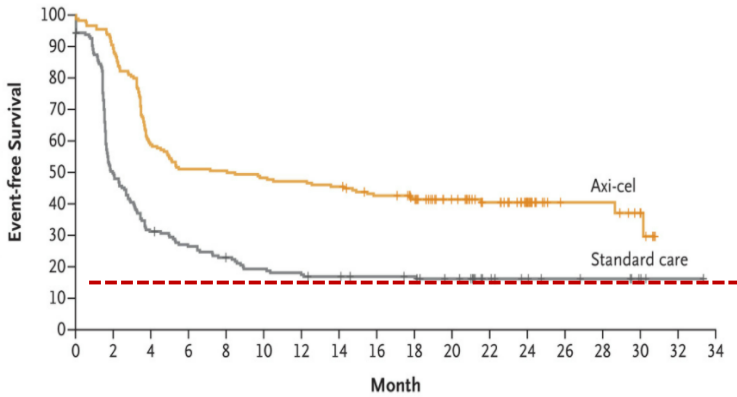


[1] Neelapu SS et al. Nat Med 2022. [2] Chavez JC et al. Blood 2023.

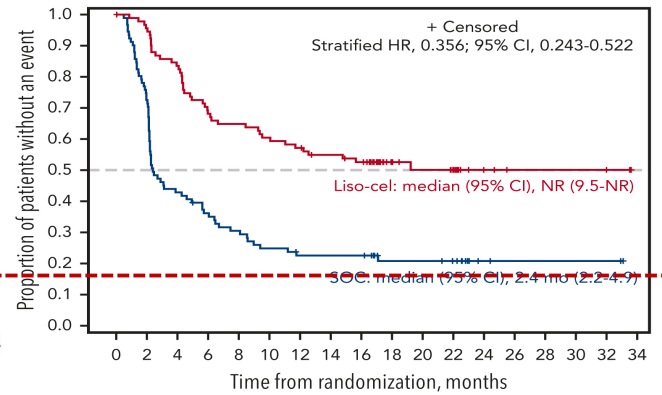
Earlier CAR: CD19-CAR T second line experience

- **Key Outcomes:**
  - N=359 (axi-cel), 184 (liso-cel) treated
  - ORR 83-87%, CRR 65-74%
  - 2-year EFS 41-50%, PFS 46-58%, OS 61-73%
  - NRM 2-4%
- FDA approved in 2L for high risk (relapse < 12 mos).

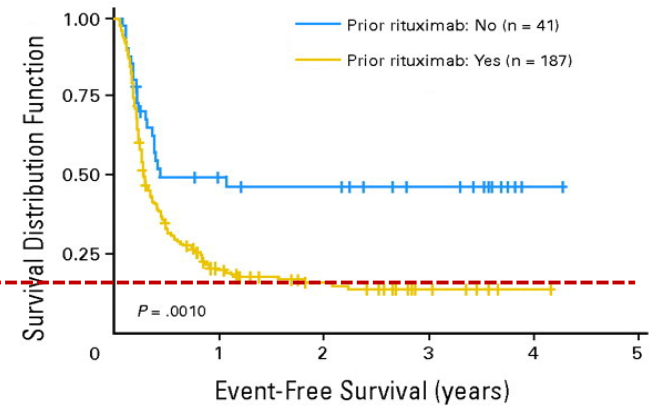
ZUMA-7



TRANSFORM



CORAL



[1] Locke FL et al. NEJM 2022. [2] Abramson JS et al. Blood 2023. [3] Kelkar AH et al. Ann Int Med 2023.

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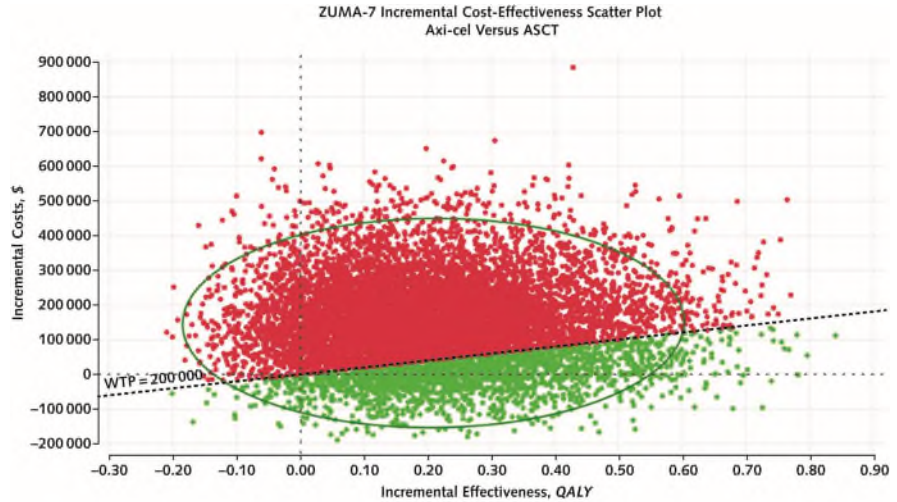
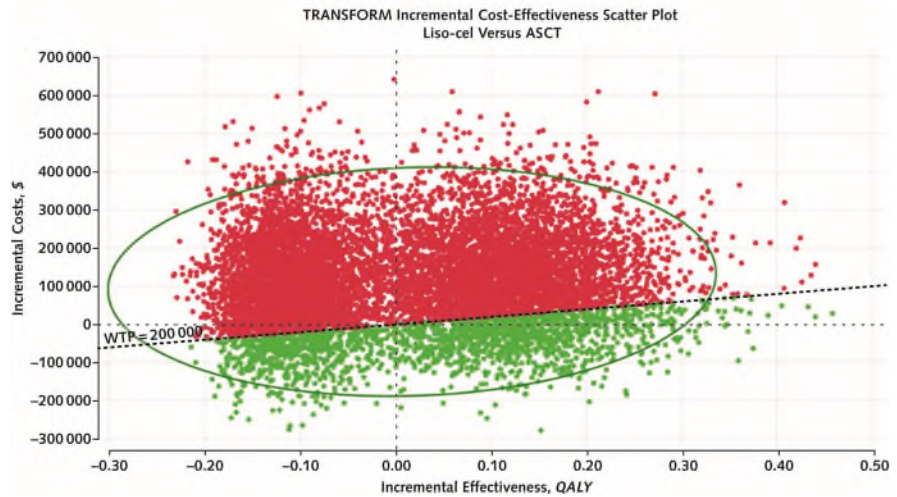
  - ORR 83-87%, CRR 65-74%
  - 2-year EFS 41-50%, PFS 46-58%, OS 61-73%
  - NRM 2-4%
- FDA approved in 2L for high risk (relapse < 12 mos).
- Cost containment remains a challenge:
  - Axi-cel was cost-effective vs ASCT in majority of simulations if WTP was **$720k per QALY**
  - Liso-cel was cost effective vs ASCT in majority of simulations if WTP was **$6.64M per QALY.**

