6th POSTGRADUATE

Lymphoma Conference

ZUMA-1 @ 5 years

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The University of Texas MD Anderson Cancer Center

Rome,
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2022

VOI Donna Camilla Savelli Hotel

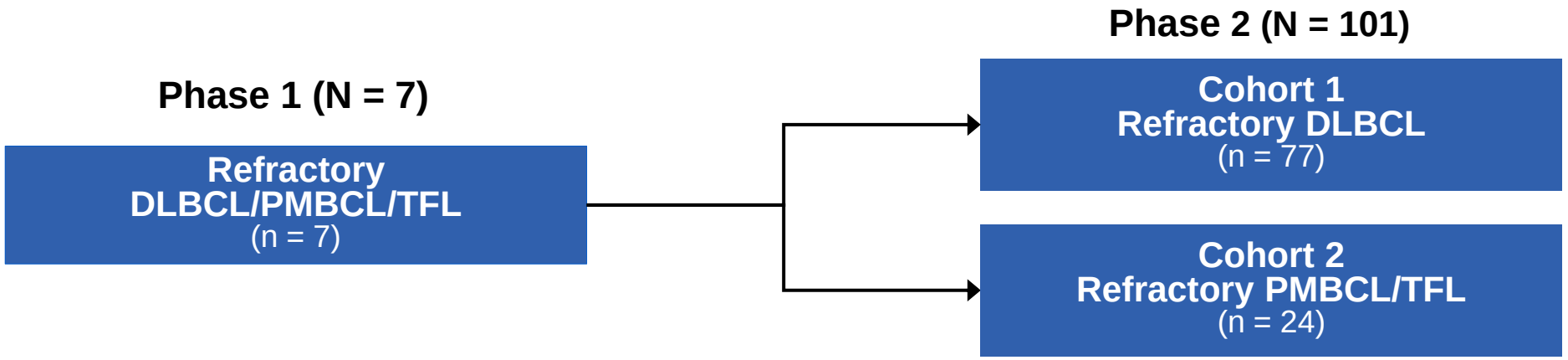
President:
P.L. Zinzani

Disclosures

Disclosure	Company name
Research Support	Kite/Gilead, BMS, Cellectis, Poseida, Allogene, Unum Therapeutics, Precision Biosciences, Adicet Bio
Advisory Board / Consultant	Kite/Gilead, Merck, Novartis, Sellas Life Sciences, Athenex, Allogene, Incyte, Adicet Bio, BMS, Legend Biotech, Bluebird Bio, Sana Biotechnology, Caribou, Astellas Pharma, Morphosys
Honoraria	Medscape, Aptitude Health, Bio Ascend, MJH Life Sciences
Speaker's Bureau	None
Employment	None
Royalties	Takeda Pharmaceuticals
Stocks / Stock Options	Longbow Immunotherapy
Patents	Related to cell therapy

- I will discuss investigational use of CAR T-cell therapy

ZUMA-1: Phase 1/2 study design



Key eligibility criteria

- No response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 monoclonal antibody and anthracycline

- **N = 108**

Conditioning regimen

- Cyclophosphamide 500 mg/m^2/d + fludarabine 30 mg/m^2/d for 3 days

Axi-cel: 2 × 10^6 CAR+ cells/kg

- 99% enrolled were successfully manufactured
- 91% enrolled were dosed
- 17-day average turnaround time from apheresis to delivery to clinical site

ASCT, autologous stem cell transplant.

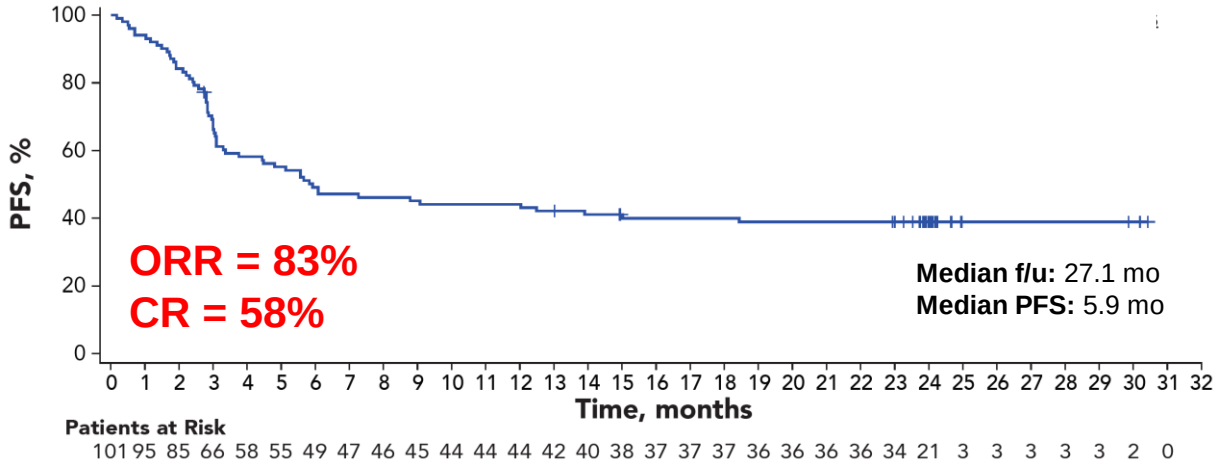
ZUMA-1: Baseline patient characteristics

Characteristic	Phase 1 and 2 N = 108
Median (range) age, y	58 (23 – 76)
≥ 65 y, n (%)	27 (25)
Male, n (%)	73 (68)
ECOG 1, n (%)	62 (57)
Disease stage III/IV, n (%)	90 (83)
IPI score 3-4, n (%)	48 (44)
≥ 3 prior therapies, n (%)	76 (70)
Refractory Subgroup Before Enrollment	**Phase 1 and 2 N = 108**
Refractory to second- or later-line therapy, n (%) Best response as PD to last prior therapy	80 (74) 70 (65)
Relapse post-ASCT, n (%)	25 (23)

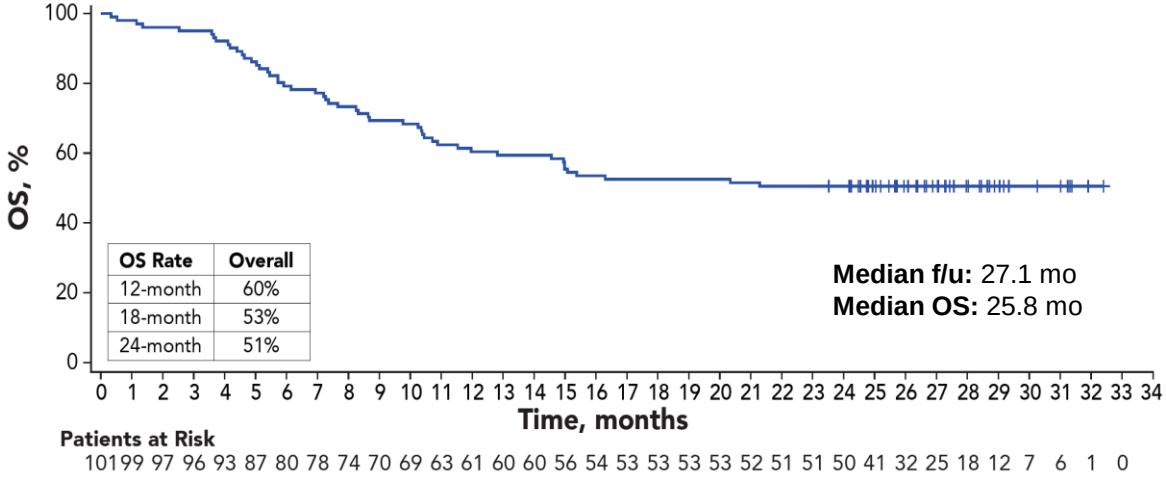
ASCT, autologous stem cell transplant; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index.

ZUMA-1: Axi-cel in r/r large B-cell lymphoma

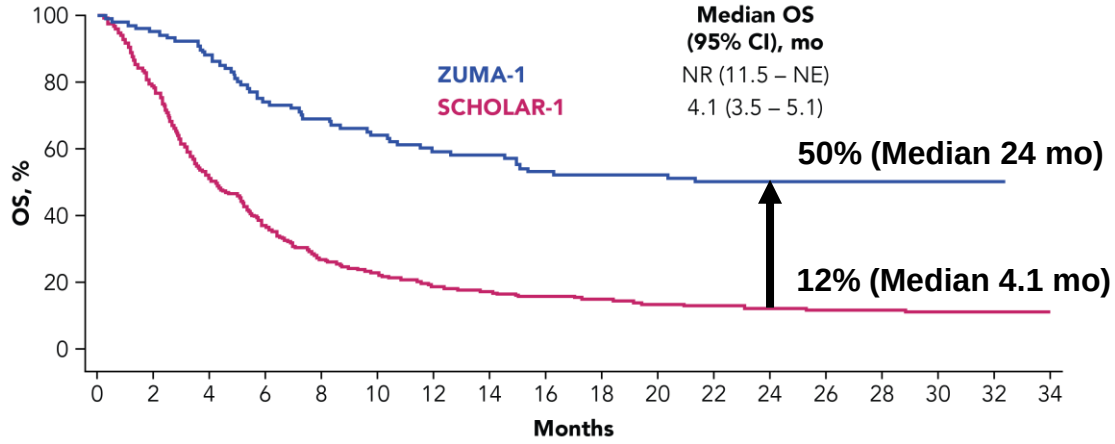
PFS: 39% progression-free at 27.1 mo



OS: 51% alive at 27.1 mo



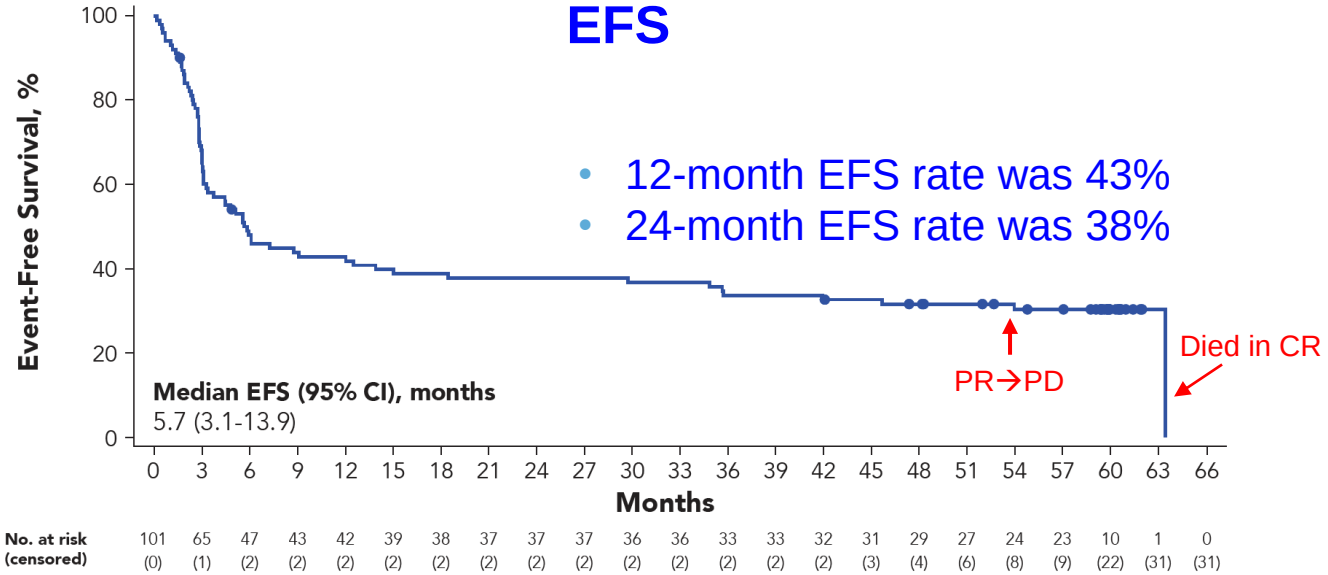
Standardized OS Comparison: ZUMA-1 vs. SCHOLAR-1 (historical)



