MD Anderson Cancer Center

It is time for definitive assessments: How many DLBCL and FL can we cure with CAR T cells?

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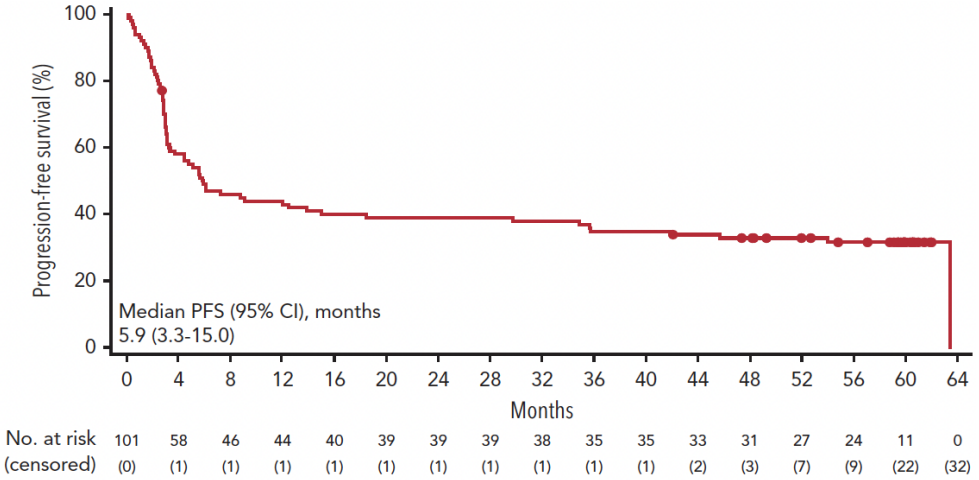
Disclosures

Disclosure	Company name
Research Support	Kite/Gilead, Allogene, Precision Biosciences, Adicet Bio, Sana Biotechnology, Cargo Therapeutics
Advisory Board / Consultant	Kite/Gilead, Sellas Life Sciences, Allogene, Adicet Bio, BMS, Fosun Kite, Caribou, Astellas Pharma, Morphosys, Janssen, Chimagen, ImmunoACT, Takeda, Synthekine, Carsgen, Appia Bio, GlaxoSmithKline, Galapagos, ModeX Therapeutics, Jazz Pharmaceuticals, ADC Therapeutics, BioOra Limited, Arovella Therapeutics, Merck, Pfizer, Poseida
Honoraria	MJH Life Sciences, PeerView, MD Education
Speaker's Bureau	None
Employment	None
Royalties	None
Stocks / Stock Options	None
Patents	Related to cell therapy

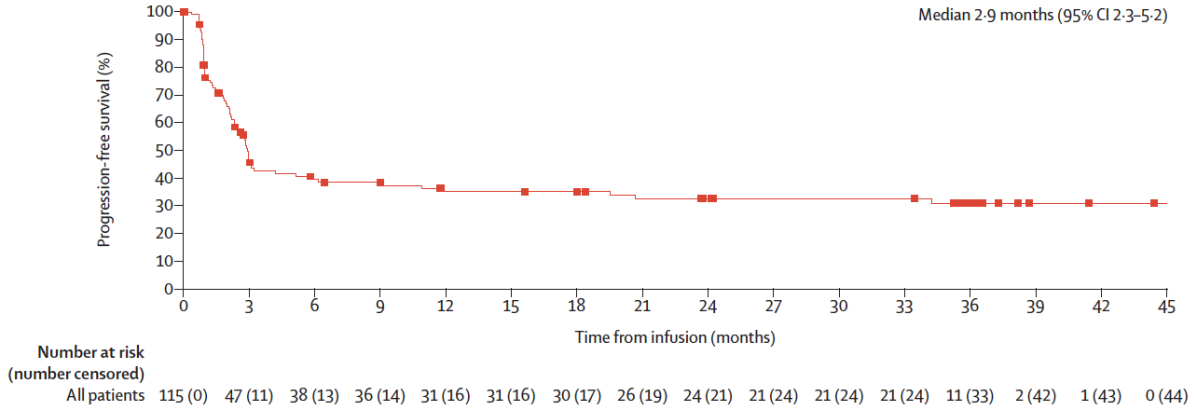
- I will discuss investigational use of CAR T-cell therapy

CD19 CAR T cell therapy in ≥3rd line LBCL

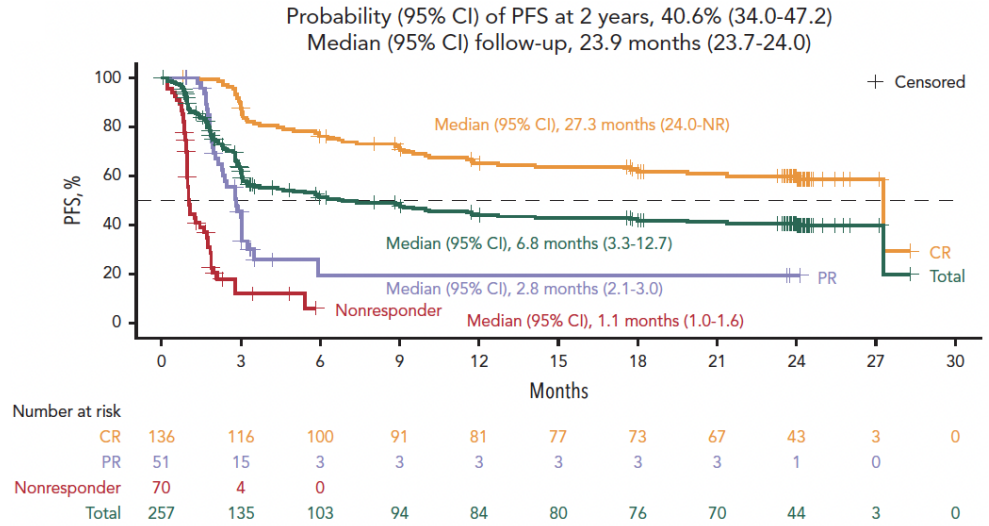
ZUMA-1
Axi-cel



JULIET
Tisa-cel



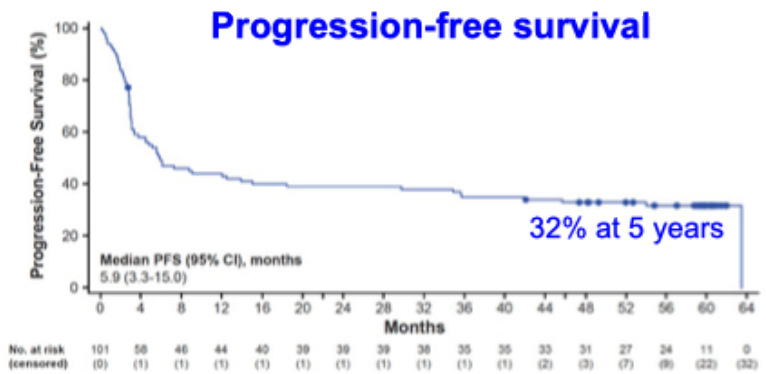
TRANSCEND
Liso-cel

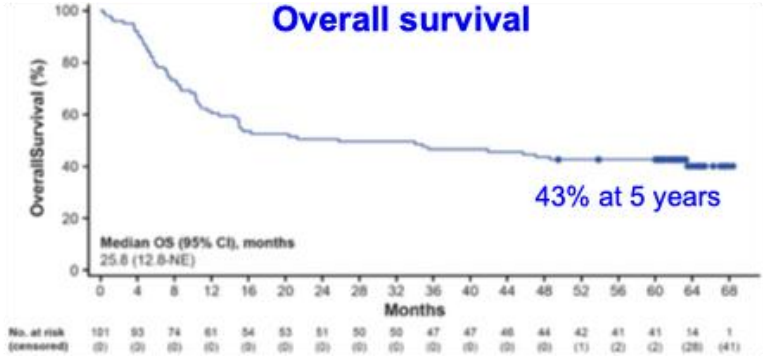


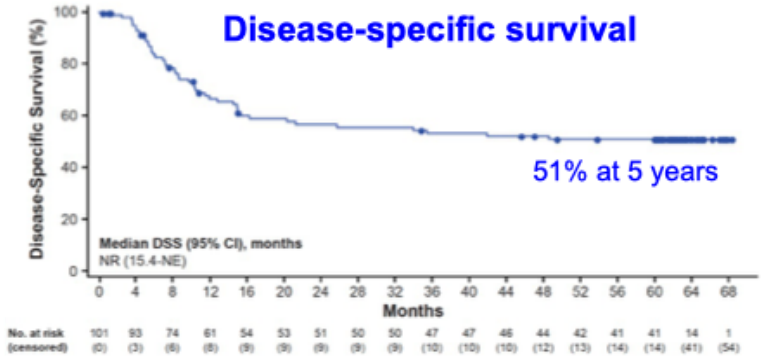
Neelapu SS et al. *Blood* 2023; 141(19):2307-2315
Schuster SJ et al. *Lancet Oncol* 2021; 22(10):1403-1415
Abramson JS et al. *Blood* 2024; 143(5):404-416

Axi-cel in ≥3rd line LBCL

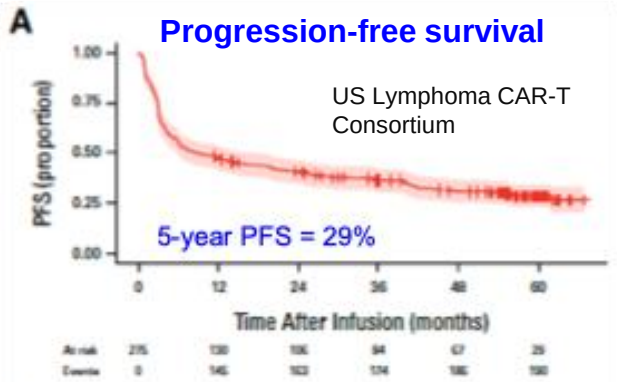
ZUMA-1@5 years

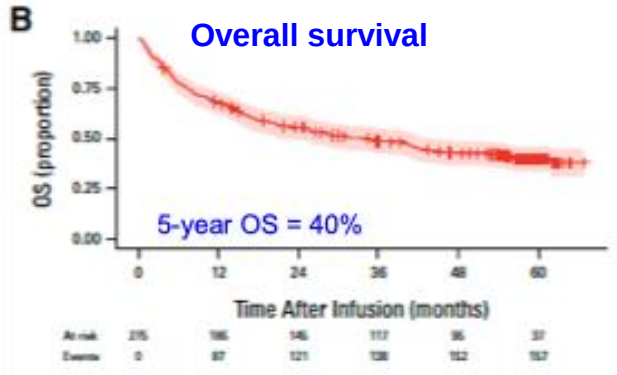


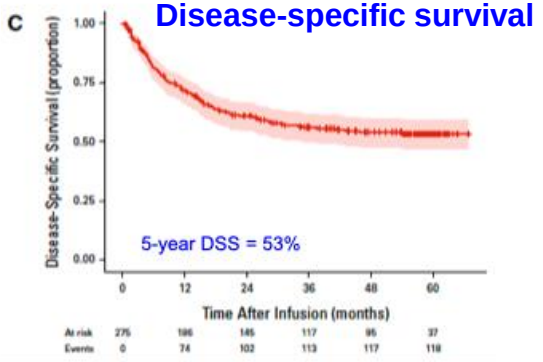




Real-world study @5 years







Neelapu et al. *Blood,* 2023 May 11;141(19):2307-2315;
Jain MD et al, *J Clin Oncol* 2024 Oct 20;42(30):3581-3592

Causes of death on ZUMA-1

n (%)	N = 101						
	Total	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* 78%	45 (45)	32 (32)	9 (9)	3 (3)	0	1 (1)	0
AE† 7%	4 (4)	3 (3)	1 (1)	0	0	0	0
Secondary malignancy 2%	1 (1)	0	0	0	0	0	1 (1)
Other‡ 16%	9 (9)	5 (5)	0	1 (1)	3 (3)	0	0

MDS, myelodysplastic syndrome.

*After year 2, 4 patients with DLBCL who had a best response of a CR later had progressive disease on days 99, 184, 266, and 546 after infusion, respectively. During ongoing safety monitoring after the data cutoff, 1 event of central nervous system lesion, which was not amenable to biopsy, was reported. Treatment for presumed progressive disease for DLBCL was initiated by the investigator.

†Two events had no causal relationship (sepsis and pulmonary embolism), and 2 events were related to axi-cel (brain injury due to cardiac arrest, and hemophagocytic lymphohistiocytosis).

‡Events included infection (n = 3), cardiac arrest (n = 2), pulmonary nocardiosis (n = 1), sepsis (n = 1), complications of allogeneic transplantation for previous treatment–related MDS not related to axi-cel (n = 1), and unknown (n = 1).