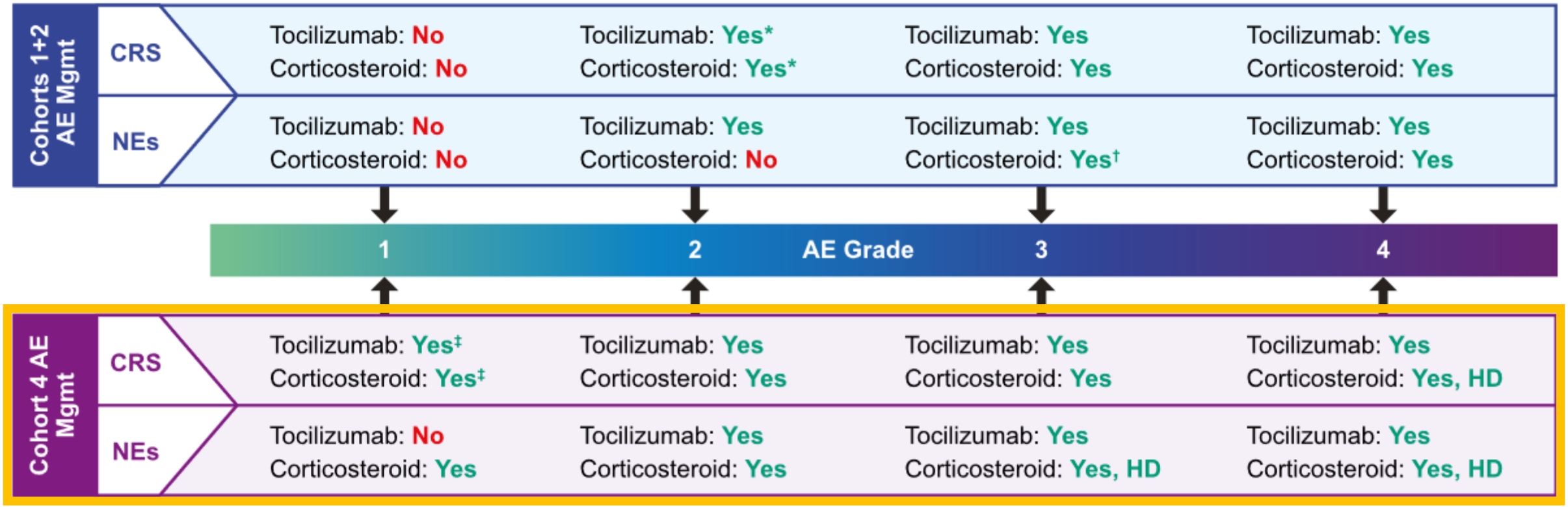




[1] Locke FL et al. NEJM 2022. [2] Abramson JS et al. Blood 2023. [3] Kelkar AH et al. Ann Int Med 2023.

Earlier CAR: Toxicity mitigation for outpatient

- Ongoing phase 2 trial of outpatient ITT (ZUMA-24)



[1] Locke FL et al. Lancet Oncol 2019. [2] Topp MS et al. Br J Haematol 2021. [3] Oluwole OO et al. Br J Haematol 2021. [4] Leslie LA et al. EHA 2024.

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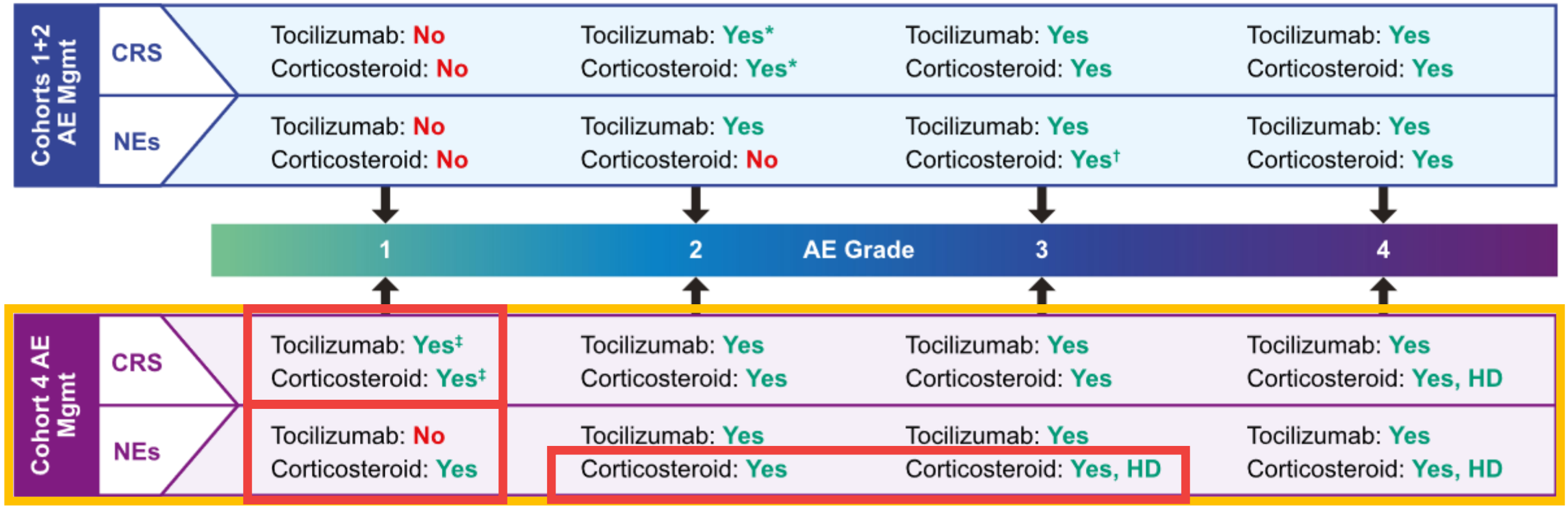