Neelapu et al. *N Eng J Med* 2017
Locke et al. *Lancet Oncol* 2019
Neelapu et al. *Blood Adv* 2021

ZUMA-1: 5-year EFS and OS

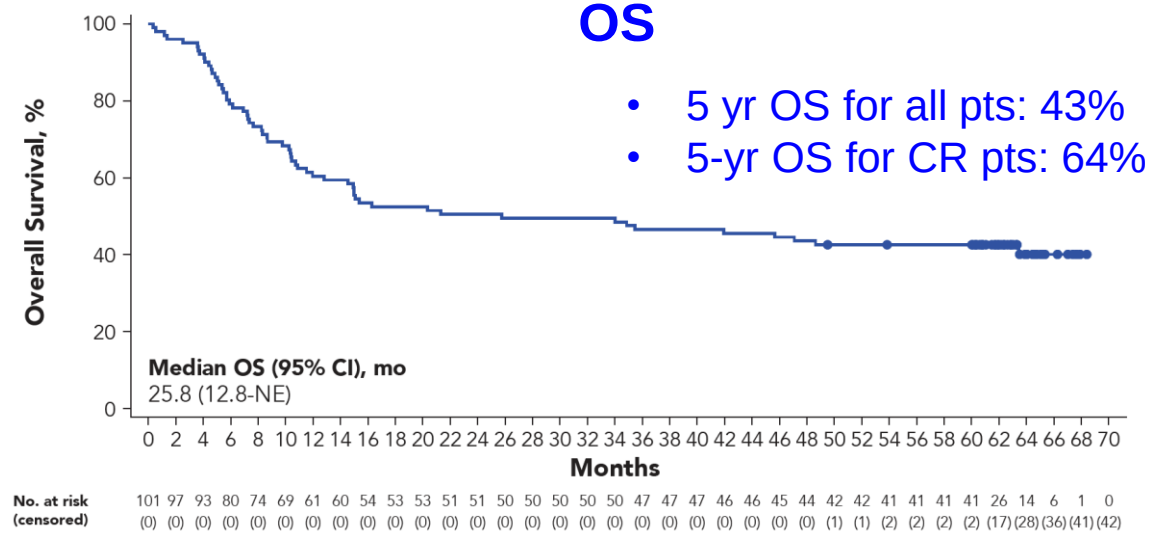
EFS



- 12-month EFS rate was 43%
- 24-month EFS rate was 38%

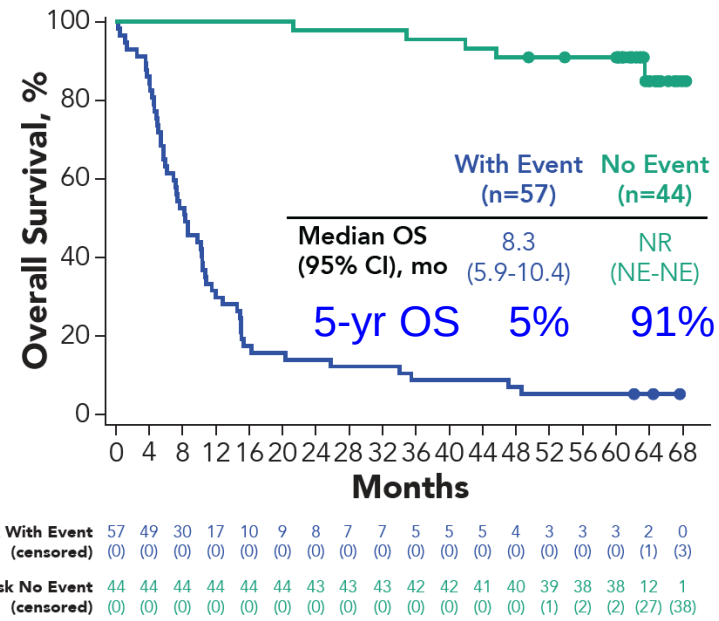
Median f/u 63.1 mo
as of Aug 11, 2021

OS



- 5 yr OS for all pts: 43%
- 5-yr OS for CR pts: 64%

OS by EFS at 12 Months



Jacobson et al, *ASH* 2021, Abstract 1764

ZUMA-1: Cause of deaths

n (%)	Total N=101	Year 1	Year 2	Year 3	Year 4	Year 5	Year >5
Patients who died	59 (58)	40 (40)	10 (10)	4 (4)	3 (3)	1 (1)	1 (1)
Primary cause of death							
Progressive disease[a]	45 (45)	32 (32)	9 (9)	3 (3)	0	1 (1)	0
Other[b]	9 (9)	5 (5)	0	1 (1)	3 (3)	0	0
Adverse event[c]	4 (4)	3 (3)	1 (1)	0	0	0	0
Secondary malignancy	1 (1)	0	0	0	0	0	1 (1)

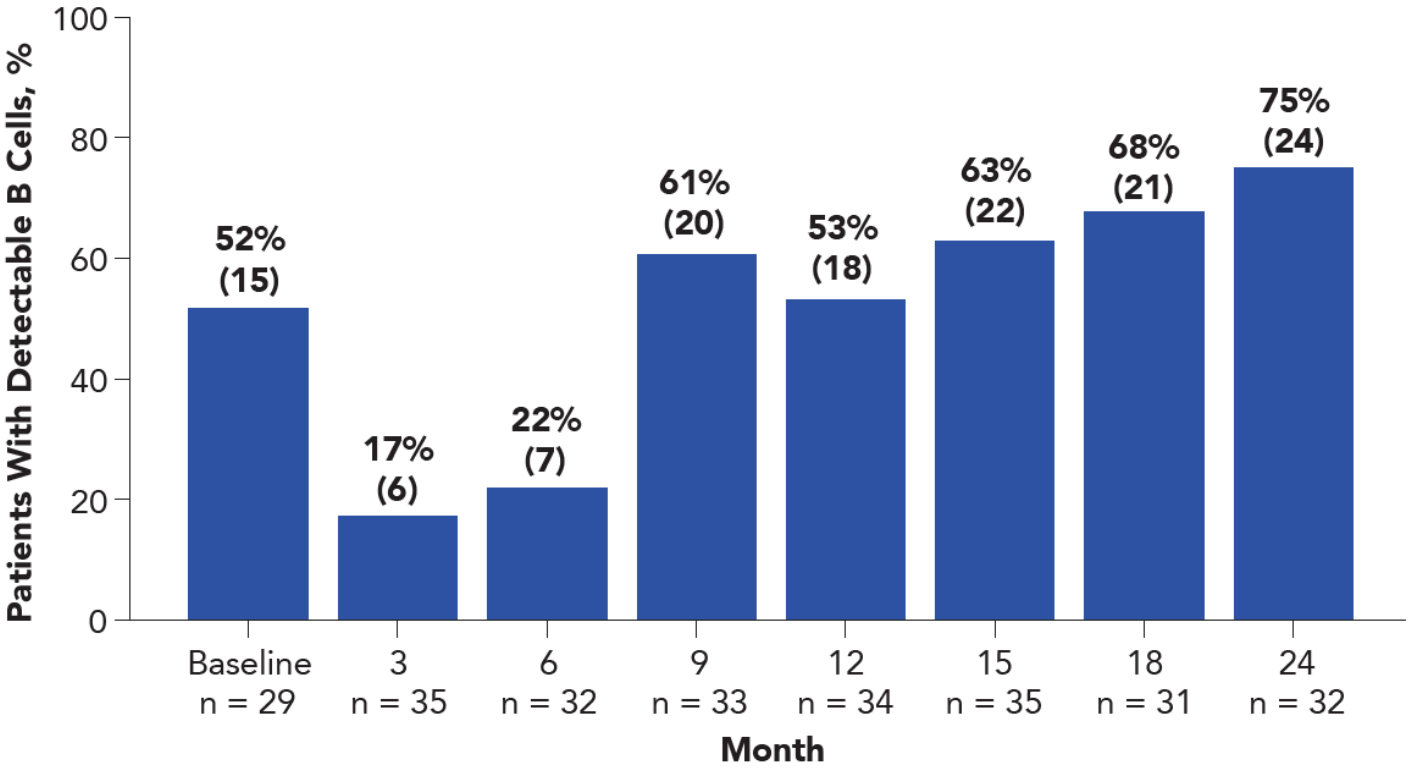
- Among treated patients, 58% have died as of the data cutoff date
- Following the 4-year data cutoff date[1]
  - There has been 1 death which was due to secondary malignancy (prior therapy- and/or conditioning chemotherapy-related MDS while in CR for LBCL)
  - No patients received intravenous immunoglobulin
- As of the 5-year data cut-off, no new safety signals have been reported, including
  - No serious adverse events related to axi-cel
  - No secondary malignancies related to axi-cel

[1] Jacobson C, et al. ASH 2020. #1187.

[a] During ongoing safety monitoring after the data cutoff, one event of CNS lesion which was not amenable to biopsy was reported. Treatment for presumed progressive disease for diffuse large B-cell lymphoma was initiated by the investigator. [b] Events included infection (n=3), cardiac arrest (n=2), pulmonary nocardiosis (n=1), sepsis (n=1), complications of allogeneic transplant for previous treatment-related MDS not related to axi-cel (n=1), and unknown (n=1). [c] Two events had no causal relationship (sepsis, pulmonary embolism) and 2 events were related to axi-cel (brain injury due to cardiac arrest and hemophagocytic lymphohistiocytosis).