Neelapu et al. *Blood*, 2023 May 11;141(19):2307-2315

Causes of death: Real-world US Lymphoma CAR T Consortium

TABLE 2. Causes of Death by Year After Axi-Cel Infusion

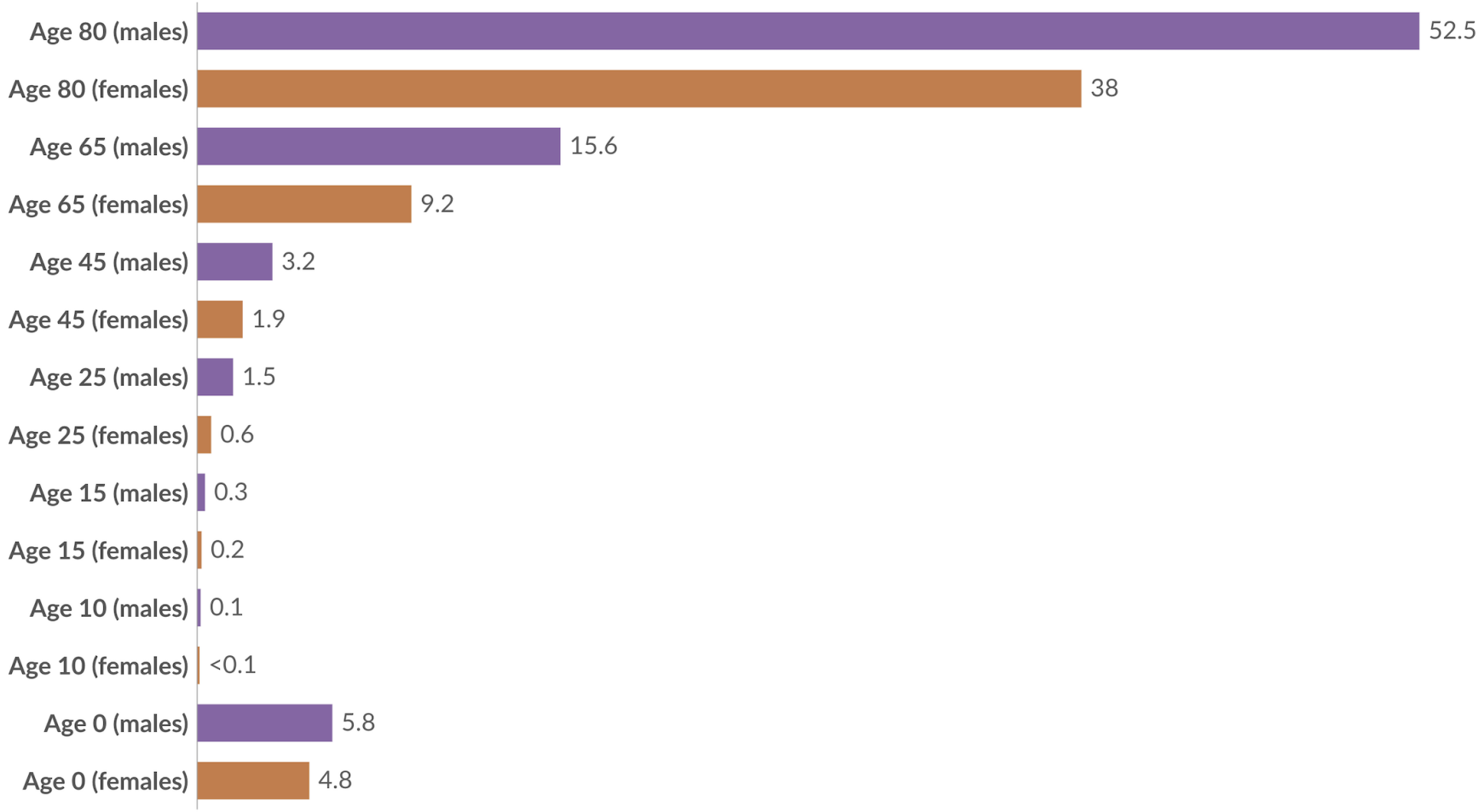
Cause of Death		Year 1	Year 2	Year 3	Year 4	Year 5	Year 6 or Later	Total
Progressive disease	63%	74	28	11	4	1	0	118
Infection	18%	8	2	4	6	1	0	21
Secondary malignancy	8%	0	3	1	3	1	1	9
CAR-T toxicity[a]	3%	3	0	0	0	0	0	3
Unknown/Other[b]	6%	2	1	1	1	2	0	7

NOTE. Infectious causes of death (n = 21) included unclassified infection (n = 6), pneumonia (n = 5), bacterial sepsis (n = 4), COVID-19 disease (n = 2), candidemia (n = 2), candidemia and concomitant pneumocystis jiroveci pneumonia (n = 1), and JC viral encephalitis (n = 1).
Abbreviations: axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; HLH, hemophagocytic lymphohistiocytosis.
[a]Includes HLH, cerebral edema, and intracranial hemorrhage.
[b]Unknown = 6, suicide = 1.

Jain MD et al, *J Clin Oncol* 2024 Oct 20;42(30):3581-3592

Annual death rates by ages, by sex, United States,2023

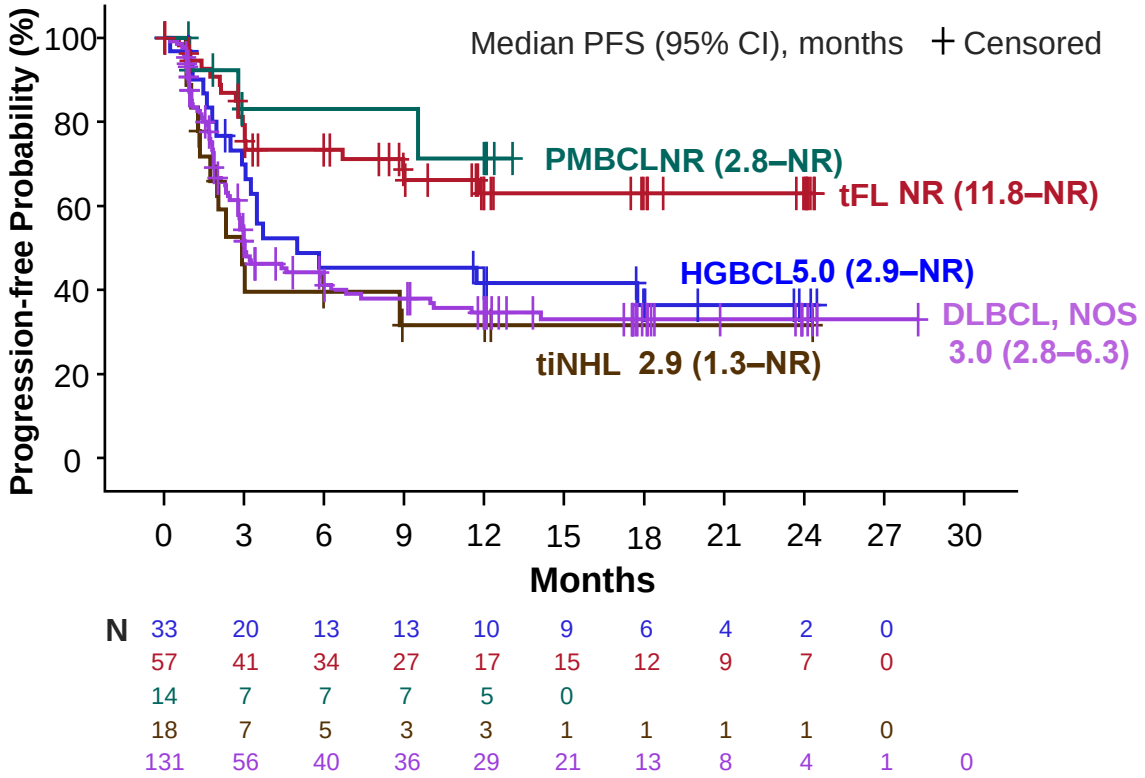
The annual death rate, per 1,000 people of a given age and sex.



Data source: Human Mortality Database (2024); UN, World Population Prospects (2024)