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Earlier CAR: Toxicity mitigation for outpatient

- **Key Outcomes:**
  - N=30 treated; 93% early relapse tx in 2L
  - ORR, CRR comparable to ZUMA-7 and RWE
  - Median time to hospitalization 4 days (10 days post LD), median IP duration 8 days
  - ICU admission in 13%, no Gr 5 AEs
- Ongoing phase 2 trial of outpatient ITT (ZUMA-24)
- Center-specific analyses to examine outpatient financial toxicities (e.g. caregiver requirements, travel, lodging) and impact on PROs, inpatient bed availability, and reimbursements are ongoing.

Cohorts 1+2 Original ZUMA-1 [N = 101]	
ORR (CR rate)	82% (54%)
Median DOR, months	8.1
6-month DOR rate	52%

Cohort 4 Early Intervention [N = 41]	
ORR (CR rate)	73% (51%)
Median DOR, months	8.9
6-month DOR rate	79%

Cohort 6 Prophylactic steroids [N = 40]	
ORR (CR rate)	95% (80%)
Median DOR, months	NR
6-month DOR rate	62%

ZUMA-24 Prophylactic steroids [N = 30]	
ORR (CR rate)	83% (67%)
Median DOR, months	*NE*
6-month DOR rate	*NE*

Baseline Tumor Burden (SPD)

Median = 3700 mm^2

Grade ≥3 CRS	13%
Grade ≥3 ICANS	28%

Median = 2100 mm^2

Grade ≥3 CRS	2%
Grade ≥3 ICANS	17%

Median = 1184 mm^2

Grade ≥3 CRS	0%
Grade ≥3 ICANS	13%

Median = 2348 mm^2

Grade ≥3 CRS	0%
Grade ≥3 ICANS	23%

[1] Locke FL et al. Lancet Oncol 2019. [2] Topp MS et al. Br J Haematol 2021. [3] Oluwole OO et al. Br J Haematol 2021. [4] Leslie LA et al. EHA 2024.

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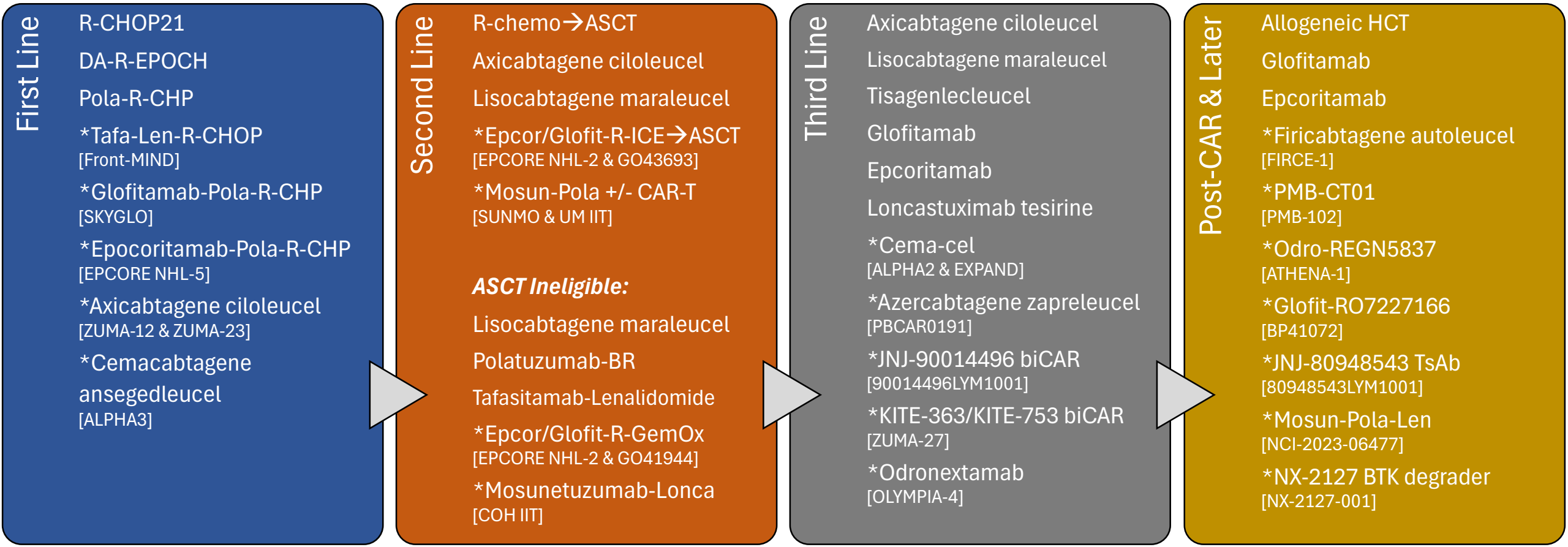