Jacobson et al, *ASH* 2021, Abstract 1764

ZUMA-1: B cell detection in blood at 2 and 3 years



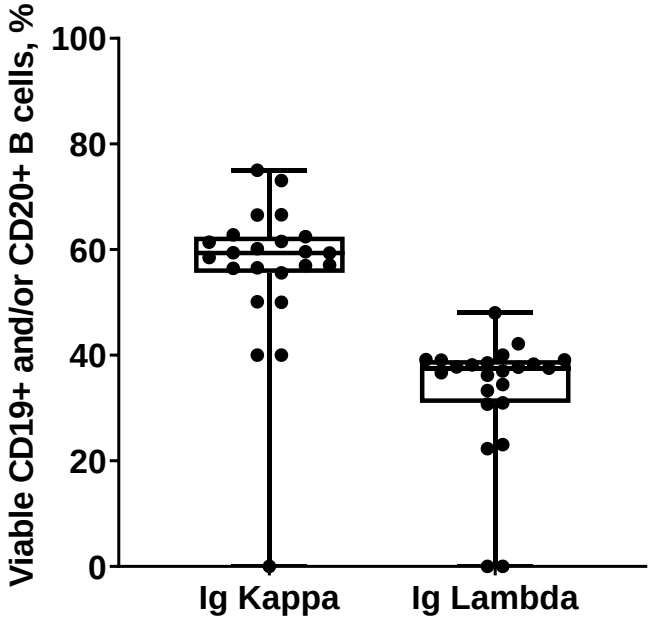
- 75% of patients (24/32) with ongoing responses had detectable B cells 2 years after axi-cel infusion
- 100% of patients (21/21) with ongoing response at ≥3 years had detectable B cells in peripheral blood (67% had detectable CAR T cells)
- Throughout the course of the study, 31% of patients received intravenous immunoglobulins

- Supports the notion that long-term persistence may not be needed to maintain durability of responses after axi-cel in LBCL

Locke et al Neelapu, *Lancet Oncol* 2019
Jacobson et al, *JSHCT* 2021, Abstract 009

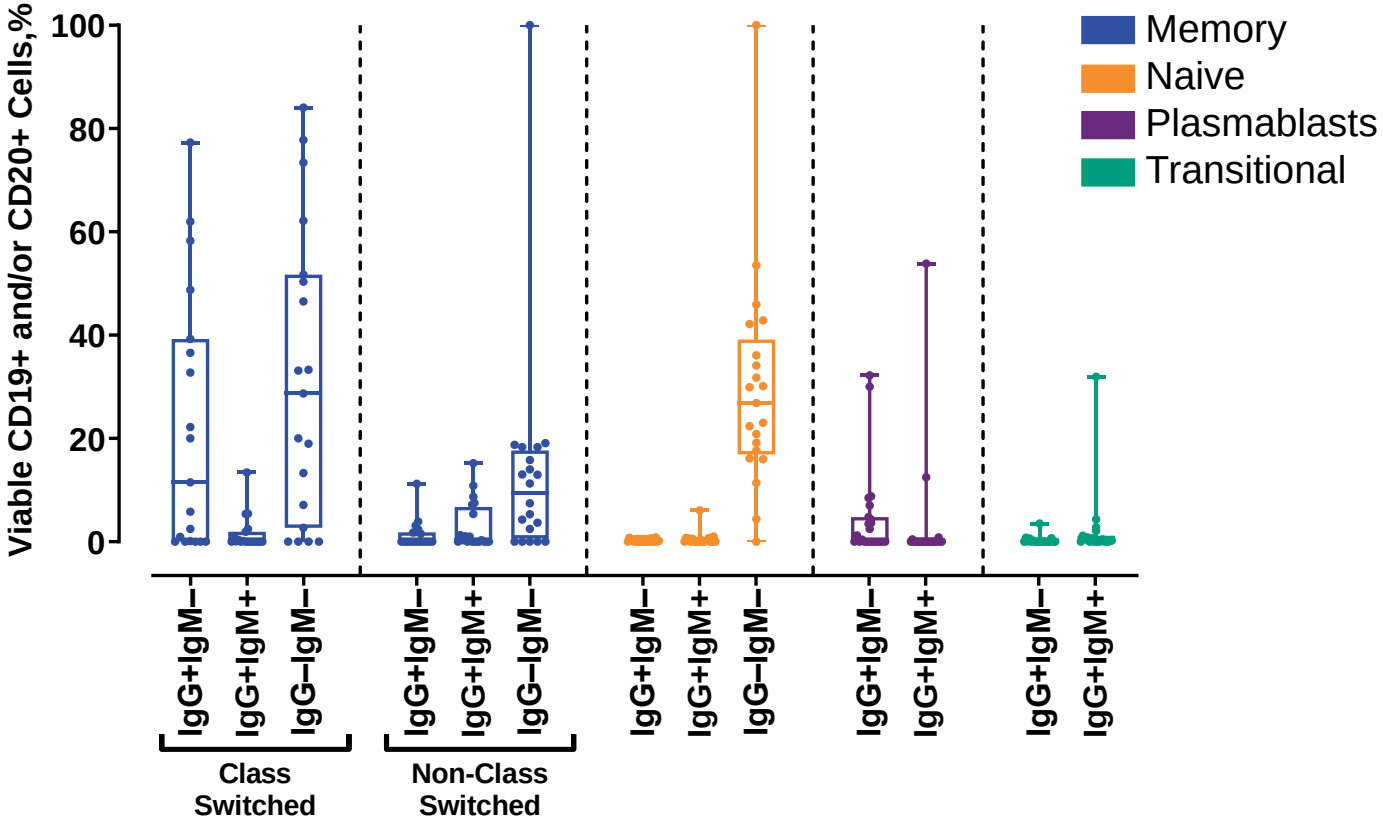
ZUMA-1: Most had polyclonal B-cell recovery and diversity at 3 years

B-Cell Recovery



- 91% of patients (n=21/23) demonstrated polyclonal B-cell recovery
- The median Ig kappa-lambda ratio was 1.6[a]

B-Cell Diversity

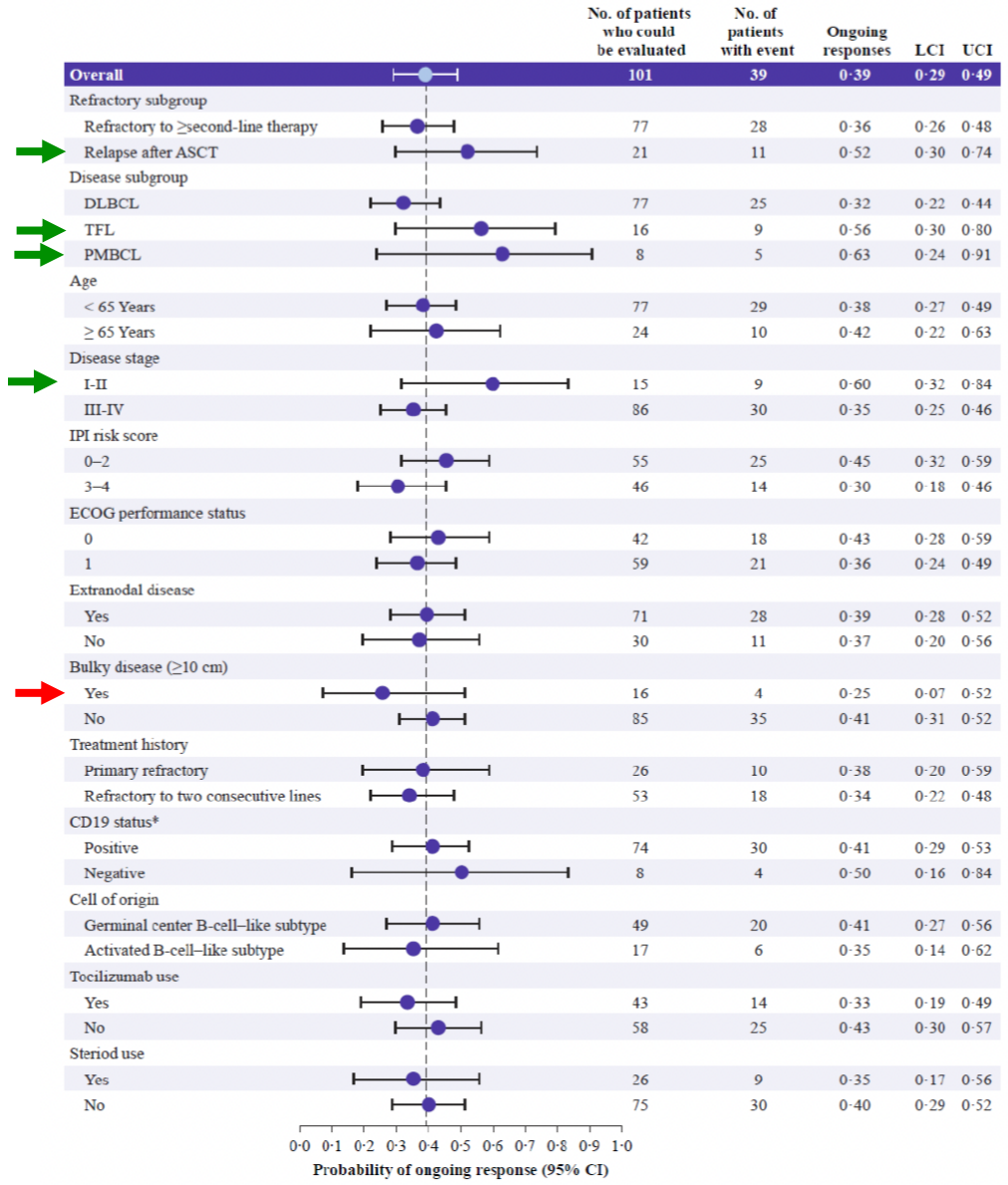


B-cell subsets were defined as CD45+CD3−CD14−CD16−CD56−CD19+ and/or CD20+ and further phenotyped as follows: Ig kappa, Ig lambda, class-switched memory (CD20+CD27+IgD−), non–class-switched memory (CD20+CD27+IgD+), naive (CD20+CD27−IgD+CD24lowCD38low), plasmablasts (CD38highCD20−), and transitional (CD20+CD27−IgD+CD24+CD38mid).

[a] n=21 patients because 2 patients had lambda value equal to 0.