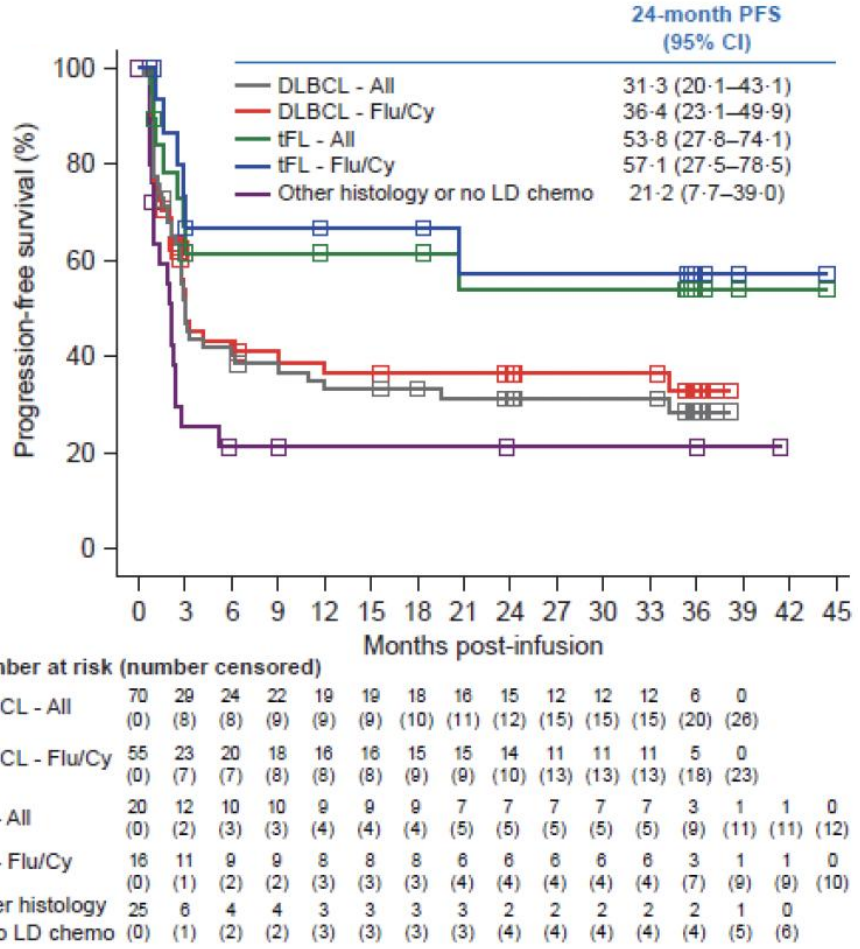
PFS by lymphoma subtype in LBCL

TRANSCEND



Abramson et al. ASH 2019, Abstract 241
Abramson et al, Lancet 2020

JULIET

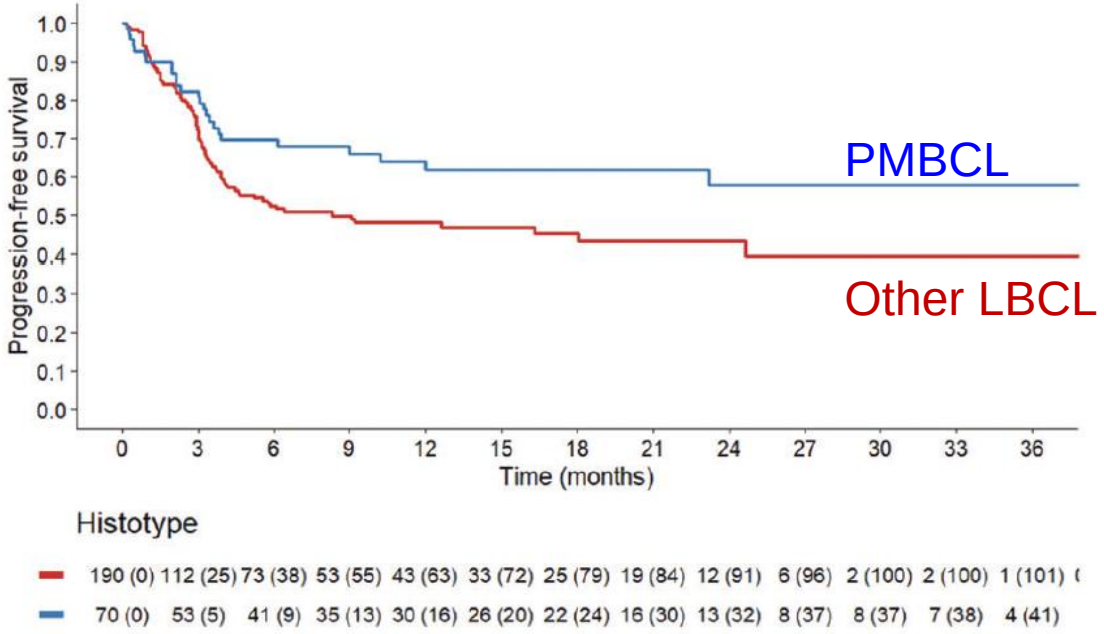


Schuster SJ et al, *Lancet Oncol* 2021 Oct;22(10):1403-1415

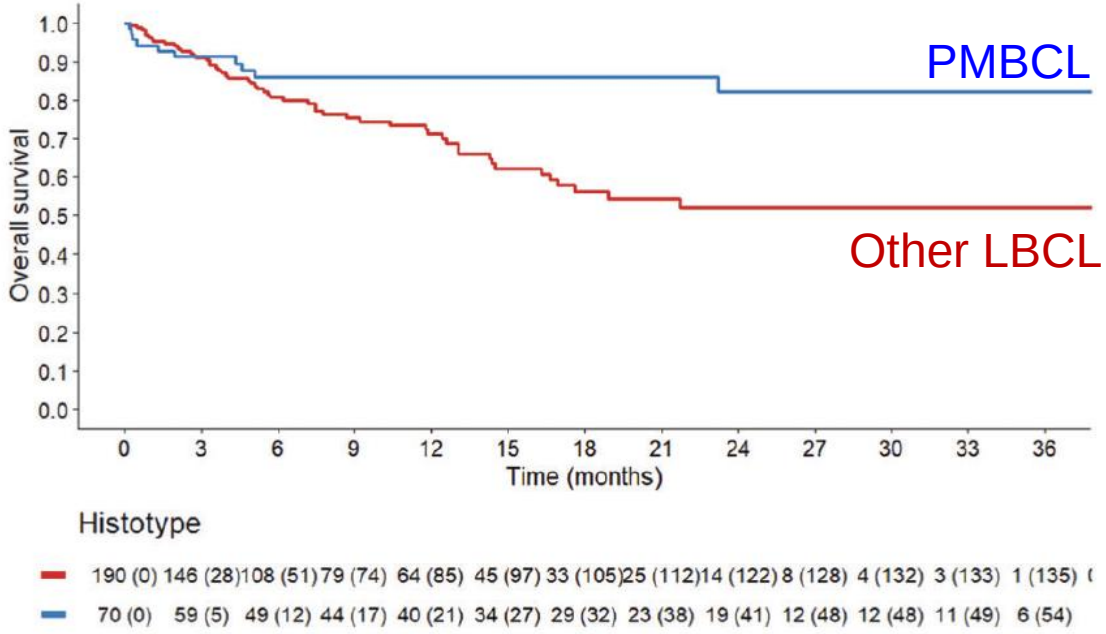
PMBCL has improved outcome with axi-cel than other LBCLs

Italian CART-SIE Study

PFS



OS



Chiappella A et al. *Leukemia* 2024 May;38(5):1107-1114

Poor outcome after CD19 CAR-T in T-cell-rich LBCL

Primary resistance to CD19-directed chimeric antigen receptor T-cell therapy in T-cell/histiocyte-rich large B-cell lymphoma

Jonathan A. Trujillo,[1,*] James Godfrey,[1,2,*] Yifei Hu,[3,4] Jun Huang,[4] Sonali M. Smith,[1] Matthew J. Frigault,[5,6] Zachariah DeFilipp,[5,7] Daniel Appelbaum,[8] Yonglin Pu,[8] Nicholas Feinberg,[8] Thomas Althaus,[1,9] Michael R. Bishop,[1,9] Peter A. Riedell,[1,9] and Justin Kline[1,9]

Blood **(2021) 137 (24): 3454–3459**

- All 9 patients treated with either axi-cel or tisa-cel had progressive disease
- Tumor cells positive for CD19 at baseline and progression
- *PD-L1* genetic alterations common in tumor cells
- PD-L1 expression high in TAMs
- PD-1 expression high on T cells in TME
- PD-1 upregulation in peripheral blood CAR T cells

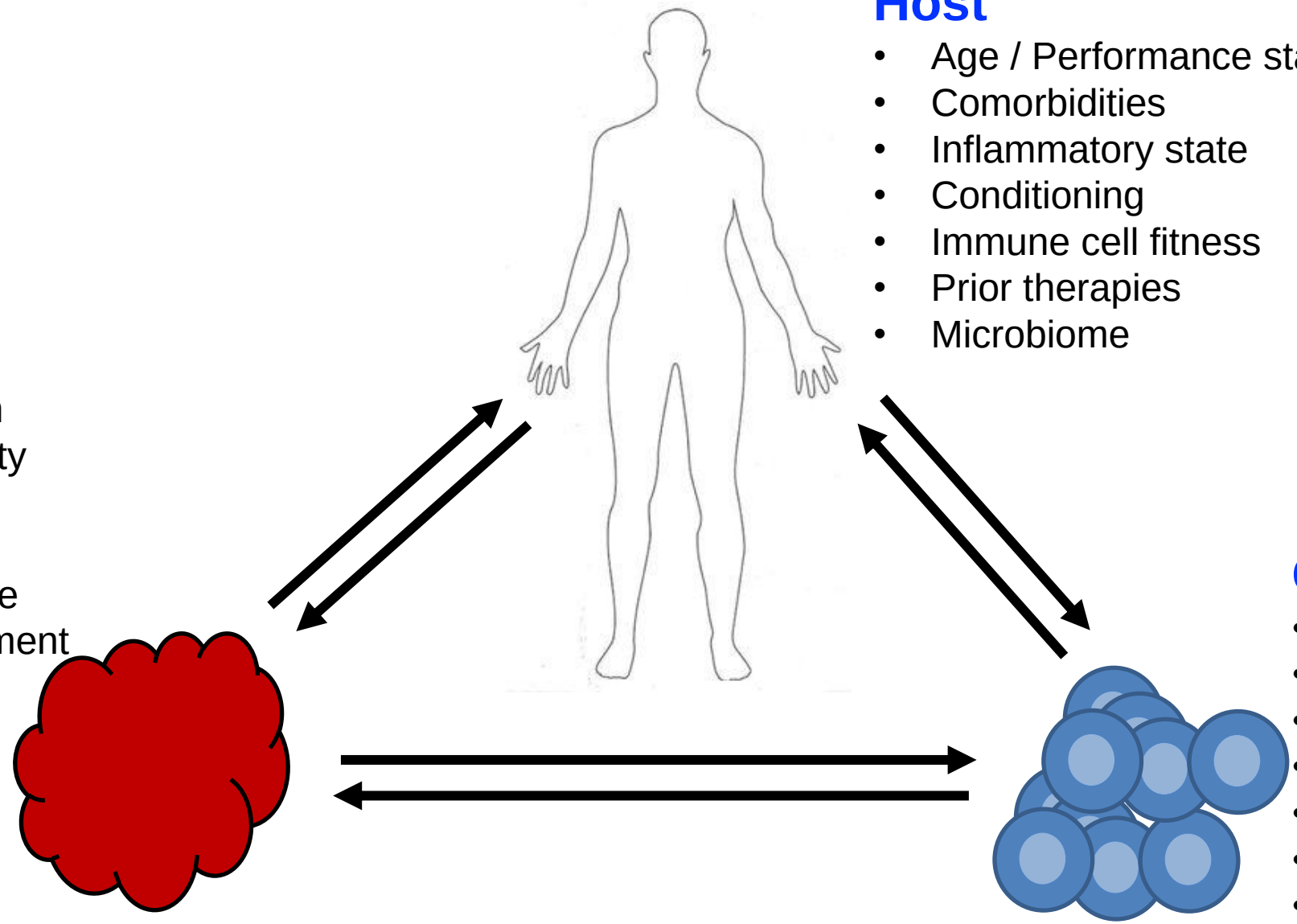
Factors impacting CAR T efficacy

Host

- Age / Performance status
- Comorbidities
- Inflammatory state
- Conditioning
- Immune cell fitness
- Prior therapies
- Microbiome

Tumor

- Tumor burden
- Antigen density
- Antigen loss
- CD58 loss
- Tumor subtype
- Microenvironment

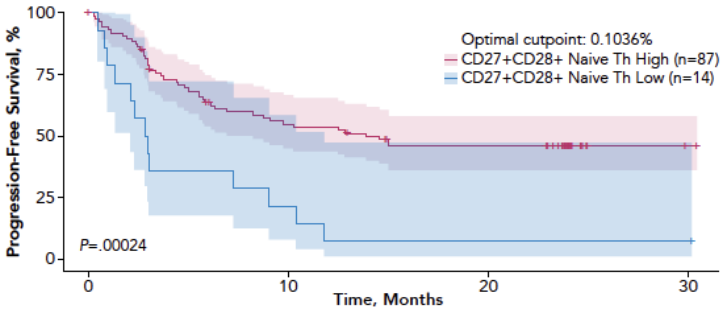


CAR-T

- Dose
- Binder – scFv
- Signaling domains
- Hinge/TM
- Phenotype
- Polyfunctionality
- Composition

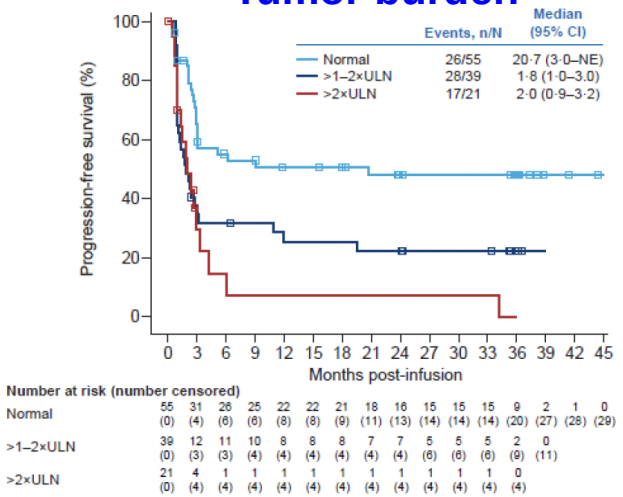
Other factors impacting CAR-T efficacy

Naïve T cell in apheresis



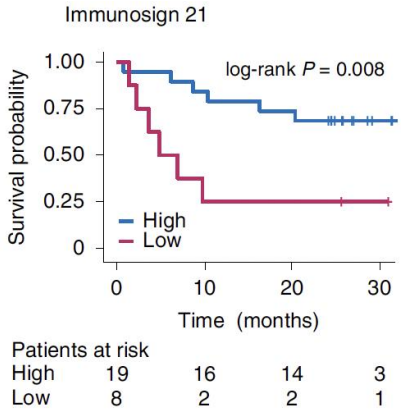
Budka et al, *AACR* 2021, Abstract #CT166

Tumor burden



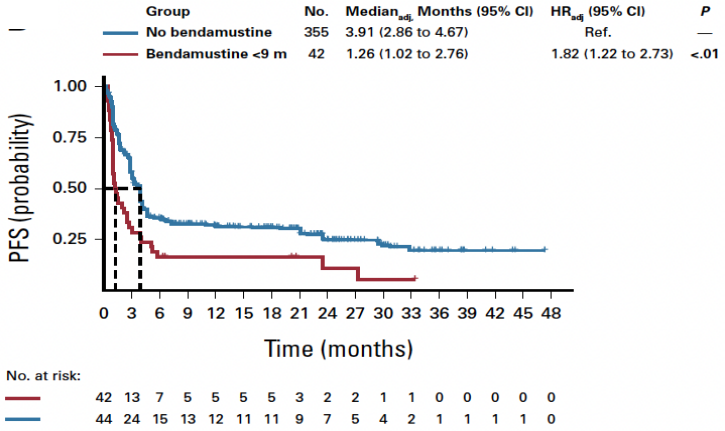
Schuster SJ et al, *Lancet Oncol* 2021 Oct;22(10):1403-1415

Favorable TME



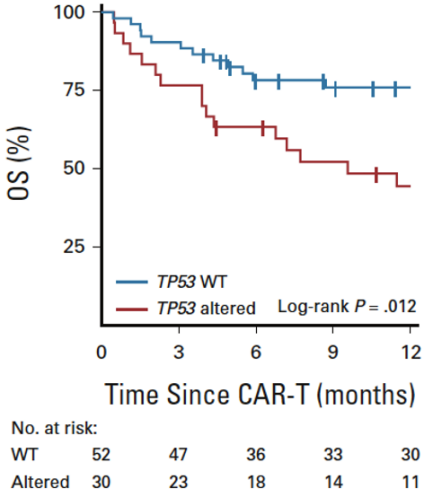
Scholler et al. *Nat Med* 2022 Sep;28(9):1872-1882

Prior bendamustine



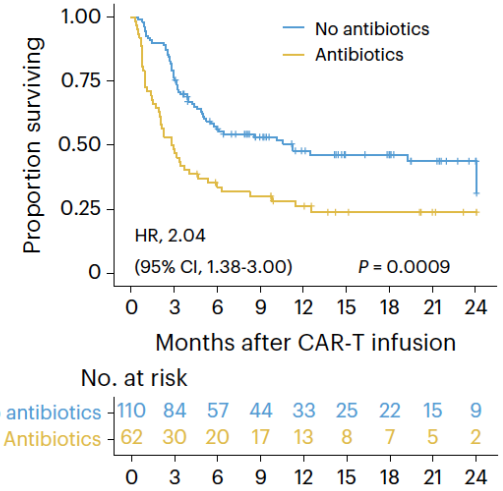
Iacoboni G et al. *J Clin Oncol* 2024;42(2):205-217