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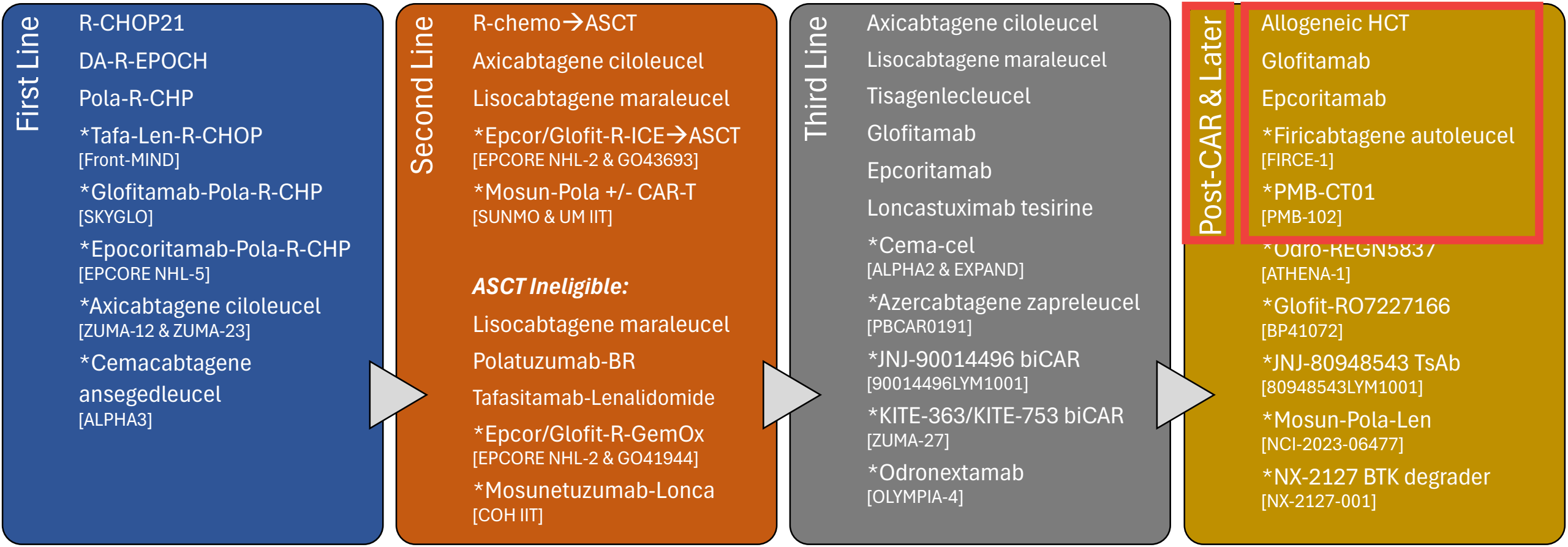

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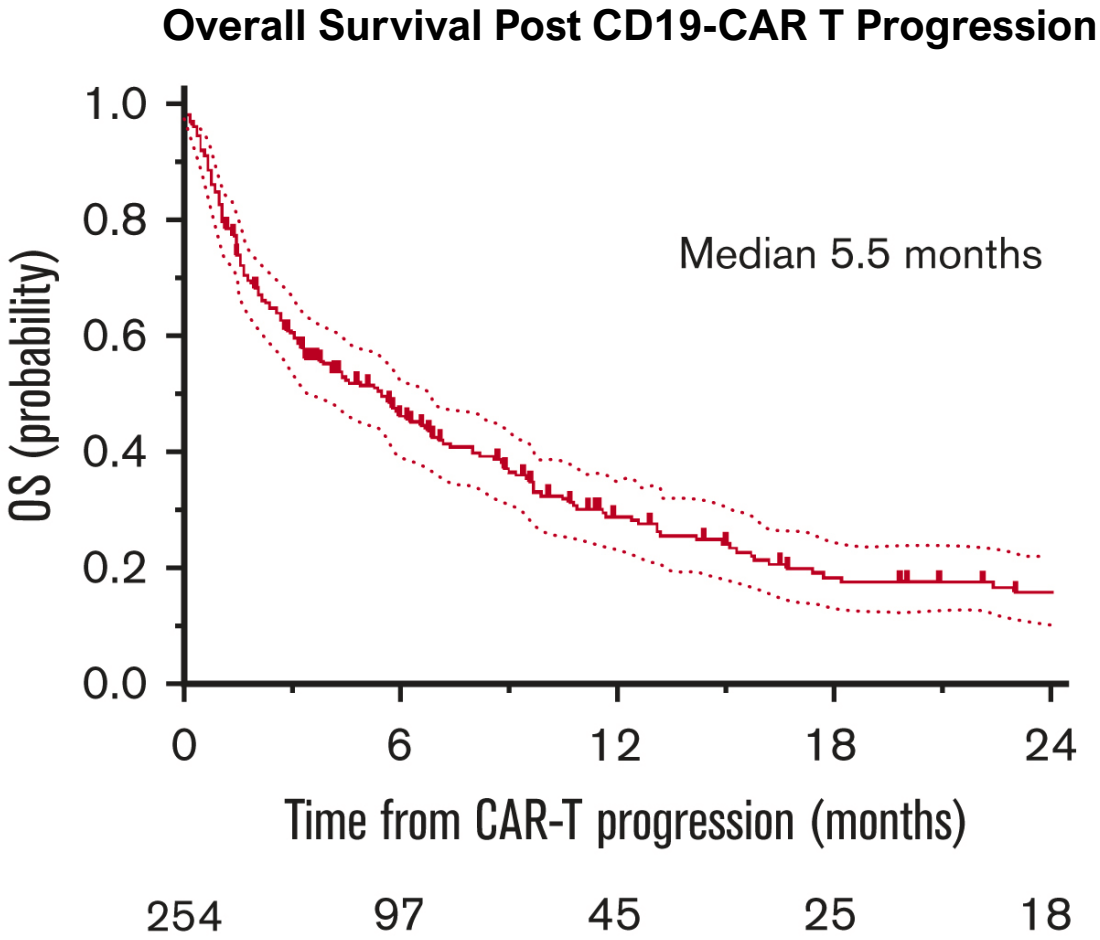
Outcomes after CD19-CAR T relapse remain poor

- R/R LBCL following CD19-CAR T has an extremely poor prognosis, with a minority achieving durable responses to salvage therapies.
  - **13 US Centers:** ORR 33-72%, CRR 12-33%; Median PFS 2.8 mos, OS 5.5 mos [1]
  - **DESCAR-T:** ORR 8-35.7%, CRR 3.8-14.3%; Median PFS 3.7 mos, OS 9.6 mos [2]
  - **17 US Centers:** ORR 18-46%, CRR 12-20%; Median PFS 1.8 mos, OS 6.0 mos [3]