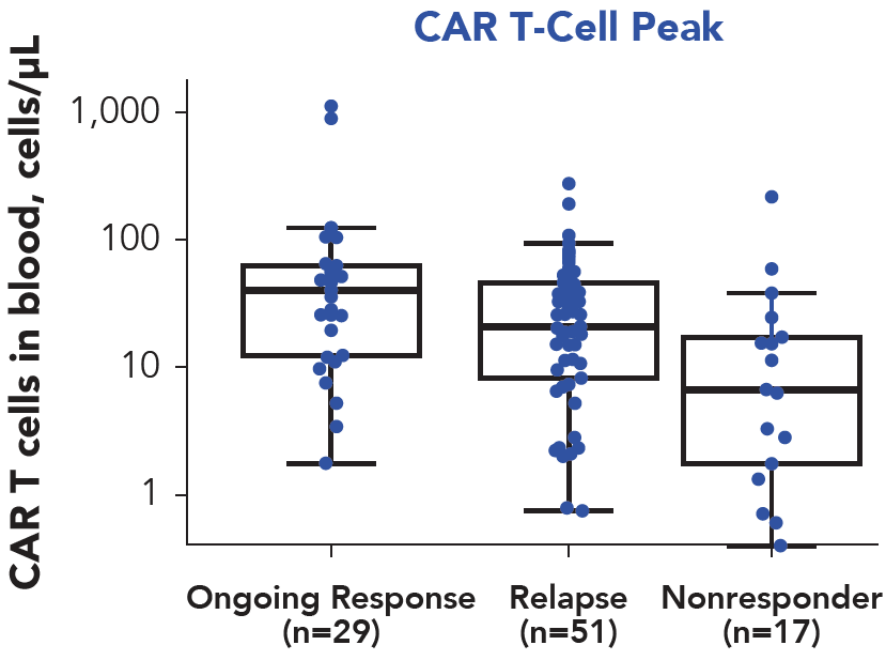
Jacobson et al, *JSHCT* 2021, Abstract 009

ZUMA-1: Ongoing responses at 2 years across key covariates

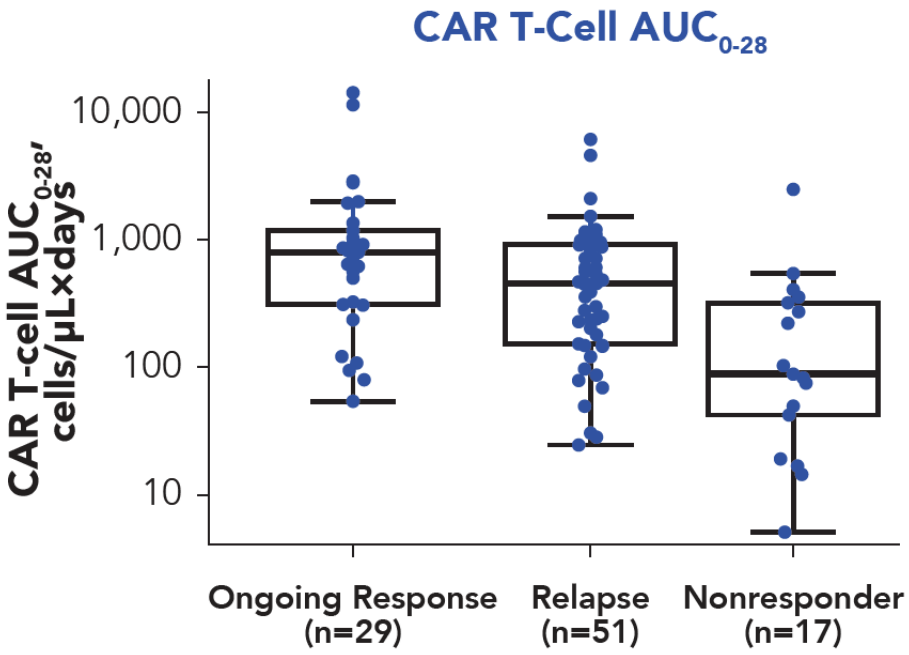


Locke et al. *Lancet Oncol* 2019

ZUMA-1: Early CAR T-cell expansion associated with ongoing response at 5 years



	Ongoing Response (n=29)	Relapse (n=51)	Nonresponder (n=17)
Median peak, cells/µL	65.76	35.27	12.08

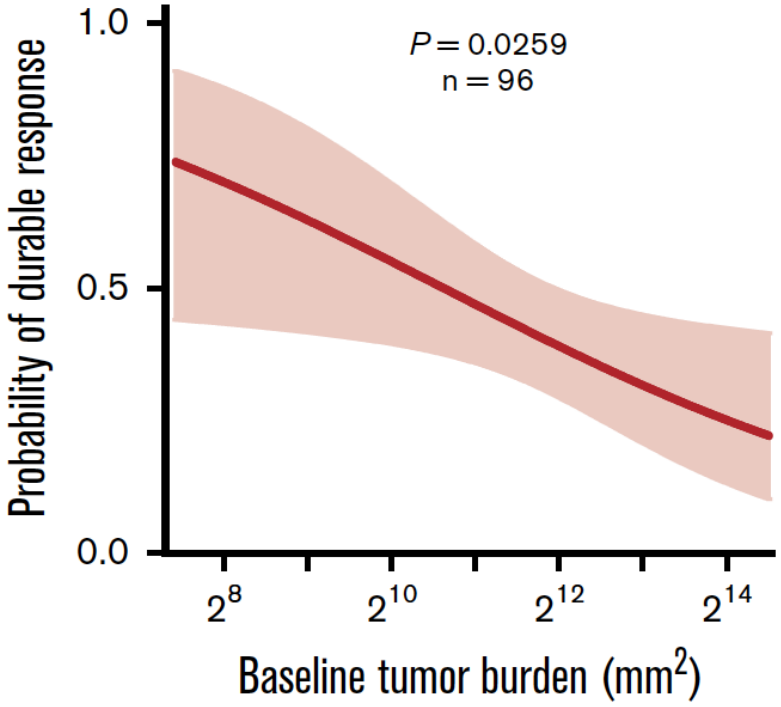


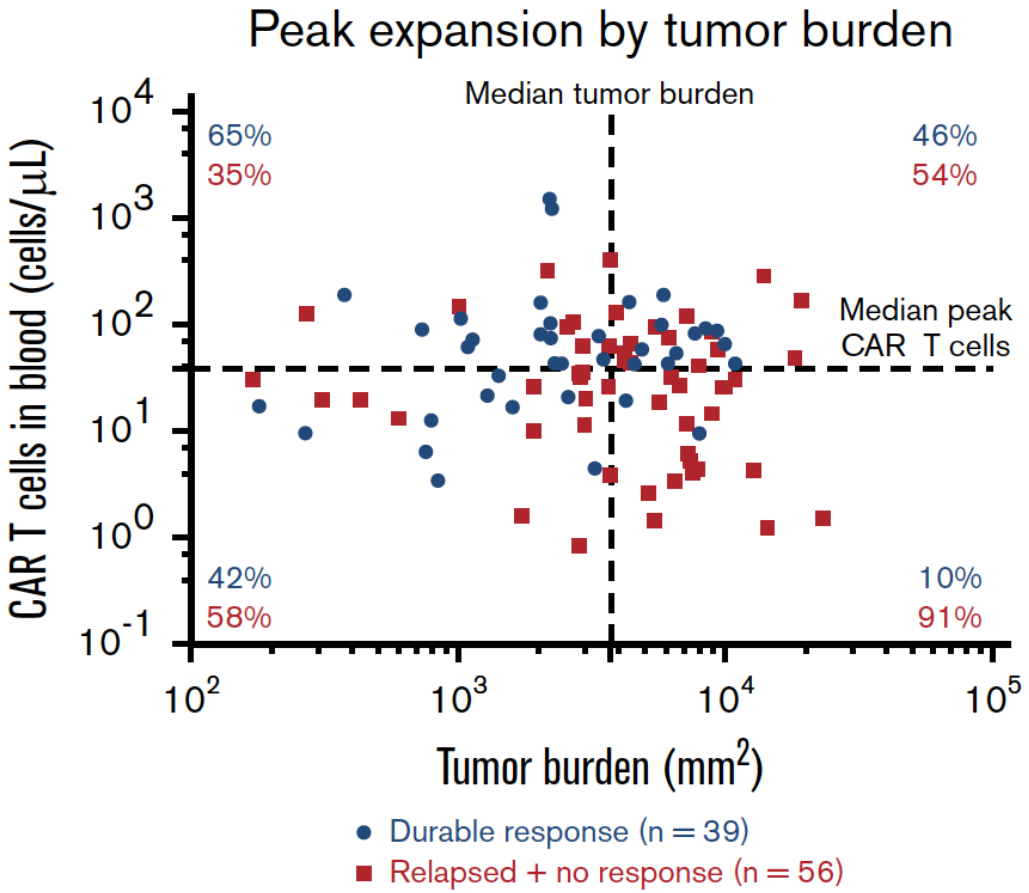
	Ongoing Response (n=29)	Relapse (n=51)	Nonresponder (n=17)
Median $AUC_{0\text{-}28}$, cells/µL×days	799.69	455.32	88.47