TP53 altered



Shouval et al. *J Clin Oncol* 2022 Feb 1;40(4):369-381

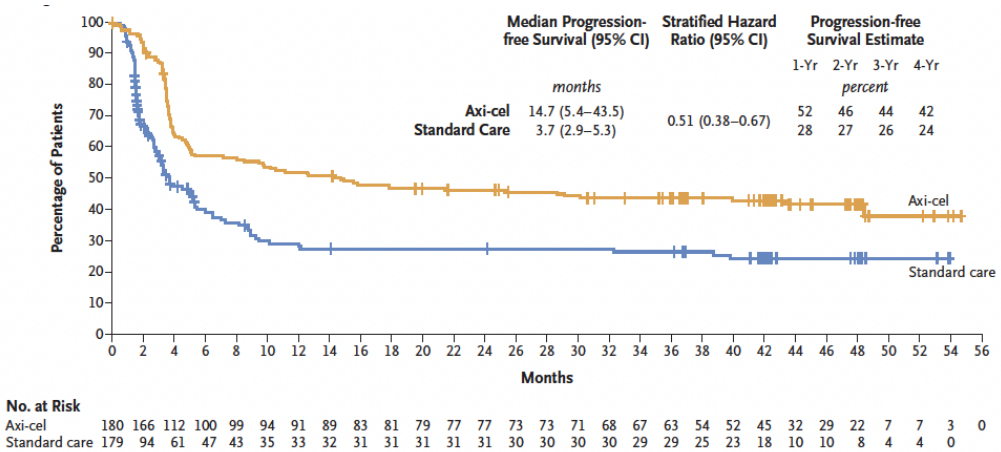
Antibiotic exposure



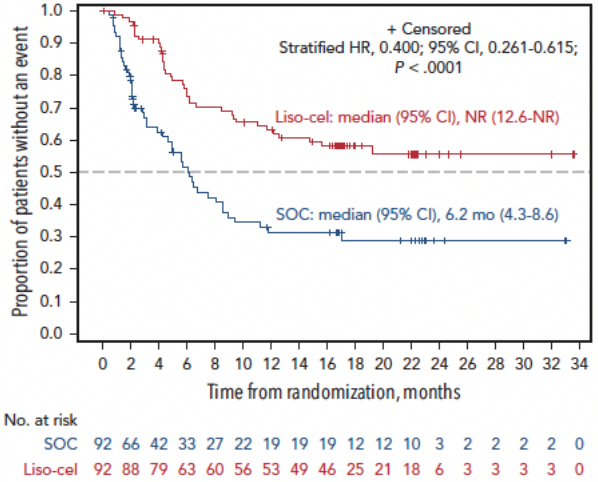
Stein-Thoeringer CK et al. *Nat Med* 2023 Apr;29(4):906-916

CD19 CAR T vs. SOC in 2nd line LBCL: PFS and OS

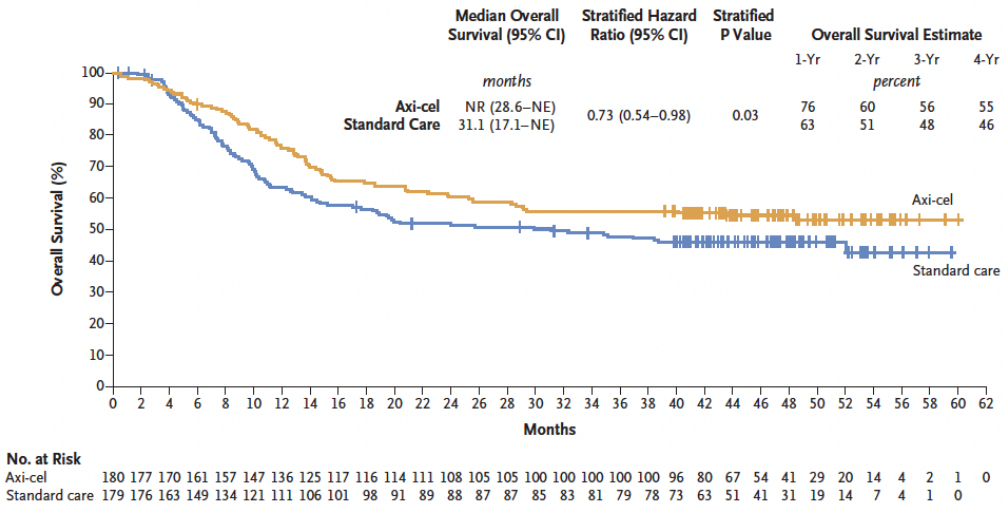
ZUMA-7 / PFS



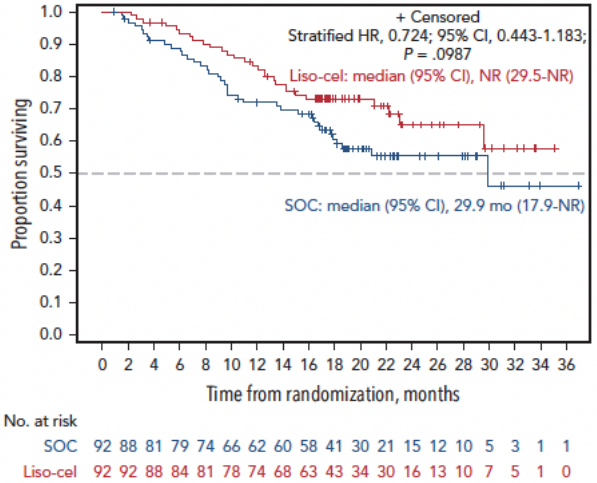
TRANSFORM / PFS



ZUMA-7 / OS



TRANSFORM / OS

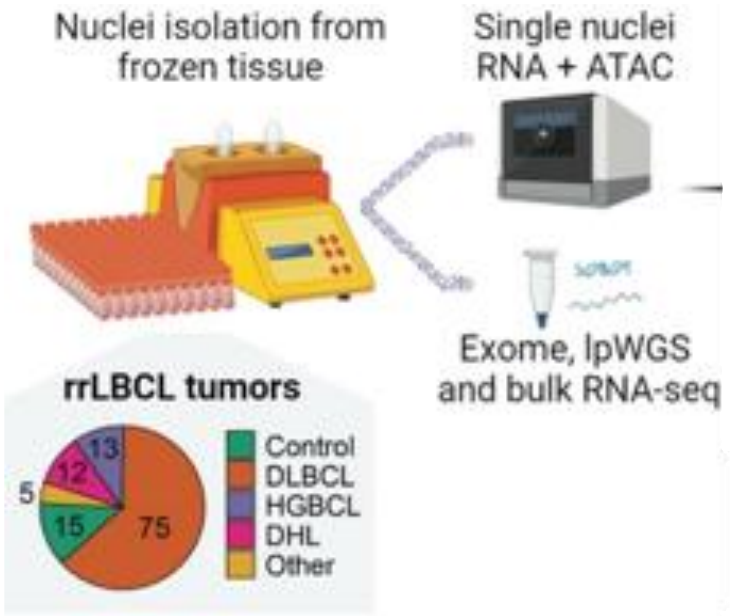


Westin JR et al. *N Eng J Med* 2023; 389(2):148-157

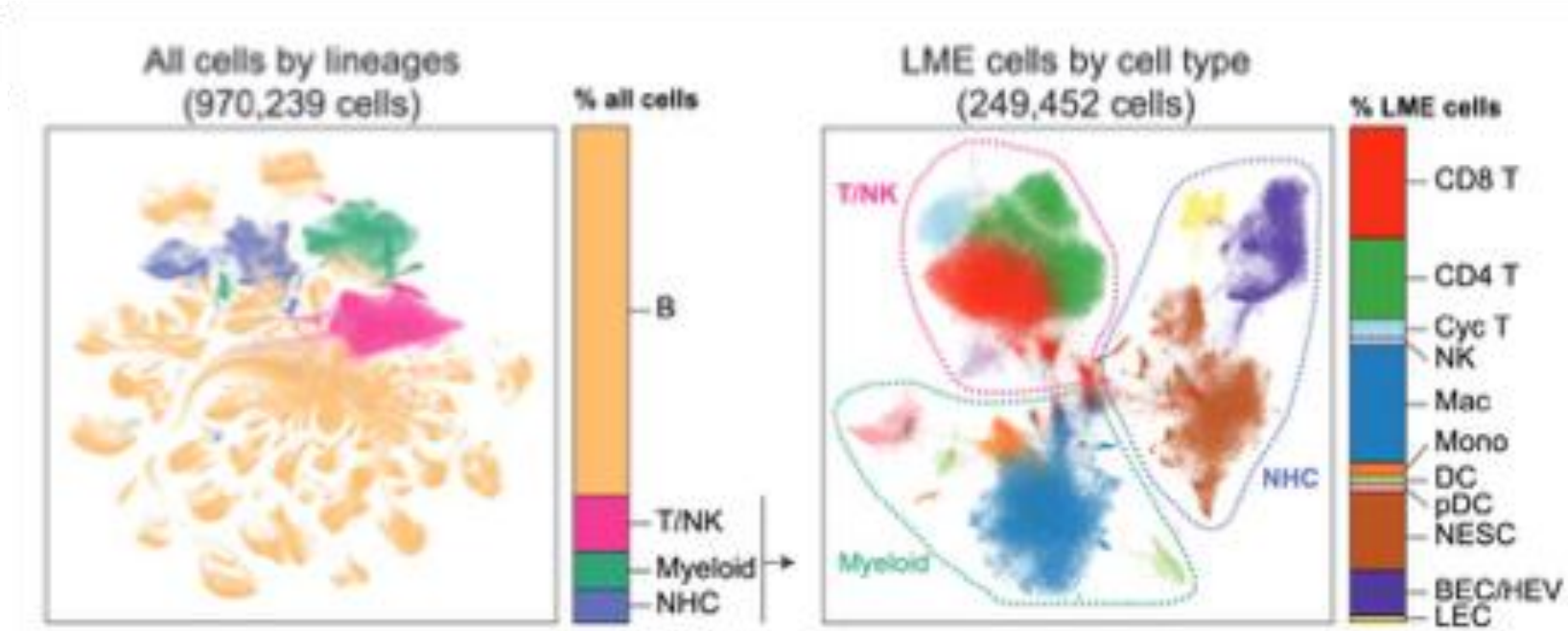
Abramson JS et al. *Blood* 2023; 141(14):1675-1684

Single cell atlas of r/r LBCL

Single nucleus multiome



N = 105 LBCL
N = 15 controls

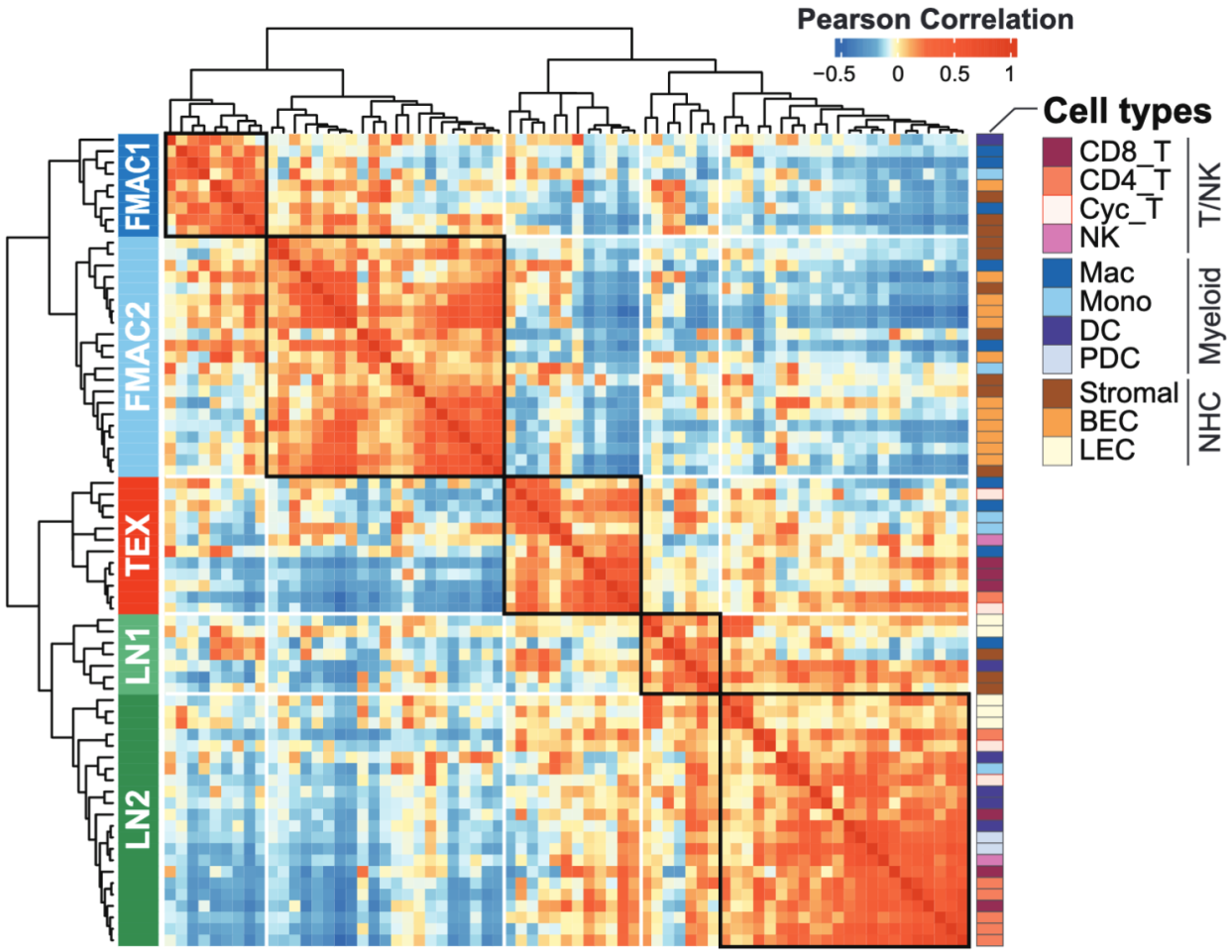


LME – Lymphoma microenvironment
NHC – Non-hematopoietic cells
Cyc T – Cycling T cells
NESC – Non-endothelial stromal cells
BEC – Brain endothelial cells
HEV – High endothelial venules
LEC – Lymphatic endothelial cells