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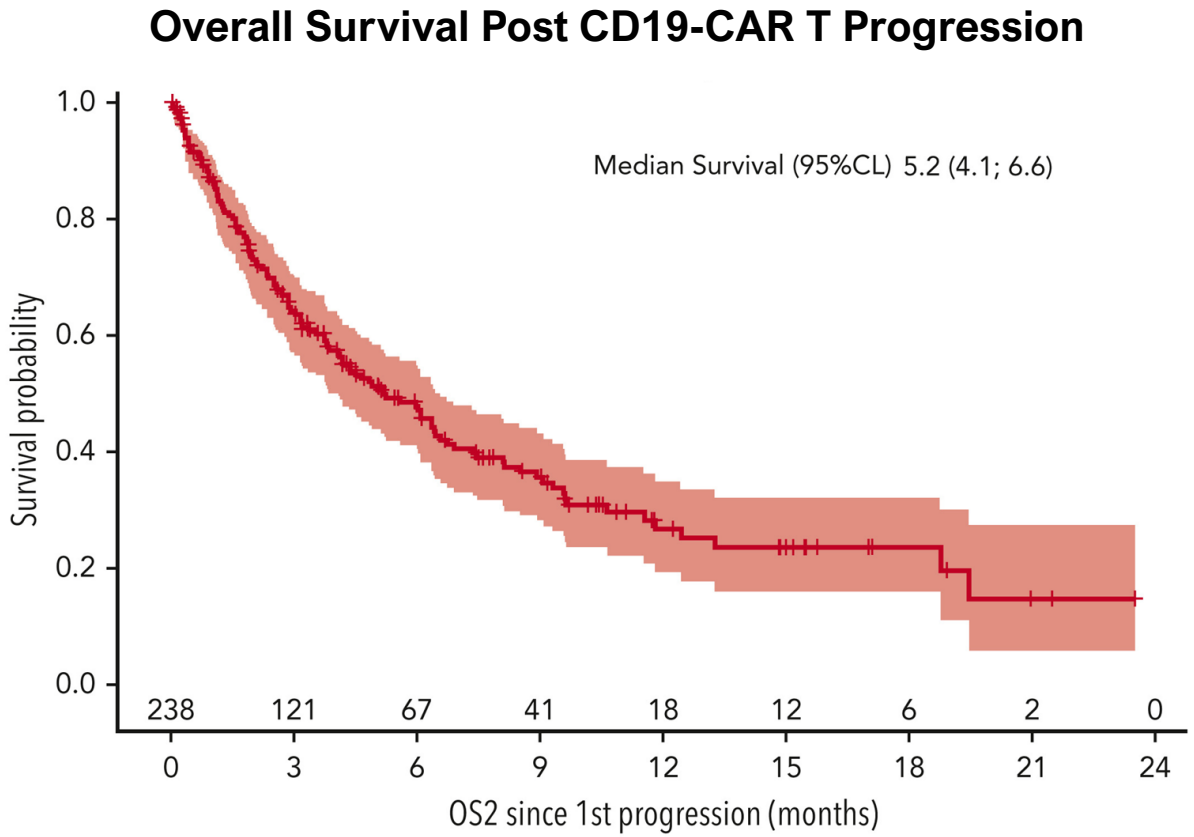

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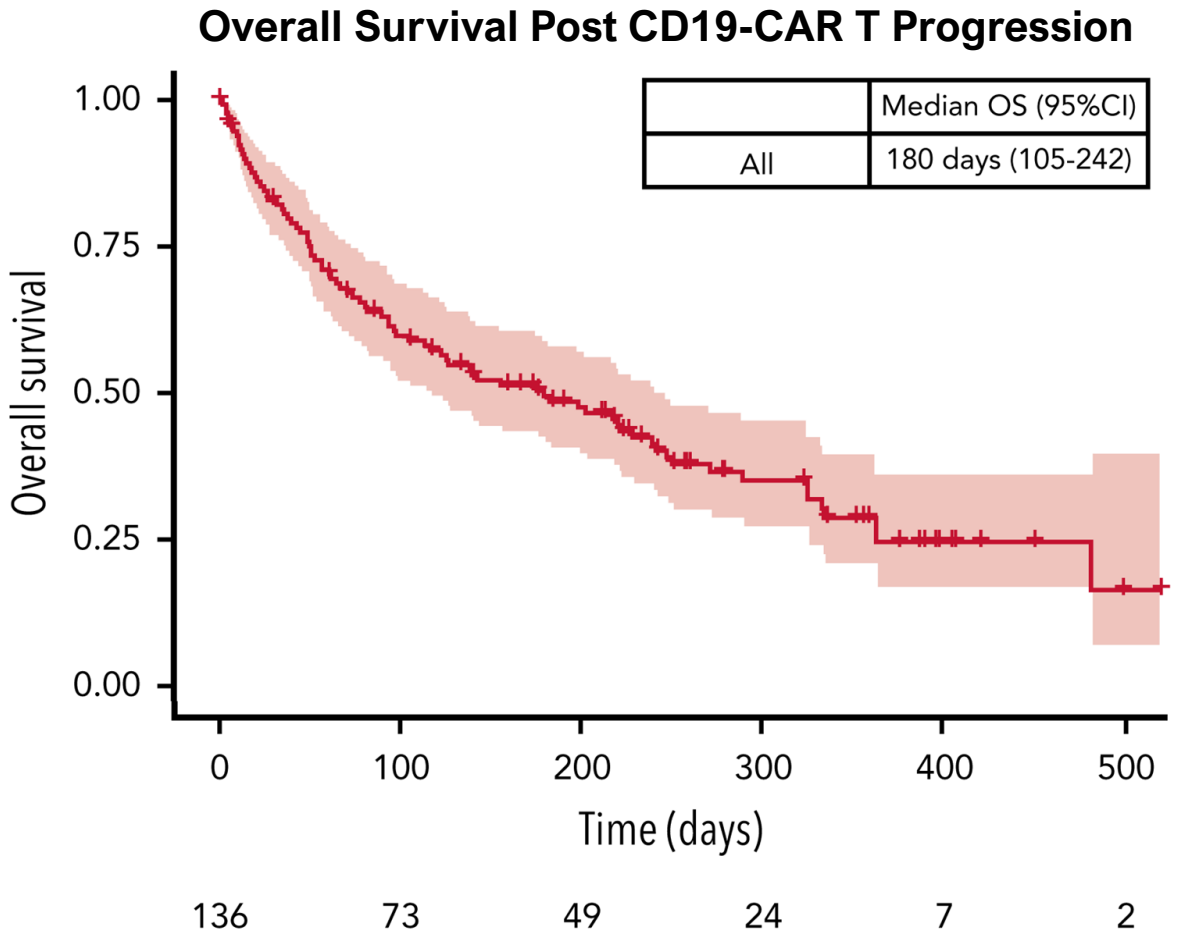