Jacobson et al, *ASH* 2021, Abstract 1764

Patients with high tumor burden have lower CAR T-cell expansion

ZUMA-1

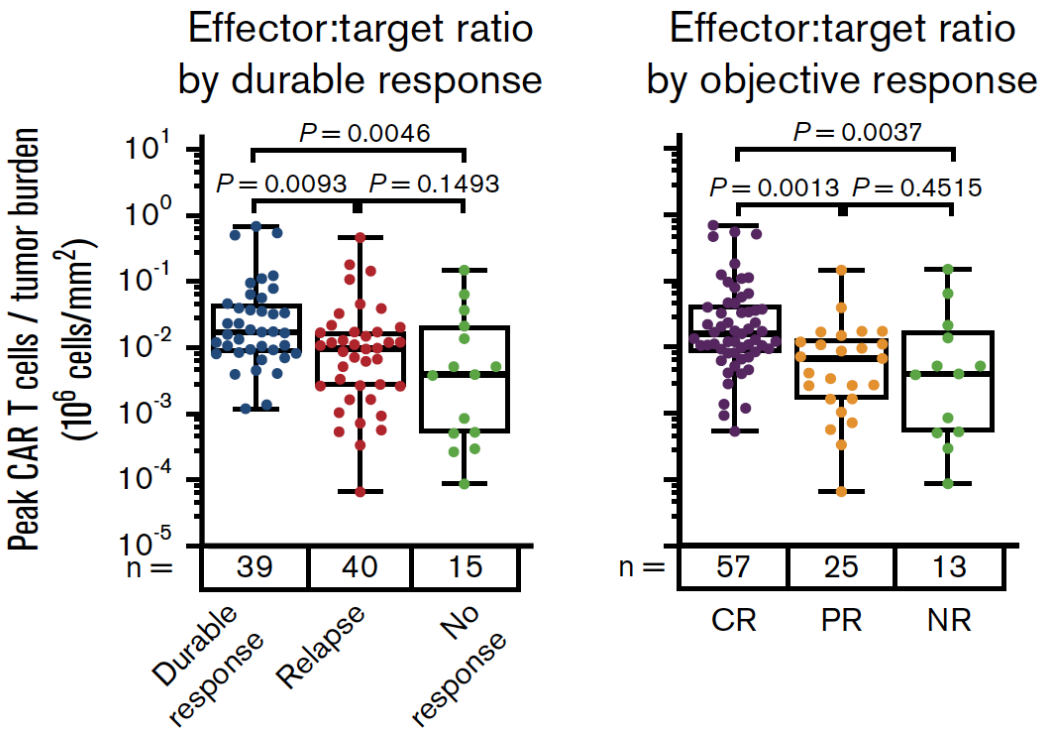


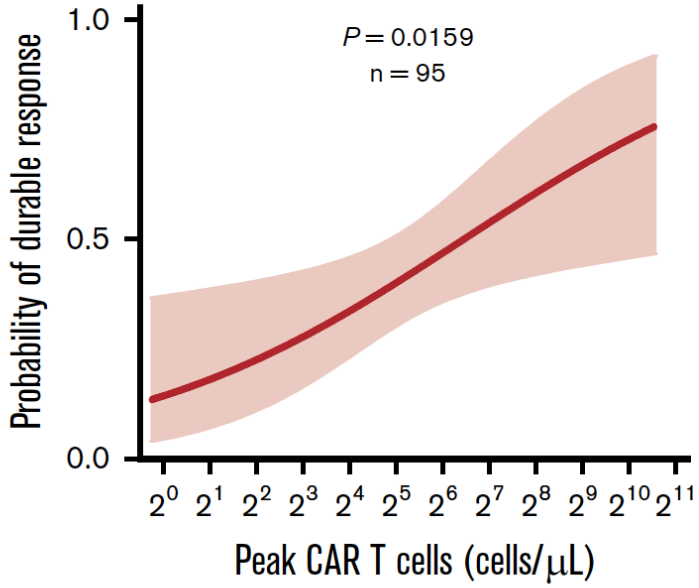


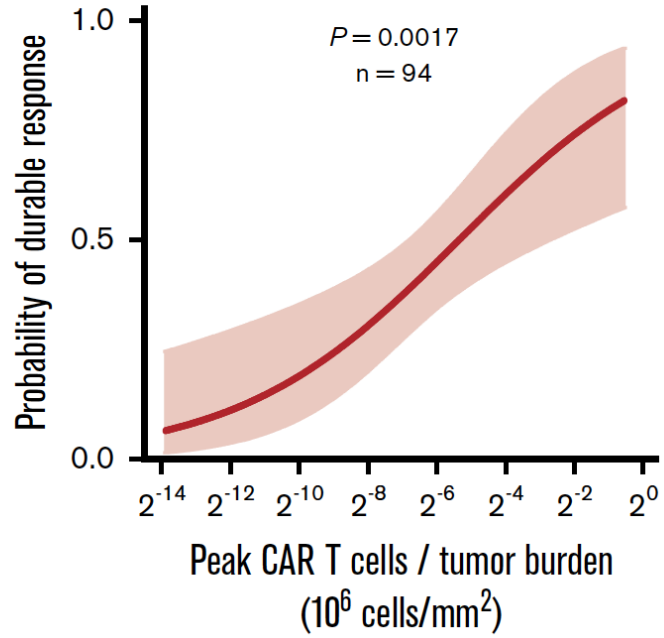
Locke et al, *Blood Adv* 2020

CAR-T expansion relative to tumor burden associated with durability

ZUMA-1



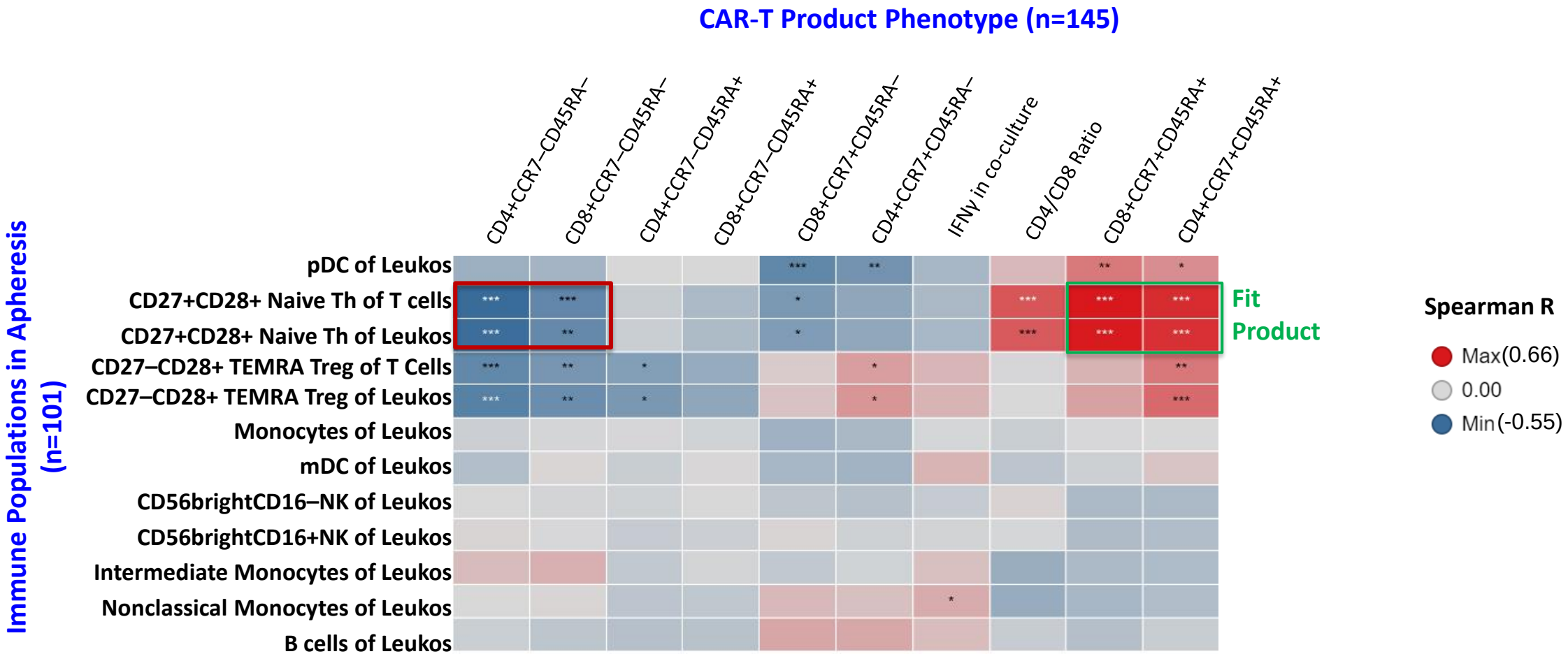




- Will patients with higher tumor burden benefit from higher CAR T dose or 2nd infusion?

Locke et al, *Blood Adv* 2020

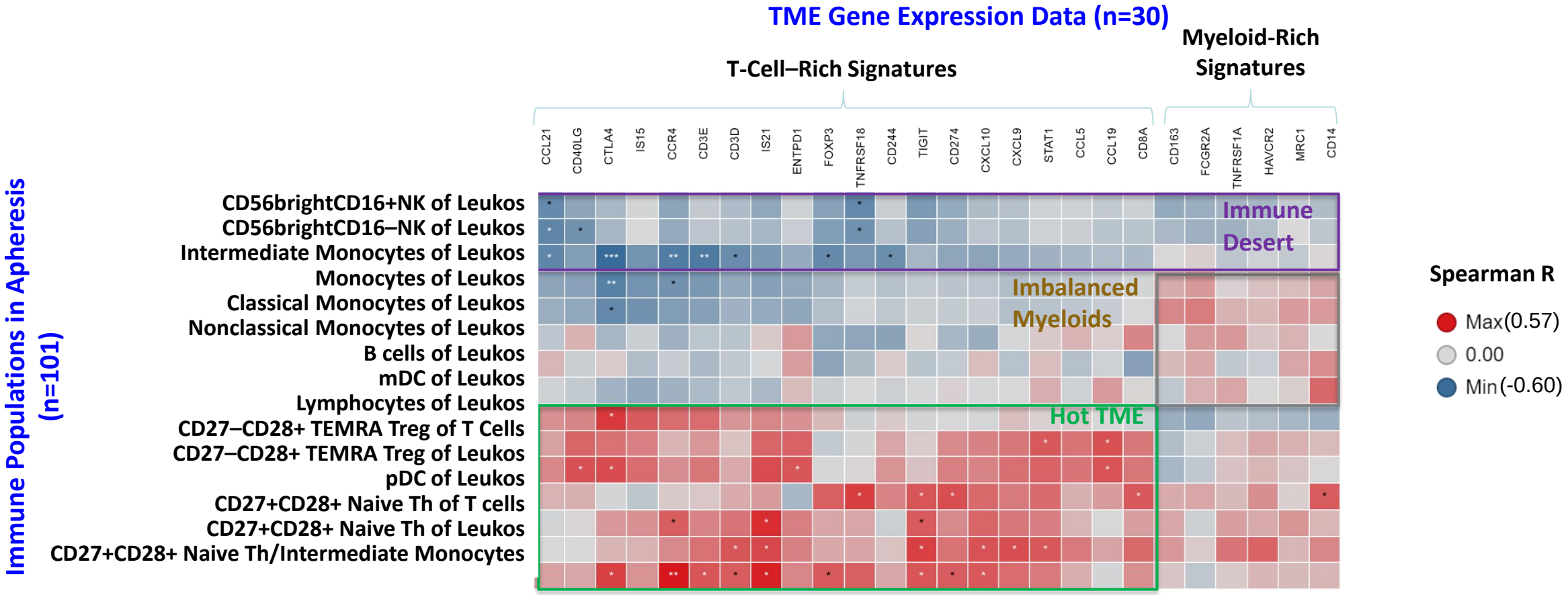
$CD27^{+}CD28^{+}$ naïve T-cells in apheresis associate with CAR-T product fitness



Red and blue shading indicate positive and negative associations, respectively, between covariates.
**P* <0.05, ***P* <0.01, and ****P* <0.001.

Budka et al, *AACR* 2021, Abstract #CT166

CD27+CD28+ naïve T cells in apheresis associated with hot TME

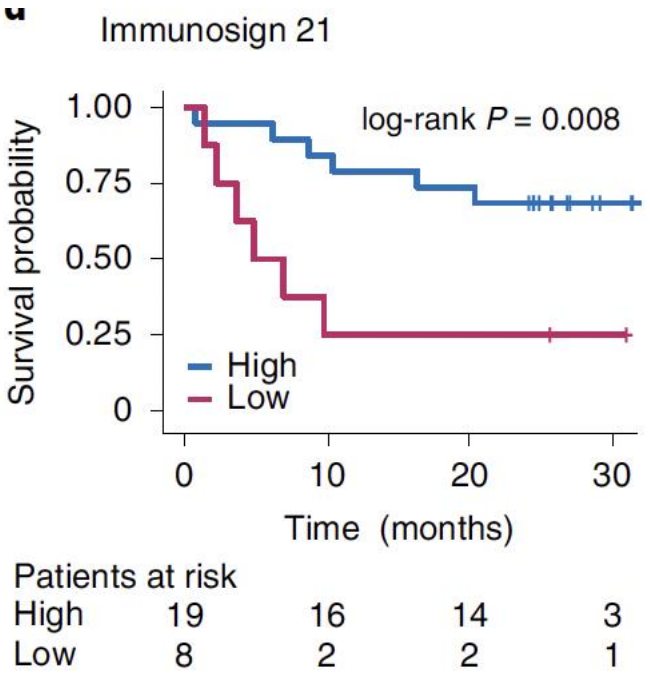


Red and blue shading indicate positive and negative associations, respectively, between covariates.
**P* <0.05, ***P* <0.01, and ****P* <0.001.