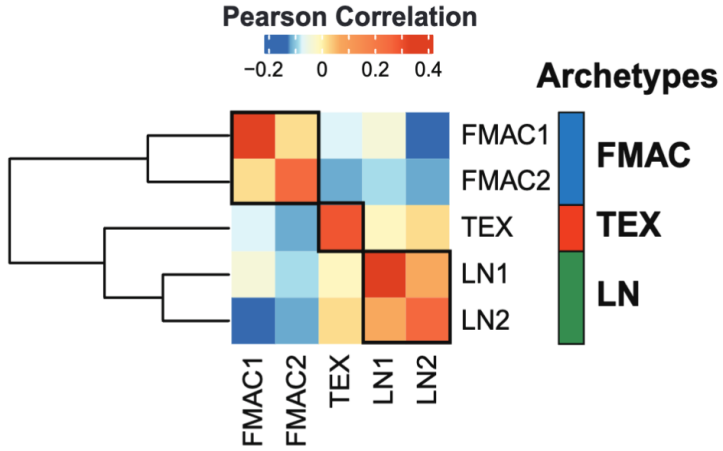
76 cell states

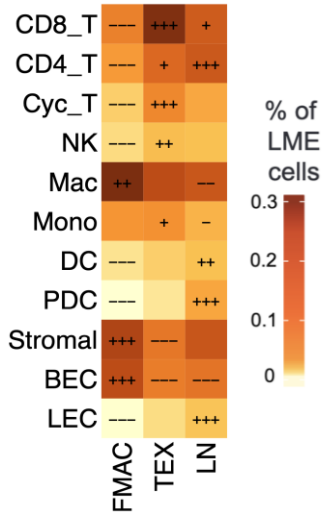
Li et al Green, *ASH* 2024, Abstract 643

Lymphoma Microenvironment Archetype Profiles (LymphoMAPs)



Non-negative matrix factorization of non-B cells

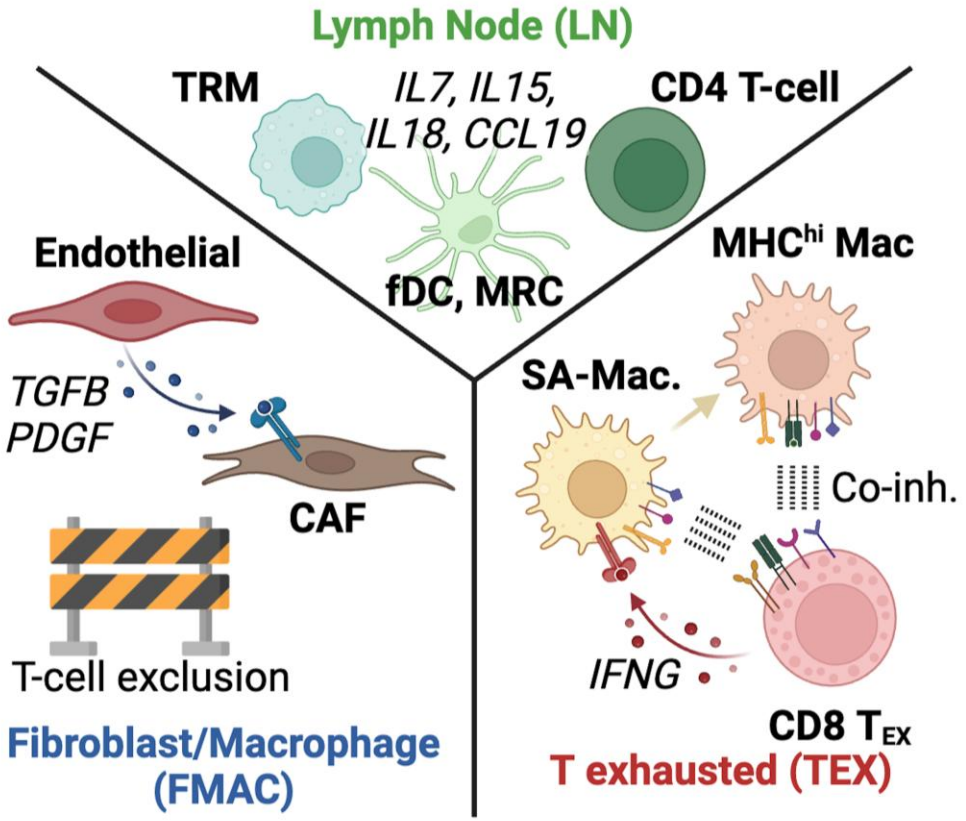




Li et al Green, *ASH* 2024, Abstract 643

LymphoMAPs: divergent microenvironments

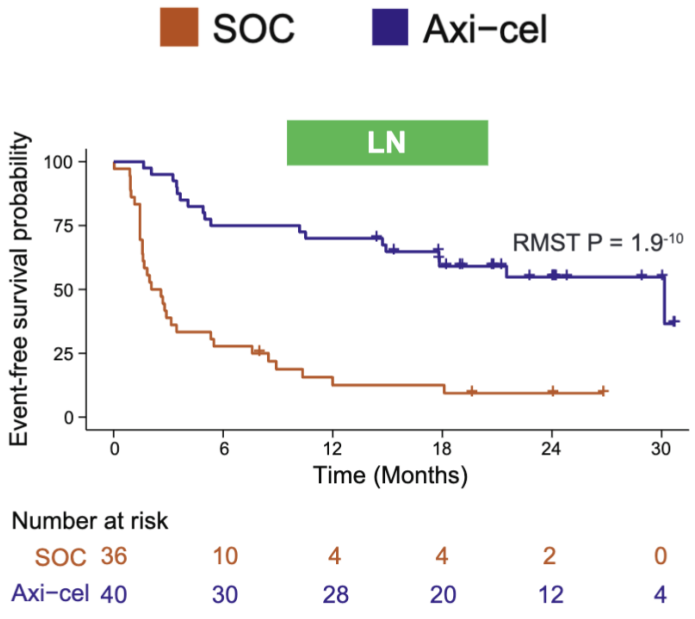
Cell-cell communication analysis revealed significant differences in predicted ligand-receptor pair interactions between archetypes

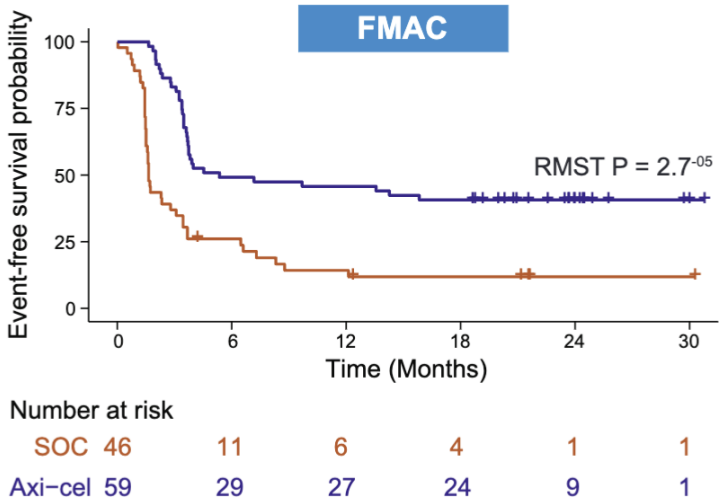


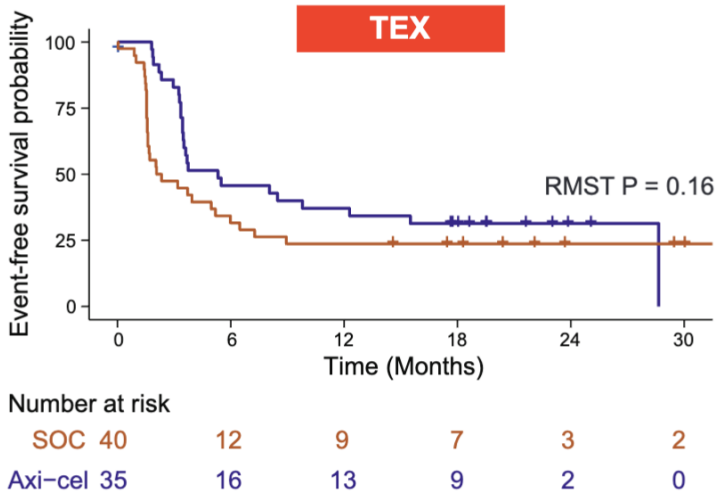
PD1
CTLA4
TIM3

Li et al Green, *ASH* 2024, Abstract 643

LN: greatest benefit, TEX: minimal benefit (ZUMA-7)







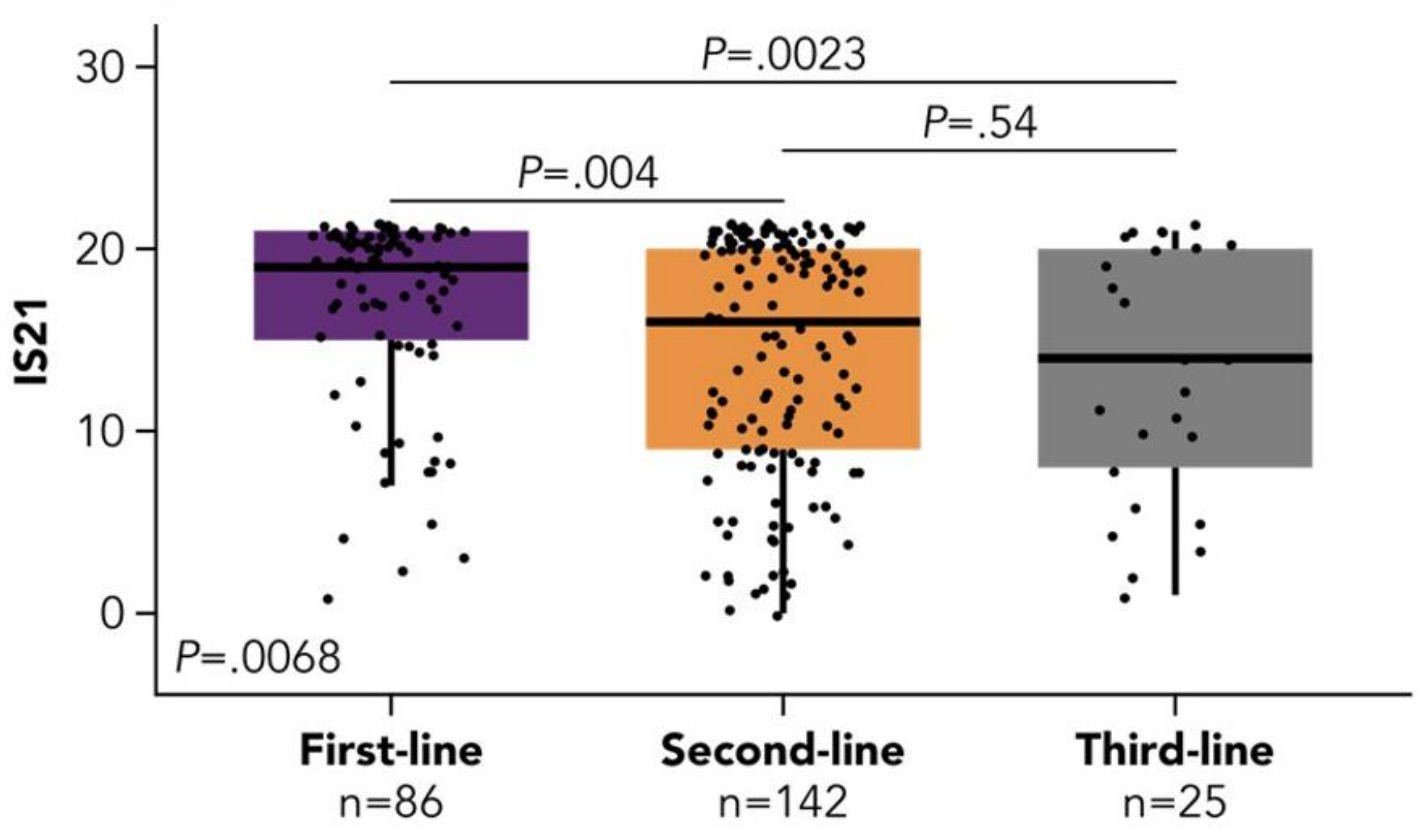
LN
- LN structural cells
- Supportive cytokines