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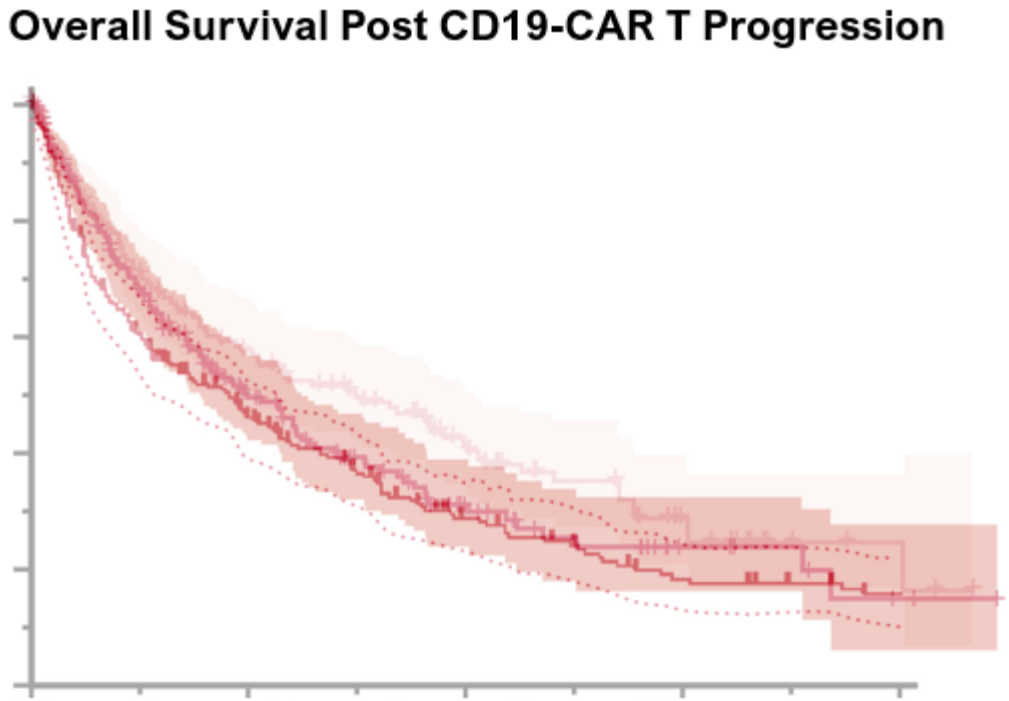

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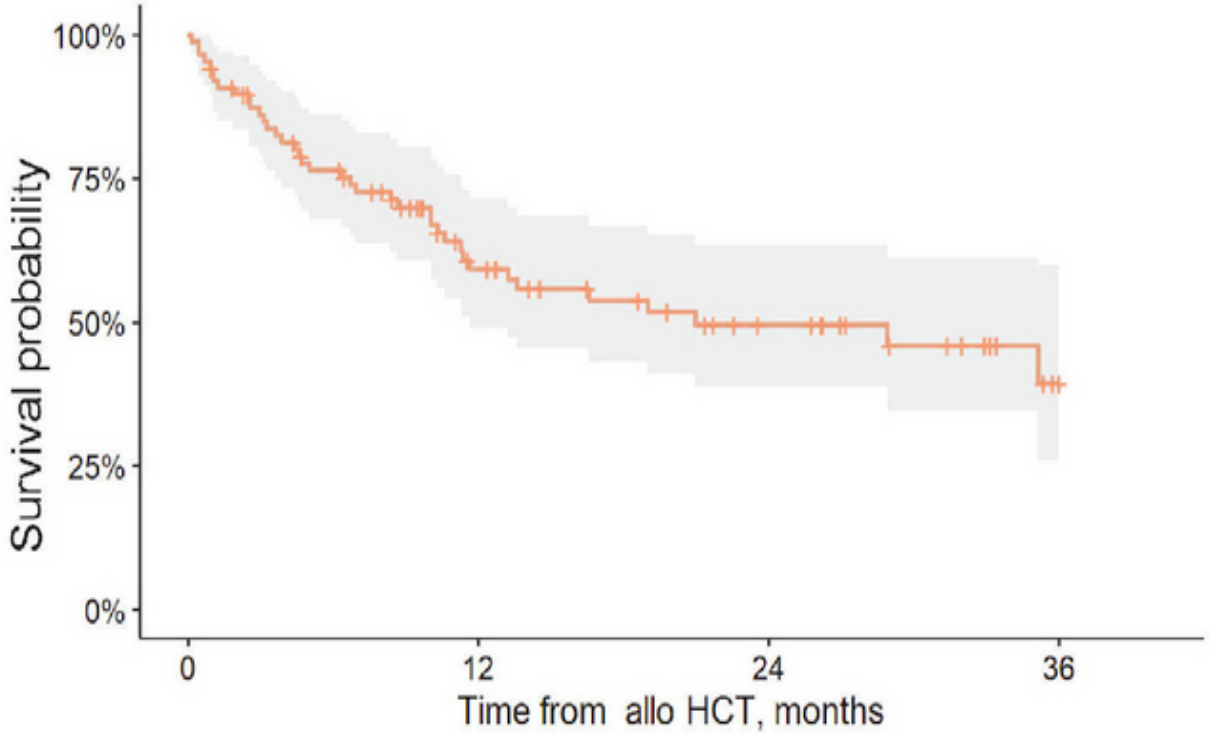
[3] Spiegel JY et al. Blood 2021.