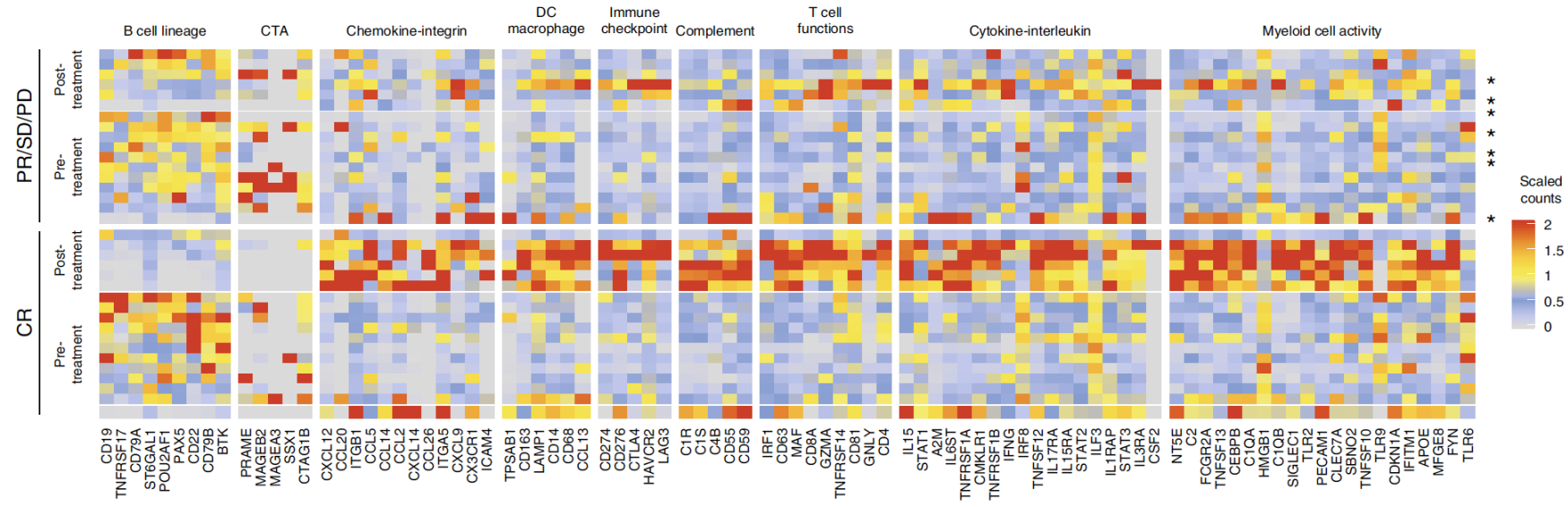
Budka et al, *AACR* 2021, Abstract #CT166

Tumor immune contexture pre- and post-infusion is associated with CAR-T efficacy

Baseline

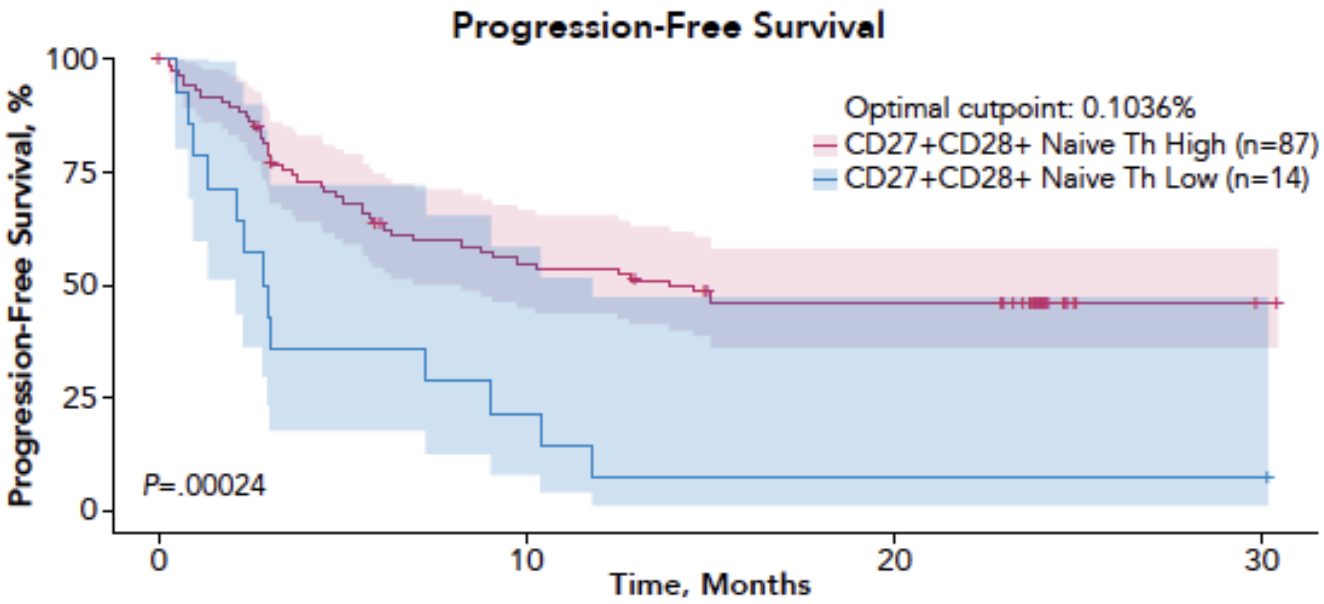


Changes in TME pre- vs. post infusion



Scholler et al. *Nat Med* 2022

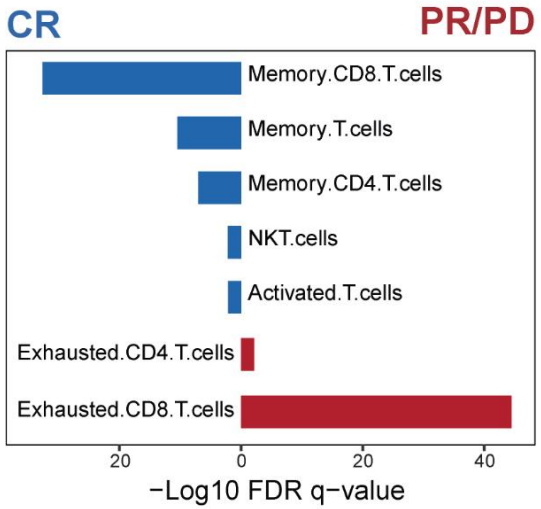
$CD27^{+}CD28^{+}$ naïve T cells in apheresis associated with better efficacy

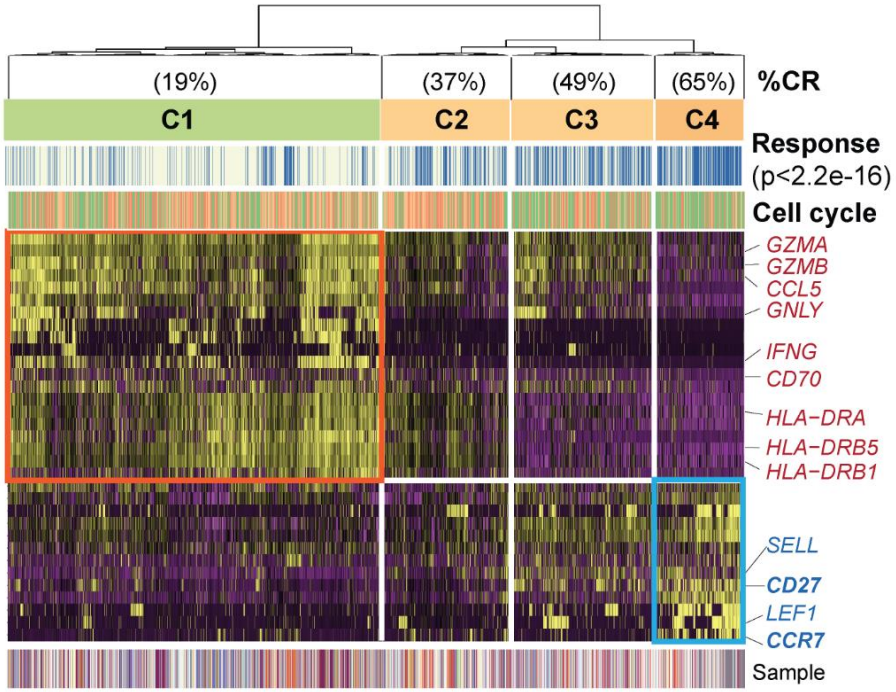


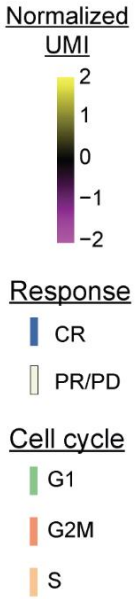
	High (n=87)	Low (n=14)
ORR, n (%)	74 (85)	10 (71)
CR rate, n (%)	52 (60)	7 (50)
Ongoing response, n (%)	36 (41)	2 (14)
Grade ≥3 NEs, n (%)	28 (32)	3 (21)
Grade ≥3 CRS, n (%)	9 (10)	2 (14)
Median CAR peak, cells/μL	42.588	19.836
Median CAR peak/tumor burden, cells/mm^2	0.01105	0.00872

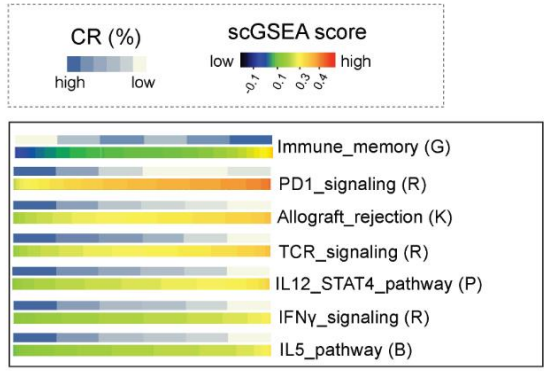
Budka et al, *AACR* 2021, Abstract #CT166

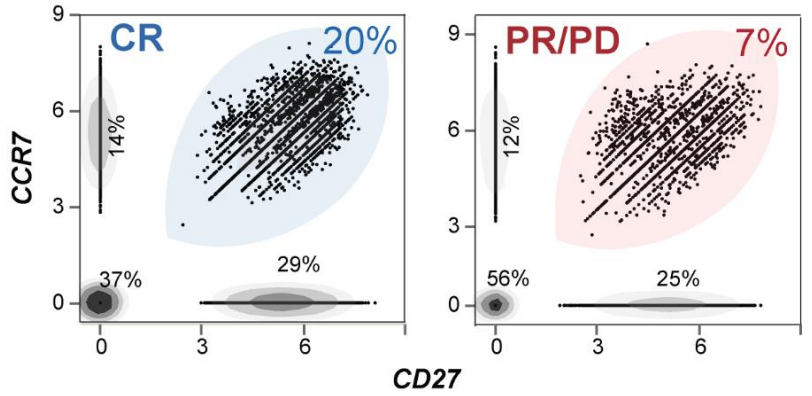
scRNA-seq of axi-cel: CD8 functional states associate with clinical response in r/r LBCL