FMAC
- CAFs and BECs
- Absence of supportive cytokines

TEX
- Co-inhibitory receptor signals
- Absence of supportive cytokines

Li et al Green, *ASH* 2024, Abstract 643

TME more favorable in first line in LBCL



Tumor samples

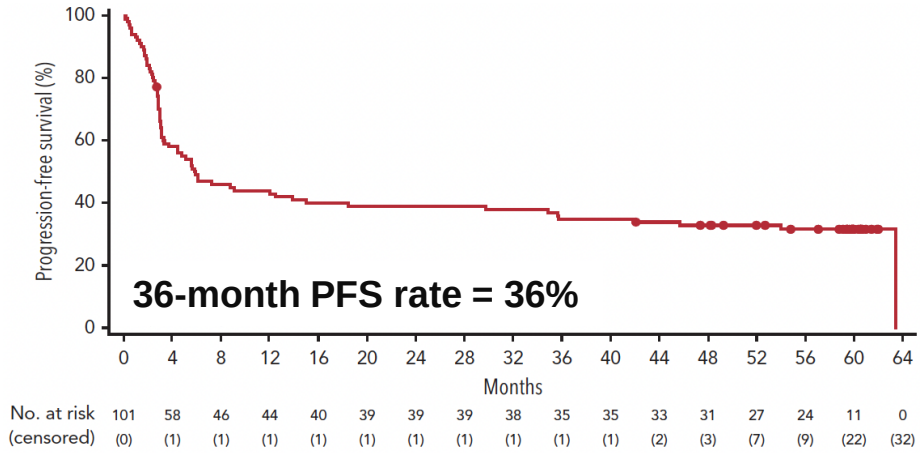
- 1st line: ZUMA-7 archival at Dx
- 2nd line: ZUMA-7 at study entry
- 3rd line: ZUMA-1

- Immunosign 21 (IS21): Prespecified immune contexture signature related to T-cell function and trafficking
- Assessed for gene expression by NanoString IO 360™ panel
- IS21 previously shown to associate with CR and PFS in ZUMA-1

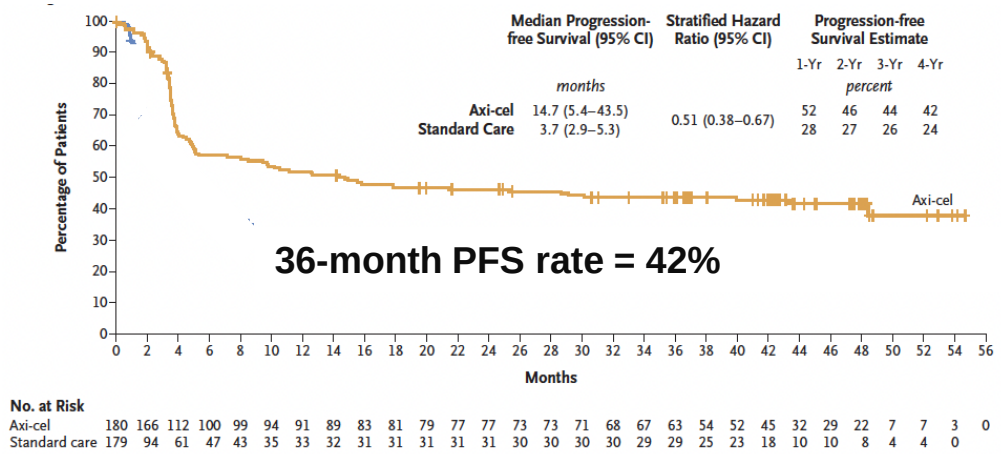
Locke et al, *Nat Med* 2024 Feb;30(2):507-518

Axi-cel in LBCL: 3rd line vs. 2nd line vs. 1st line

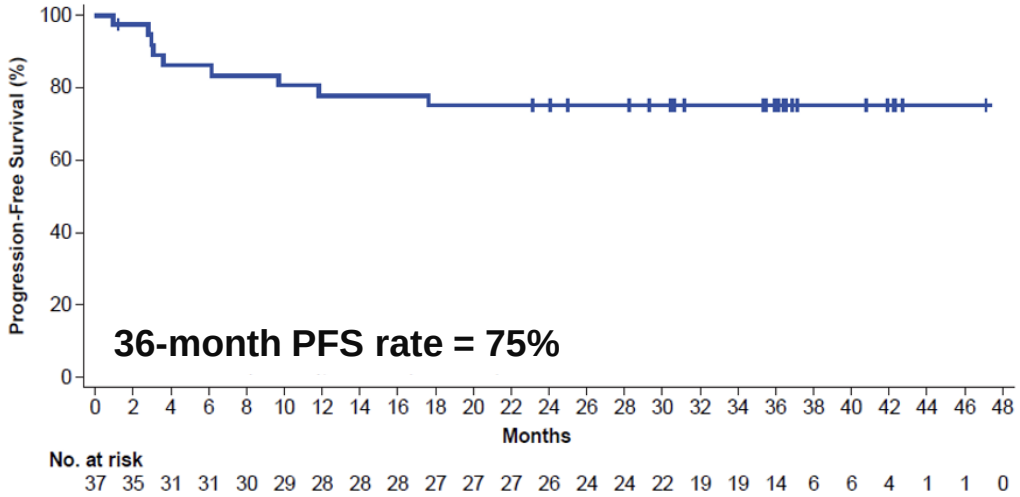
ZUMA-1: Axi-cel in ≥3rd line



ZUMA-7: Axi-cel in 2nd line



ZUMA-12: Axi-cel in 1st line



Neelapu et al, *Blood* 2023; 141(19):2307-2315
Westin JR et al. *N Eng J Med* 2023; 389(2):148-157
Neelapu et al, *Blood* 2025 Feb 12

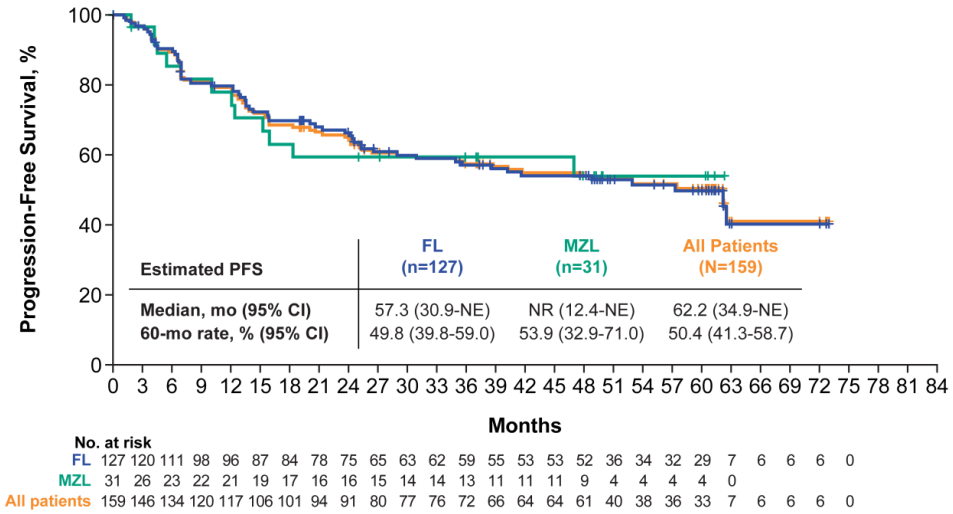
How many LBCL can we cure with CAR T cells?

It depends

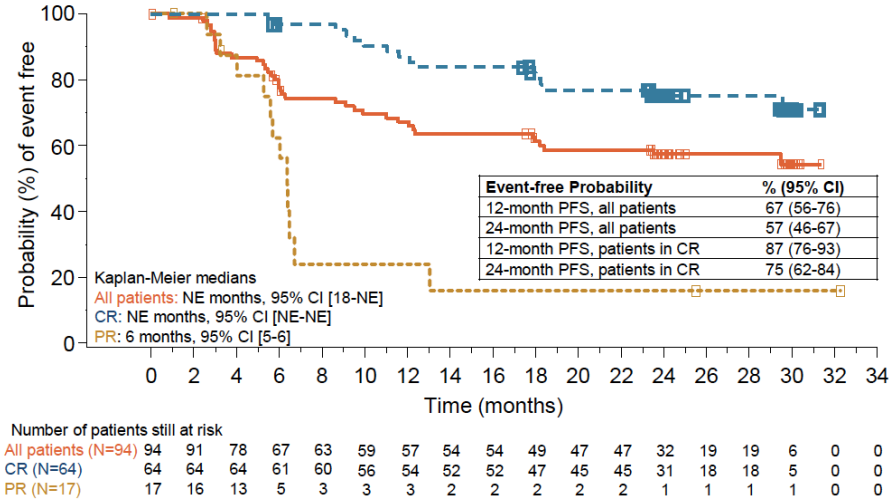
	Category	% Cured
3rd line	All LBCLs treated with CAR-T	~40%
	PMBCL and tFL	~60%
	DLBCL-NOS and HGBCL	~30%
	THRLBCL	0%
	2nd line LBCL	~40-50%
	1st line high-risk LBCL	~75%
	All 3rd line R/R LBCL (up to 40% treated with CAR-T)	~15%

PFS outcomes with CD19 CAR-T in R/R FL

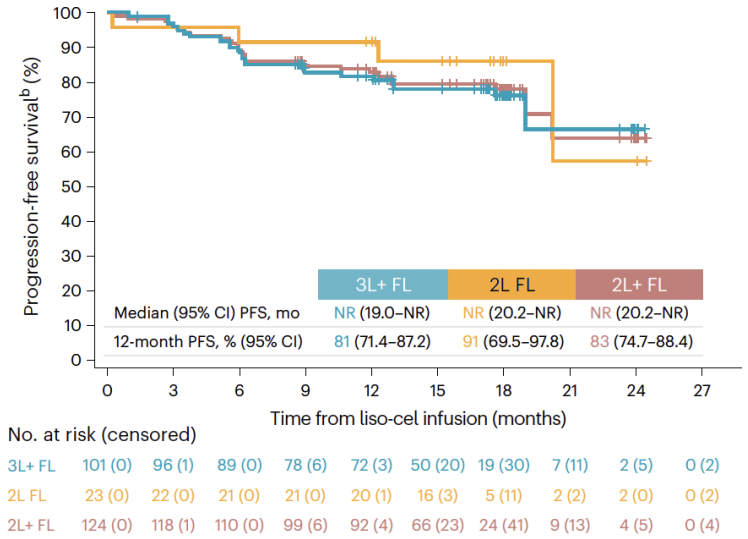
ZUMA-5 / PFS



ELARA / PFS

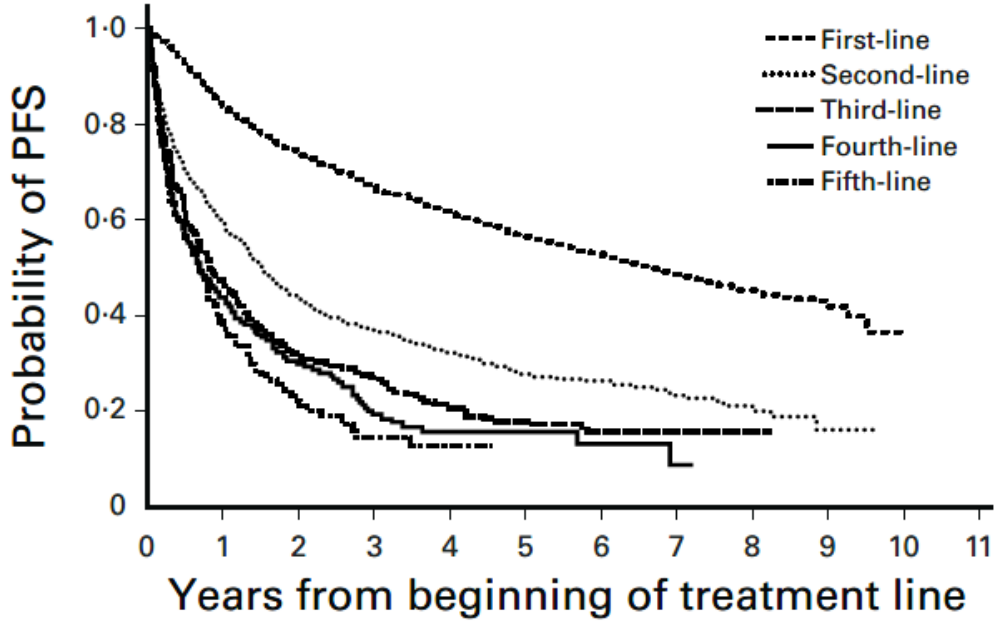


TRANSCEND FL / PFS



Neelapu et al. *ASH 2024*, Abstract 864
Dreyling M et al. *ASH 2022*, Abstract 608
Morschhauser F et al. *Nat Med* 2024 Aug;30(8):2199-2207

Historical outcomes in FL by line of therapy



No. at risk

First-line	2429	1916	1602	1381	1202	1035	869	635	329	96	1	0
Second-line	889	489	331	256	199	137	104	57	24	5	0	
Third-line	438	181	109	78	50	30	18	5	1	0		
Fourth-line	229	91	49	24	14	8	3	1	0			
Fifth-line	123	42	19	9	5	0						

Table I. Distribution of first-line to fifth-line treatment.