Allogeneic HCT outcomes after CD19-CAR T relapse are heavily dependent on antecedent disease control

- Allogeneic HCT for post CD19-CAR T R/R LBCL can provide durable remissions with reduced intensity conditioning, however it is heavily dependent on achieving optimal disease control pre-transplant.
  - **CIBMTR:** 1-year CI NRM 22%; Median GRFS 5.7 mos, OS 21 mos [1]
  - **OS Predictors:** HR 4.32, PR vs CR; HR 3.63, ≥2 vs 0 lines of therapy between
  - **NRM Predictors:** HR 4.02, PR vs CR; HR 17, ≥2 vs 0 lines of therapy between; HR 0.25, RIC/NMA vs MAC regimen

Overall Survival Post CD19-CAR T Progression



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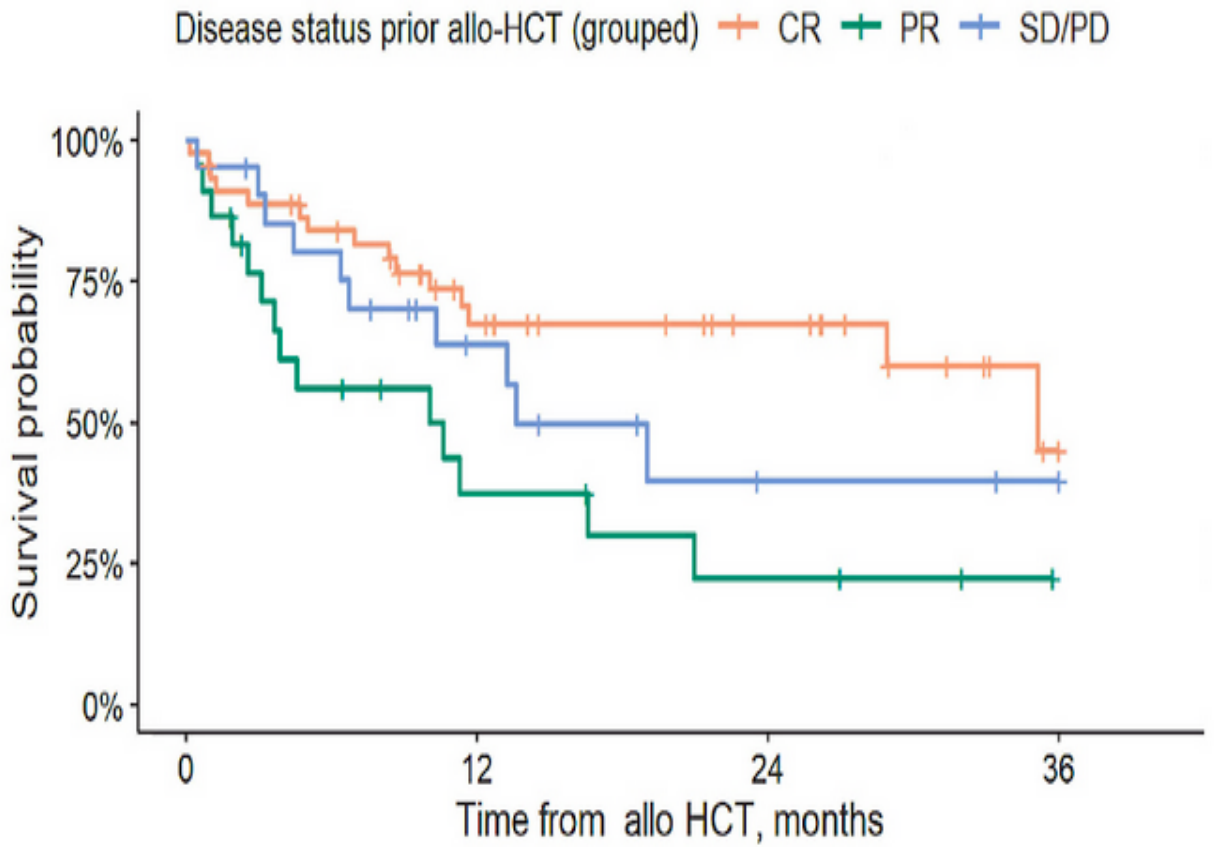
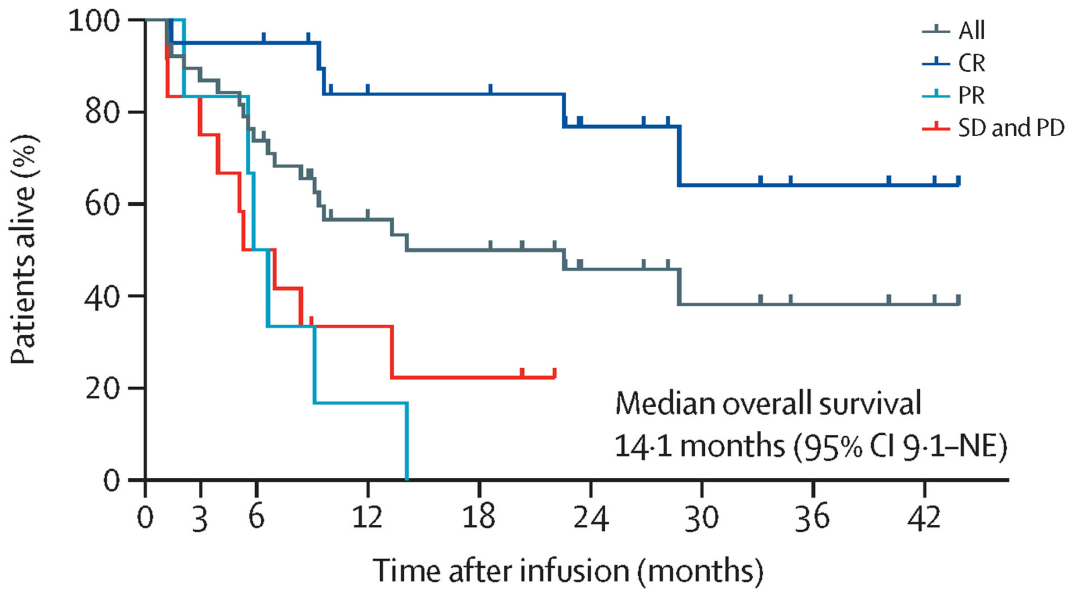


[1] Zurko J et al. Haematologica 2023.