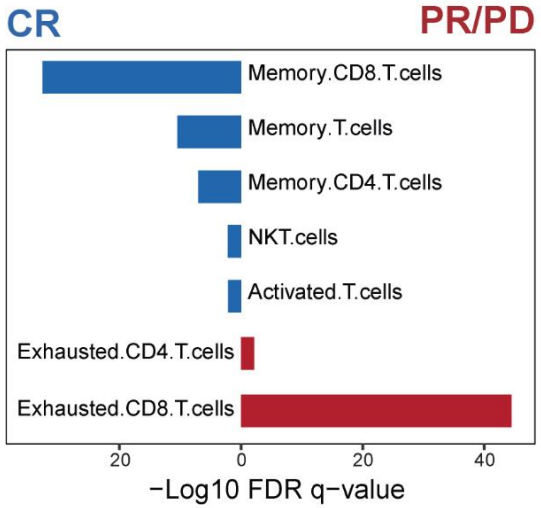


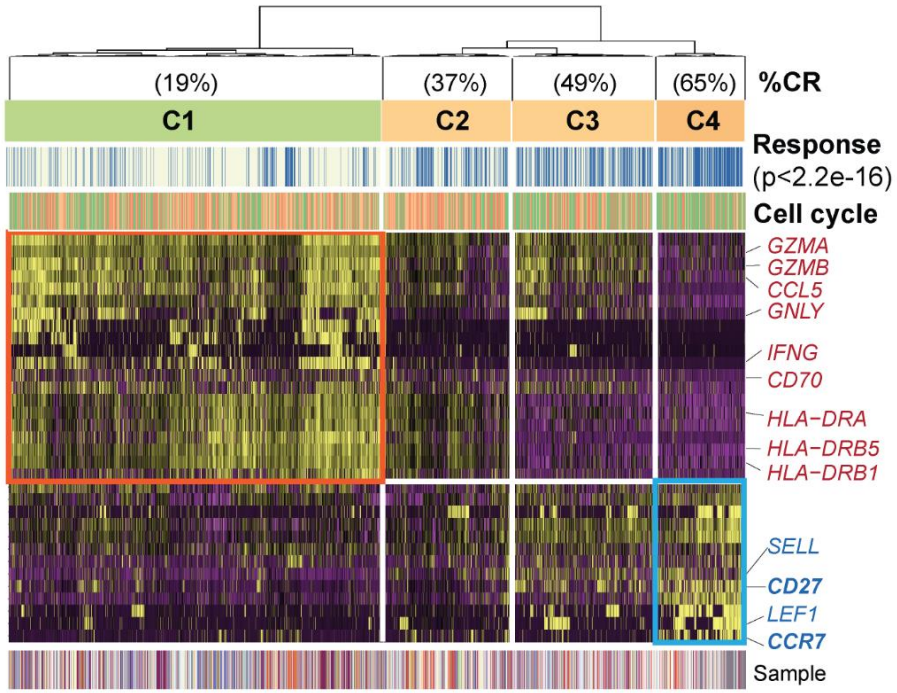


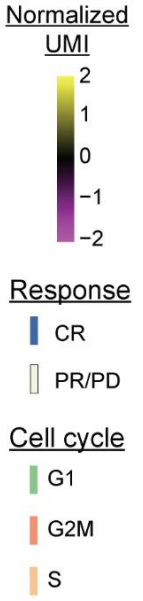
- **Higher proportions of memory CD8 T-cells (CCR7+CD27+) are associated with CR**

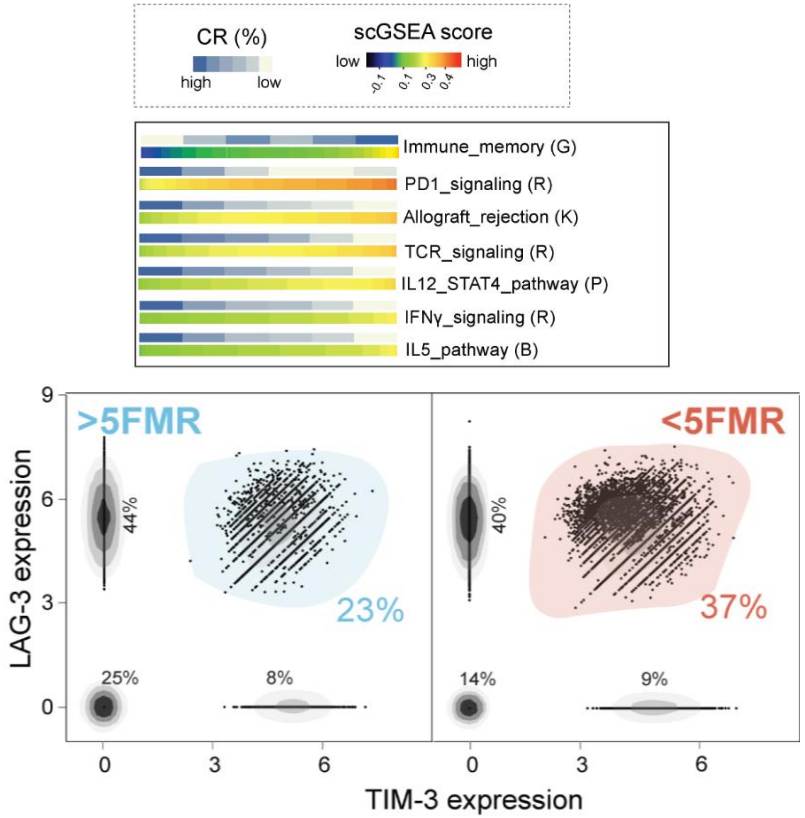
Deng, Han, et al. *Nat Med* 2020

scRNA-seq of axi-cel: CD8 functional states associate with clinical response in r/r LBCL









- **Higher proportions of memory CD8 T-cells (CCR7+CD27+) are associated with CR**
- **Exhausted phenotype (LAG3+ and TIM3+) CD8 T cells associated with PR/PD**

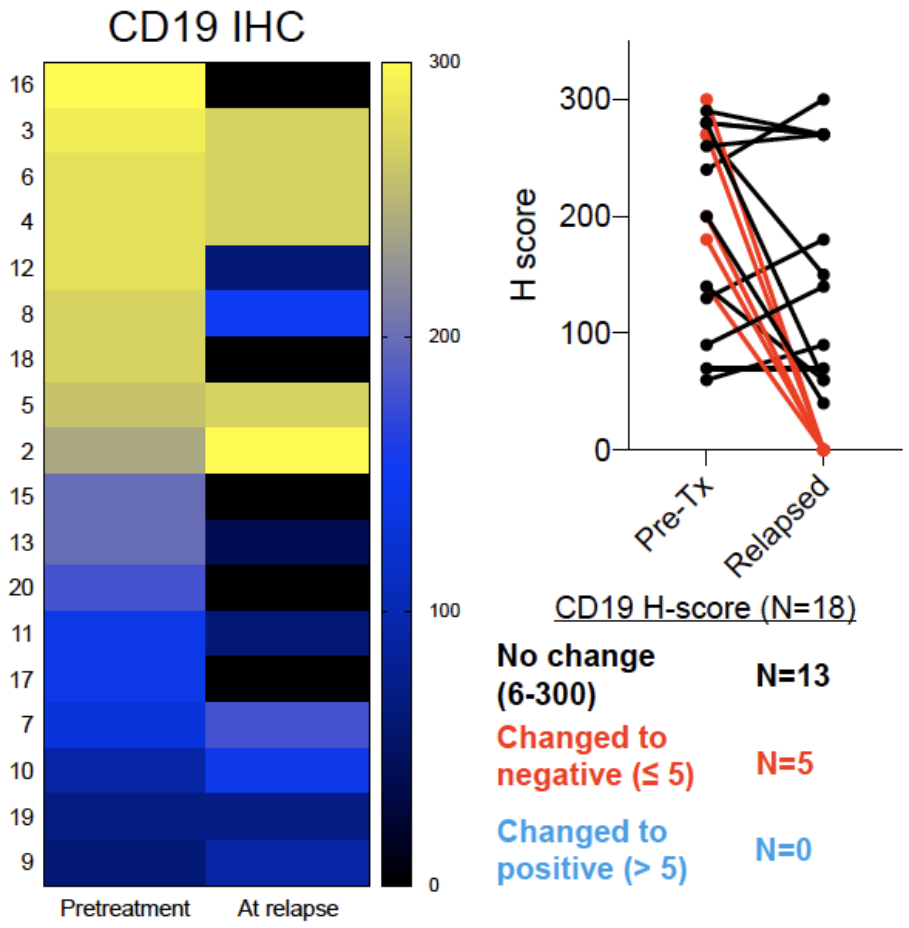
Deng, Han, et al. *Nat Med* 2020

ZUMA-1: CAR T-cell fitness by prior lines of therapy

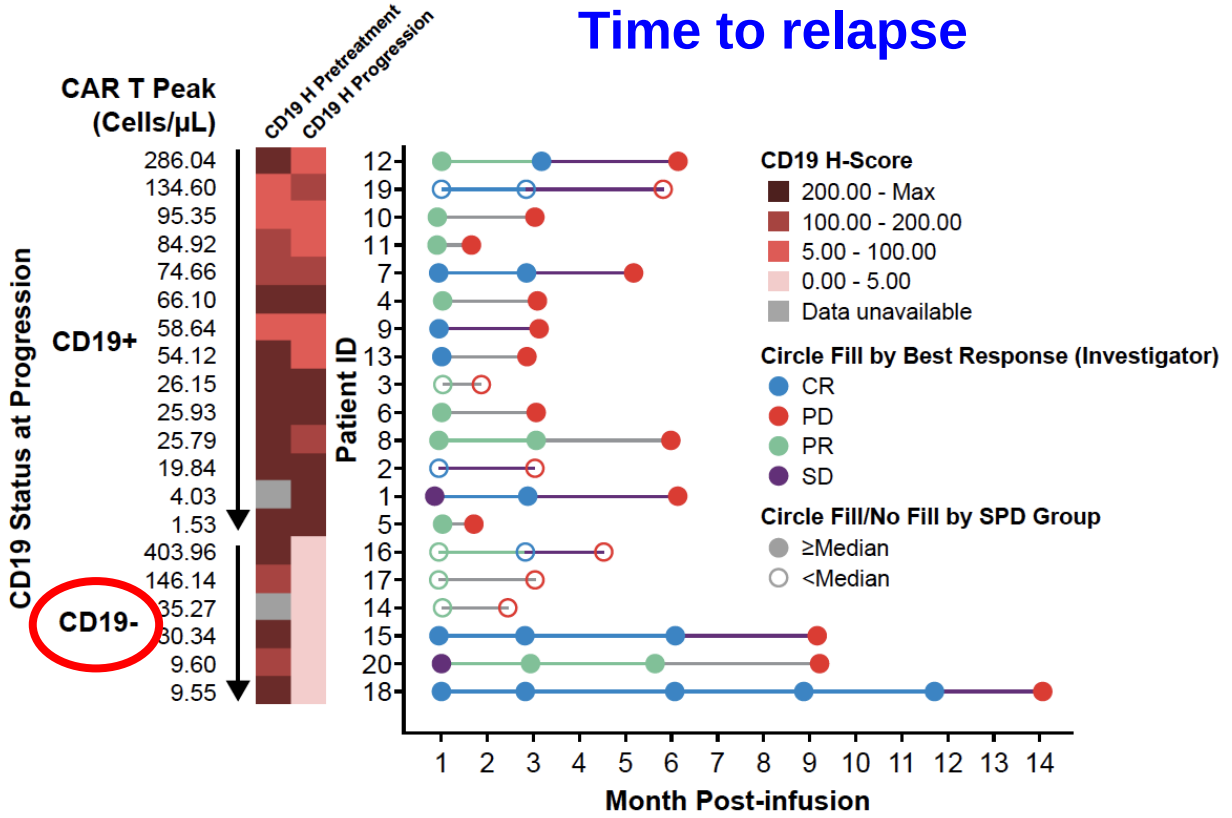
# Prior Lines	Quartile (# Subjects)	Doubling Time	Median CAR $AUC_{D_y0\text{-}28}$	%ORR (n, %)	%Ongoing @12Mth (n, %)
Healthy Donor	n=152	1.34	-	-	
≤2 Lines	Q1 (n=31)	1.42	469.3	28 (90%)	12 (39%)
3 Lines	Q2 (n=29)	1.51	476.6	28 (97%)	10 (34%)
4 Lines	Q3(n=28)	1.7	491.4	23 (82%)	13 (46%)
≥5 Lines	Q4 (n=12)	1.68	211.0	5 (42%)	3 (25%)