Treatment	Rx1 (n = 2429)	Rx2 (n = 889)	Rx3 (n = 438)	Rx4 (n = 229)	Rx5 (n = 121)
Rituximab	457 (19%)	279 (31%)	98 (22%)	35 (14%)	18 (15%)
R-chemo	1413 (58%)	345 (39%)	170 (39%)	79 (35%)	44 (36%)
Rituximab + anthracycline	828 (34%)	111 (12%)	51 (12%)	12 (5%)	8 (7%)
Rituximab + alkylator	424 (17%)	180 (20%)	89 (20%)	50 (22%)	25 (21%)
Rituximab + fludarabine	142 (6%)	43 (5%)	26 (6%)	11 (5%)	5 (4%)
Other R-chemo	19 (1%)	11 (1%)	4 (1%)	6 (3%)	6 (5%)
Chemotherapy	85 (3%)	77 (9%)	59 (13%)	37 (15%)	24 (20%)
BMT	6 (<1%)	17 (2%)	13 (3%)	17 (7%)	10 (8%)
Radiation (XRT)	261 (11%)	31 (7%)	31 (7%)	23 (10%)	15 (12%)
Radioimmunotherapy	10 (<1%)	45 (5%)	26 (6%)	11 (5%)	2 (2%)
Investigational	183 (8%)	45 (5%)	34 (8%)	21 (9%)	7 (6%)
Other therapies	14 (1%)	16 (2%)	7 (3%)	6 (5%)	1 (1%)

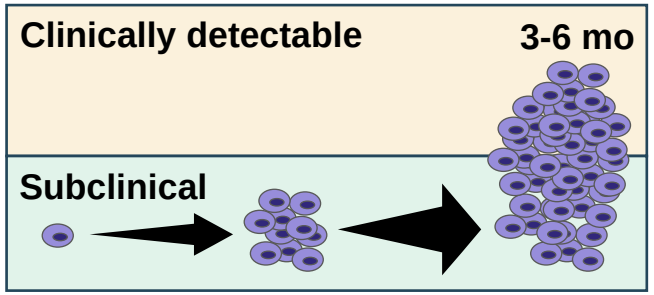
BMT, bone marrow transplant; R-chemo, rituximab plus chemotherapy; Rx, active treatment line; XRT, external beam radiation therapy.

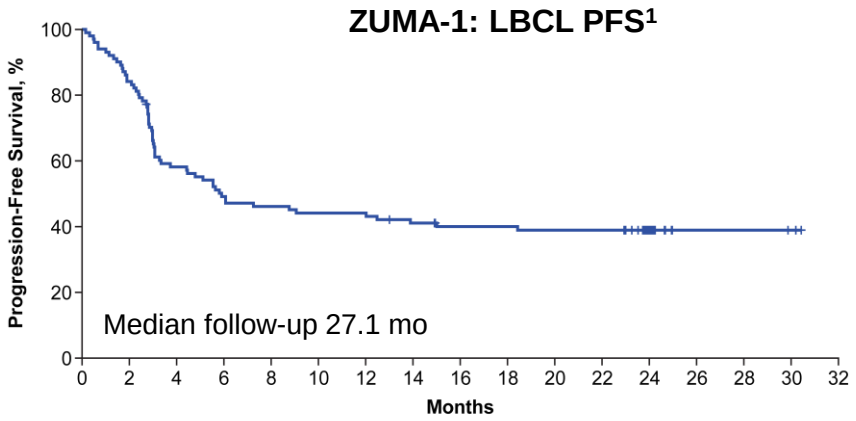
Median PFS (yrs)	6.6	1.5	0.8	0.7	0.7

Link et al. *Br J Haematol* 2019; 184(4):660-663

Difference in relapse pattern between LBCL and FL

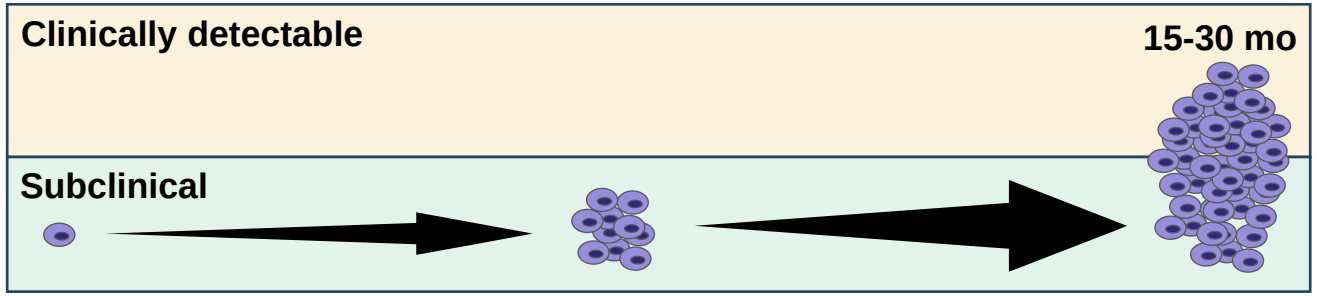
LBCL

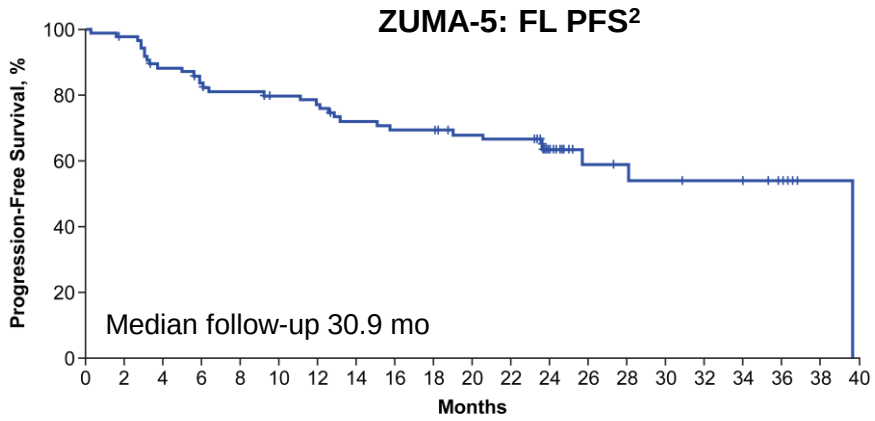




- With curative therapies in LBCL, most PFS events are PD-related, occurring early and resulting in a plateau within 2 years

FL





- In FL, PFS events are likely to occur over a longer period, including PD- and non–PD-related events, with no obvious plateau within 2 years
- Lymphoma-specific assessment of survival may be necessary to determine curative potential in FL
- Here we evaluate updated outcomes from ZUMA-5 after a median follow-up of ≥5 years, including lymphoma-specific survival analyses

Neelapu et al. ASH 2024, Abstract 864

ZUMA-5: Five-year analysis methods

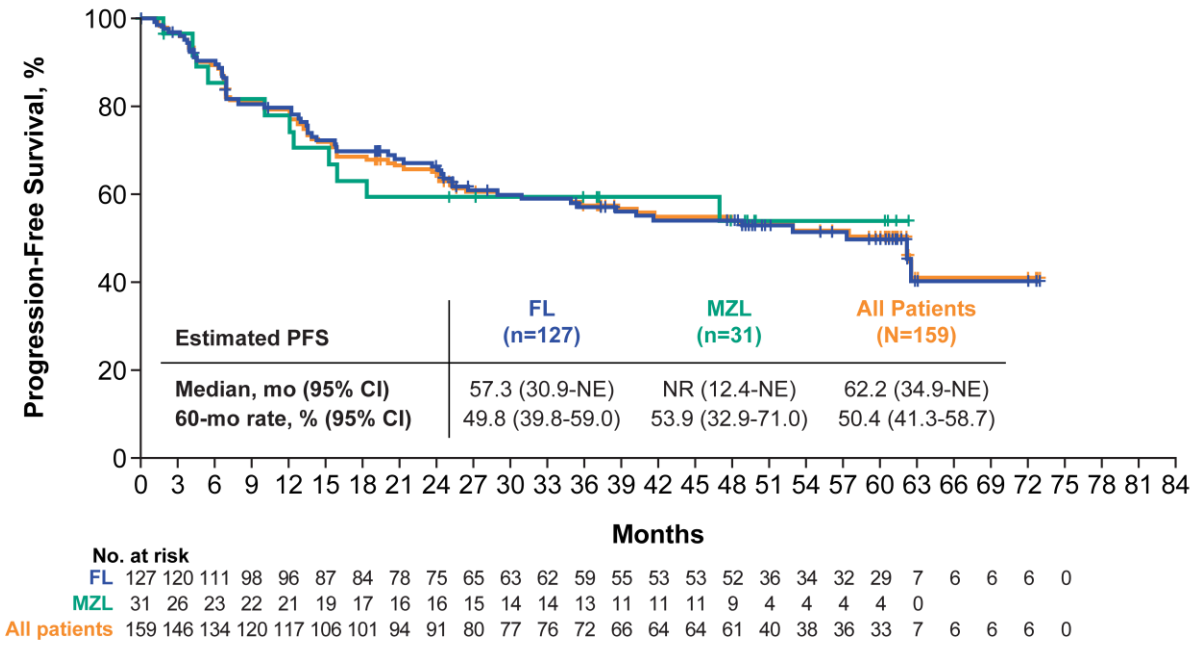
- The 5-year analysis occurred after the median follow-up of all enrolled patients reached ≥60 months post-infusion (N=159; FL, n=127; MZL, n=31)

- Exploratory analyses of lymphoma-specific survival were performed
  - Events of interest in lymphoma-specific PFS were PD and death due to lymphoma or complications from study treatment (axi-cel or lymphodepleting chemotherapy)
  - Events of interest in lymphoma-specific survival were death due to lymphoma or study treatment
  - Competing risks were deaths due to reasons other than lymphoma or study treatment