CAR After CAR: CD22-CAR T phase 1 experience

- **Key Outcomes:**
  - Successful manufacturing for 38/40 (95%) leukapheresed for ≥ 2nd autologous CAR T
  - ORR 68%, CRR 53%
  - DOCR NR (17/20 ongoing at last f/u)
  - 2-year OS at DL1 52%
  - DL1 (1E06 CAR+ cell/kg) is RP2D
  - 1 (3%; at DL2) Gr ≥ 3 CRS
  - 0 Gr ≥ 3 ICANS
  - IEC-HS treated in 5 (13%; 3 at DL2)
- Now in multicenter phase 2 trial as firi-cel (CRG-022)

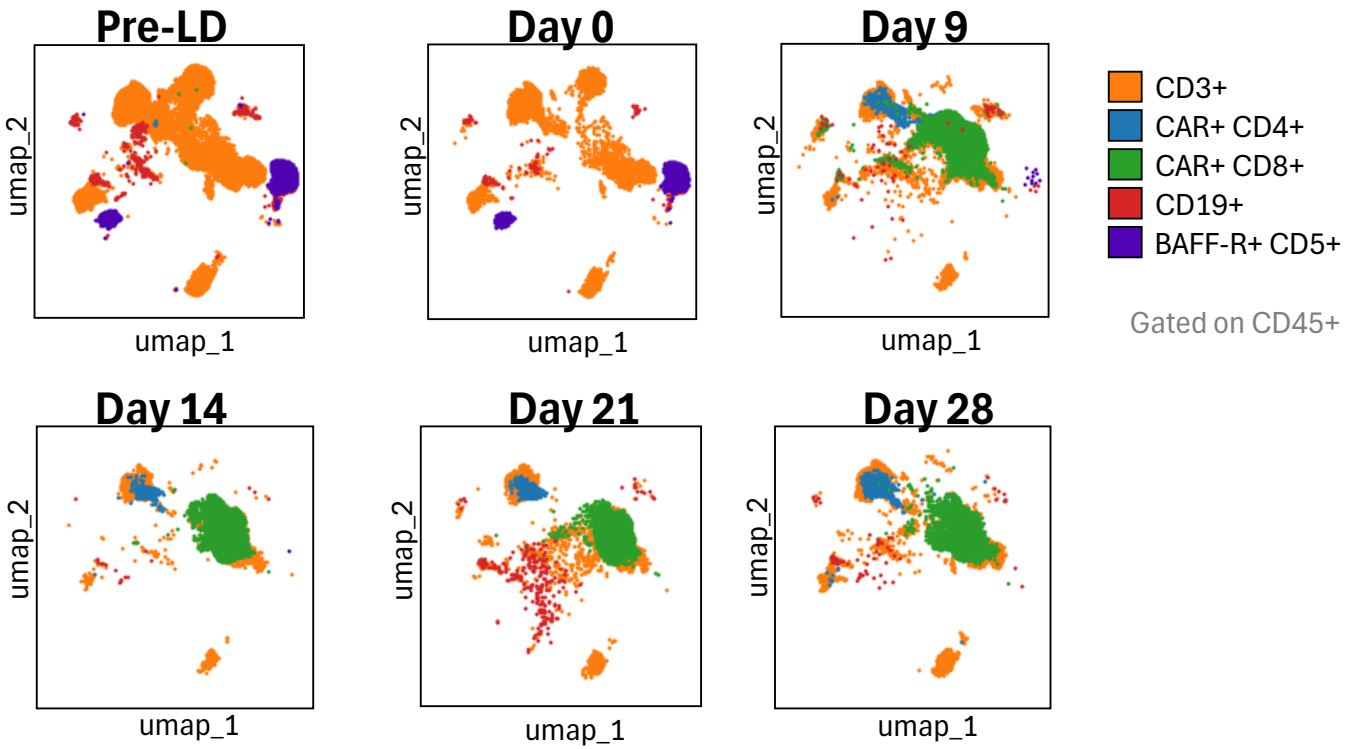
LBCL	DL1 (N = 29)	DL2 (N = 9)	Tot (N = 38)
Median follow up, months [range]	21.8 [6.4-43.8]	34.7 [29.5-38.4]	23.3 [6.4-43.8]
ORR, n (%)	19 (66%)	7 (78%)	26 (68%)
CR Rate (%)	15 (52%)	5 (56%)	20 (53%)
Median PFS (months, 95% CI)	3.0 (1.6 - NE)	2.6 (1.8 - NE)	3.0 (1.8 - NE)
Median OS (months, 95% CI)	**NR (9.1 - NE)**	**14.1 (2.1 - NE)**	**14.1 (9.1 - NE)**



[1] Frank MJ, Baird JH et al. Lancet 2024.

CAR After CAR: BAFF R-CAR T phase 1 experience

- **Key Outcomes:**
  - Successful manufacturing for 3/3 (100%) leukapheresed for ≥ 2nd autologous CAR T
  - DL1 (50M CAR+ cells): 1 THRLBCL in ongoing CR at 12+ mos f/u
  - 0 Gr ≥ 3 CRS
  - 0 Gr ≥ 3 ICANS
- Now in dose expansion at DL2 (200M CAR+ cells)



[1] Del Real M, Baird JH et al. Blood 2024.

Fin.

- Thanks for your attention! See you in the Q&A portion.

- Contact: jbaird@coh.org