- Early referral may improve the efficacy of CAR T-cell therapy

CD19 loss after axi-cel in r/r LBCL



Time to relapse



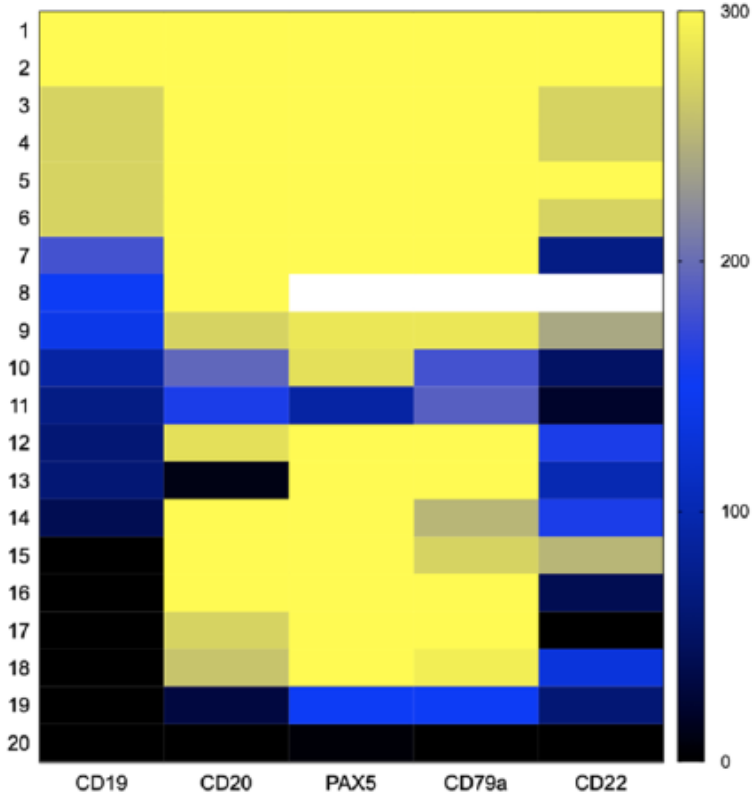
- All 3 relapses beyond 6 months were CD19 negative

- Likely cause of CD19 loss is due to genomic aberrations

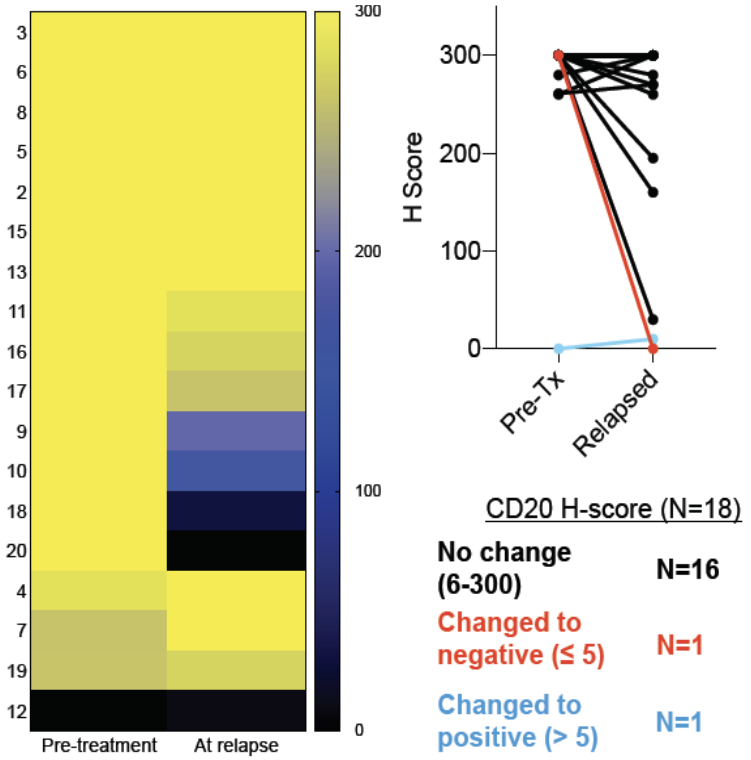
Plaks et al. *Blood*, 2021

Other B-cell antigens are preserved after CD19 loss

Relapsed LBCL tumors after axi-cel



CD20 in paired LBCL tumors



- Provides a rationale for multiantigen targeting to minimize antigen escape and improve efficacy

Plaks et al. *Blood*, 2021

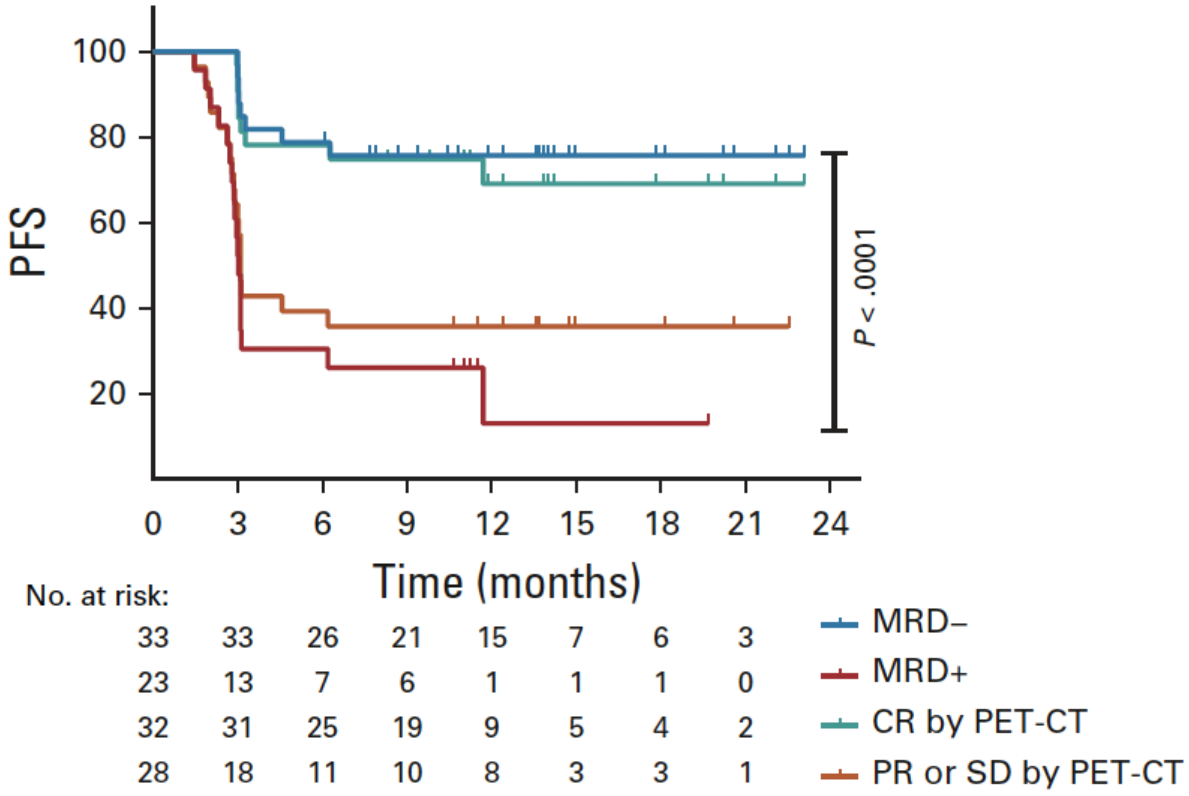
Tumor intrinsic mechanisms associated with CD19 CAR T-cell resistance in LBCL

Resistance mechanism	Comment	Reference(s)
CD19 loss	30-40% of DLBCL, tFL, and PMBCL after axi-cel	Plaks et al. *Blood* 2021 Spiegel et al. *Blood* 2021 Spiegel et al. *Nat Med* 2021
CD58 alteration	Required for CD2 co-stimulation in CAR T cells	Majzner, et al. *ASH 2020, Abstract 556* Romain et al, *J Clin Invest* 2022
***TP53* genomic alterations**	Associated with dysregulation of IFN and death receptor signaling pathways and reduced CD8 T-cell infiltration	Shouval et al. *J Clin Oncol* 2021
DNA copy number alterations	Deletion 10q23.3 leading to loss of FAS death receptor was most highly associated with poor PFS and OS	Cherng et al. *Blood* 2022
Complex genomic features	Complex structural variants, APOBEC mutational signatures, genomic damage from ROS, deletion 3p21.31 containing *RHOA* tumor suppressor	Jain et al. *Blood* 2022

MRD negativity at day 28 strongly associated with durability in LBCL after axi-cel

N = 72; Tumor clonotype detected in 96% of patients

PFS by Day 28 MRD or Day 28 PET



Frank et al, *J Clin Oncol* 2021

Summary

- Long-term safety and efficacy established with axi-cel after 5 years of follow-up on ZUMA-1 in ≥3rd-line LBCL
  - OS of 43% for all patients at 5 years
  - OS of 64% for CR patients at 5 years
  - No new safety signals since the 2-year f/u
- Durable responses at 5 years were strongly associated with peak CAR T-cell expansion, which is associated with tumor burden and T-cell fitness in apheresis material
- 100% of evaluable patients with ongoing remission at 3 yrs had B-cell recovery with 91% being polyclonal
- 30% of tumors at progression have CD19 loss but expression of other B-cell antigens is preserved supporting multi-antigen targeting to enhance efficacy

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