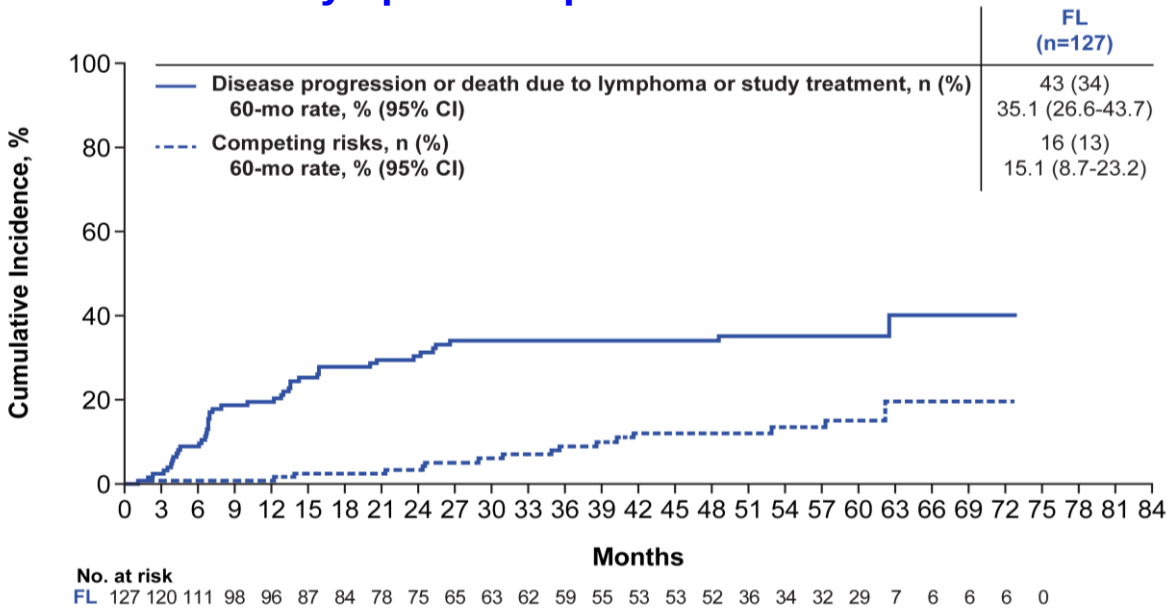
Neelapu et al. ASH 2024, Abstract 864

ZUMA-5: PFS and Cumulative incidence of progression and lymphoma-specific death

Progression-Free Survival



Cumulative Incidence of Progression and Lymphoma-Specific Death in FL

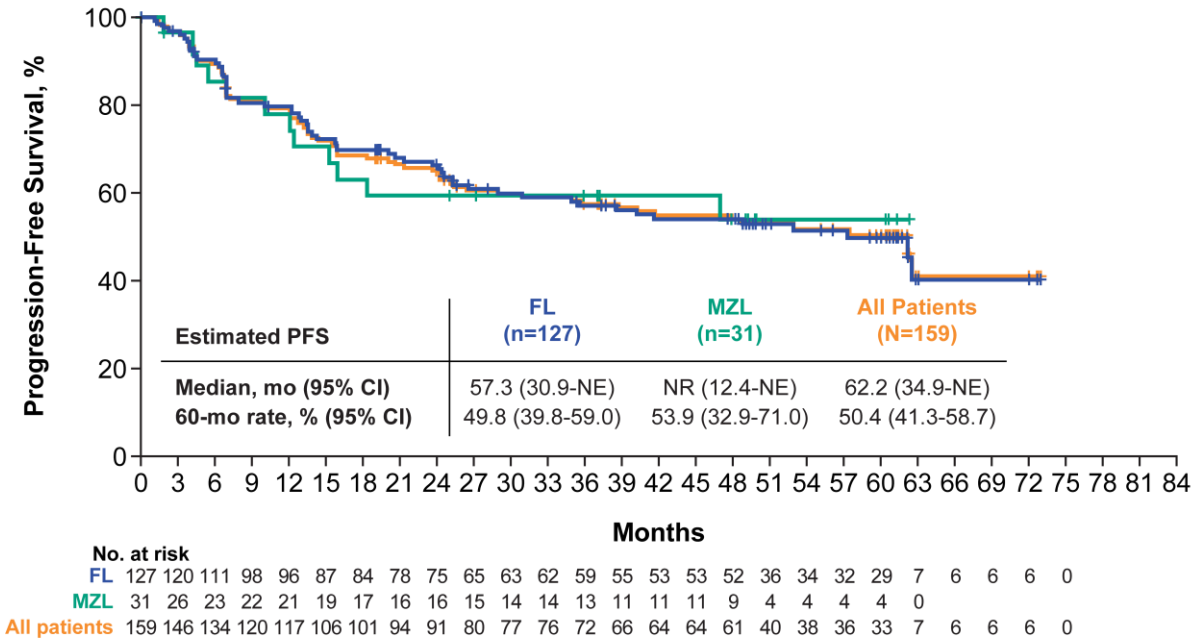


- Median PFS was 62.2 months; the 60-month PFS rate was 50.4%
  - 60-month PFS rates in patients with FL were consistent regardless of high-risk factors, including POD24
  - In those with a CR, the 60-month PFS rate was 61.9%; in those with PR, the rate was 9.1%
- Among patients with FL, the 60-month rate of progression or lymphoma-specific death was 35.1%

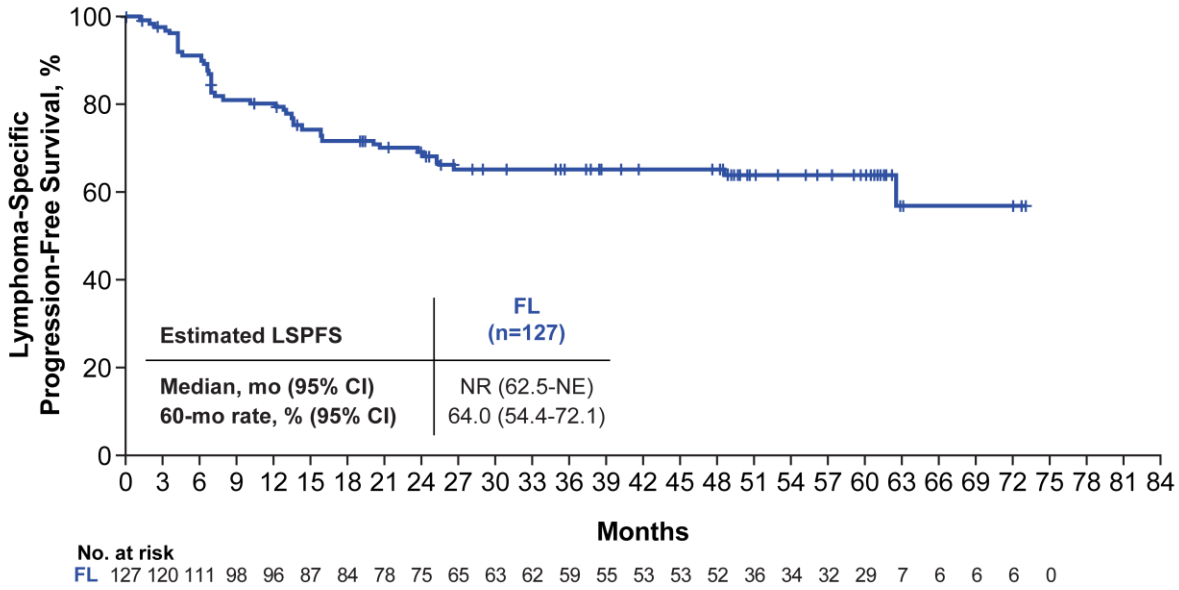
Neelapu et al. ASH 2024, Abstract 864

ZUMA-5: PFS and Lymphoma-specific PFS

Progression-Free Survival



Lymphoma-Specific PFS

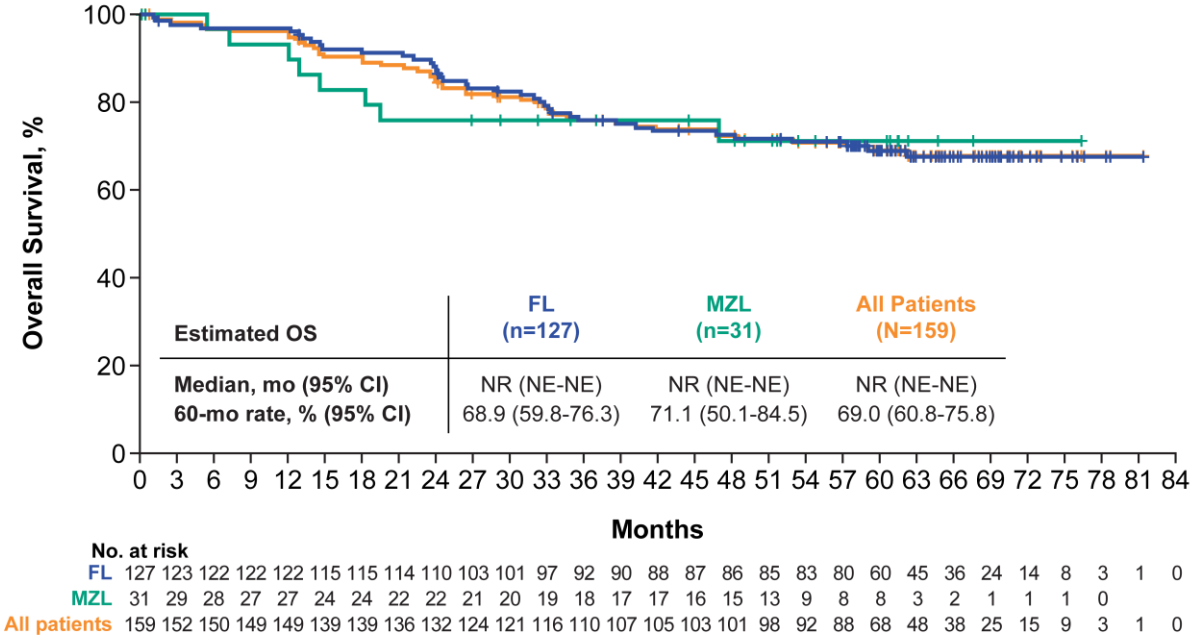


- Median lymphoma-specific PFS in FL was not reached (95% CI, 62.5-NE)
- 60-month lymphoma-specific PFS was 64.0%
  - Only 4 patients progressed >24 months post-leukapheresis; 2 patients progressed >30 months post-leukapheresis

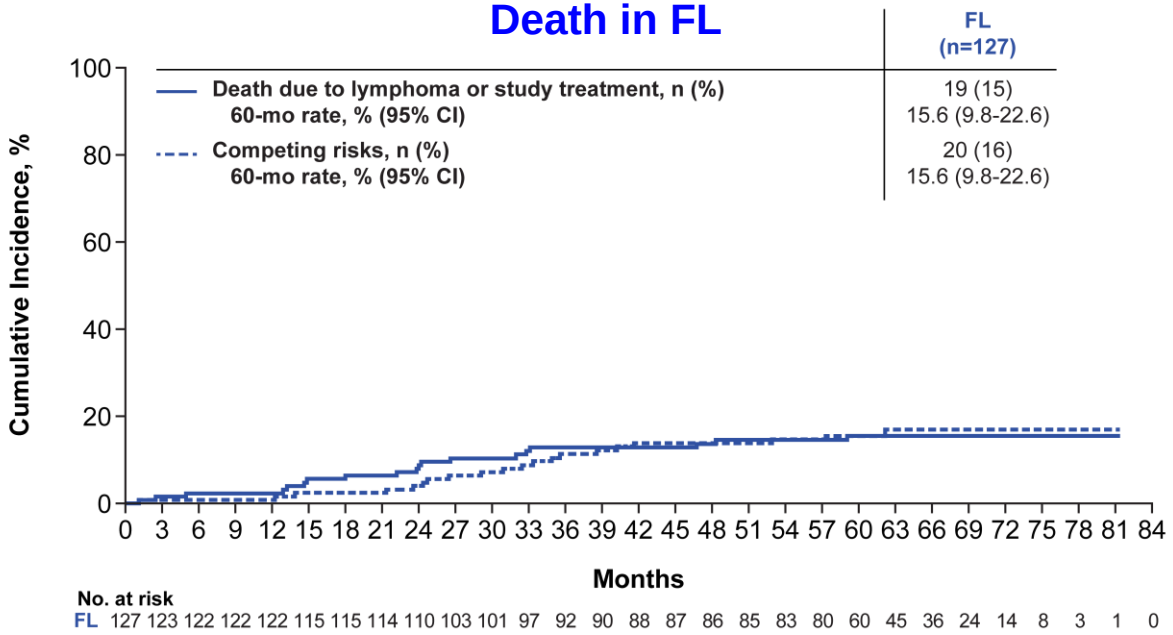
Neelapu et al. ASH 2024, Abstract 864

ZUMA-5: OS and Cumulative incidence of lymphoma-specific death

Overall Survival



Cumulative Incidence of Lymphoma-Specific Death in FL

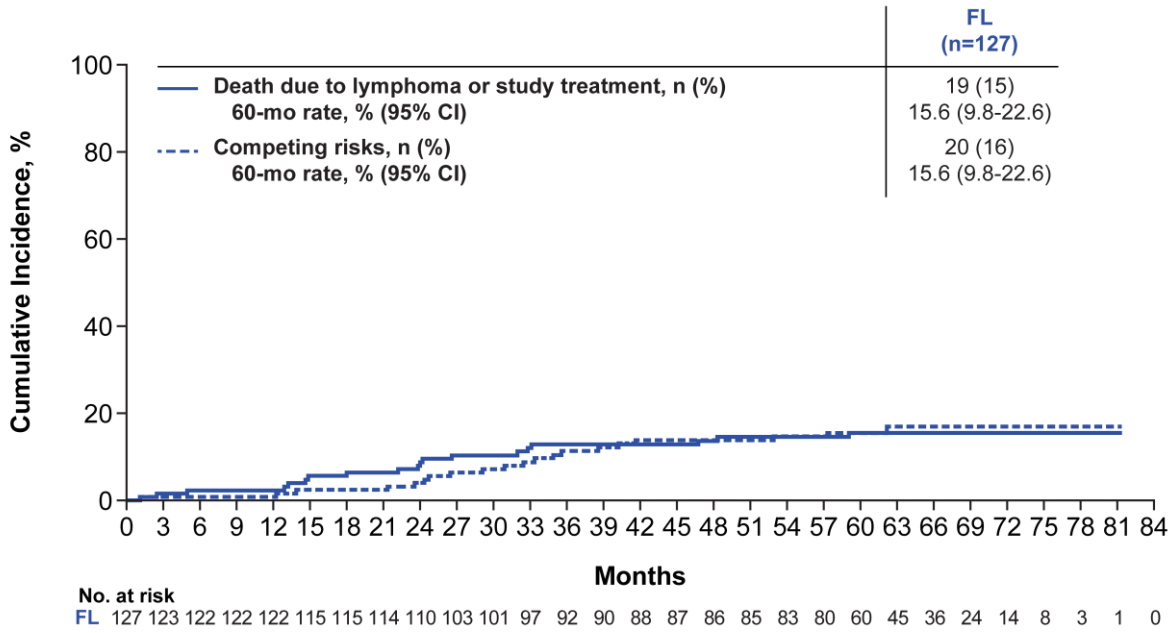


- Median OS was not reached
- The rate of lymphoma-specific death at 60 months in FL was 15.6%
  - A total of 19 patients died due to lymphoma or study treatment (lymphoma, n=15; study treatment, n=4)

Neelapu et al. ASH 2024, Abstract 864

Cumulative incidence of lymphoma-specific death: ZUMA-5 vs. Historical

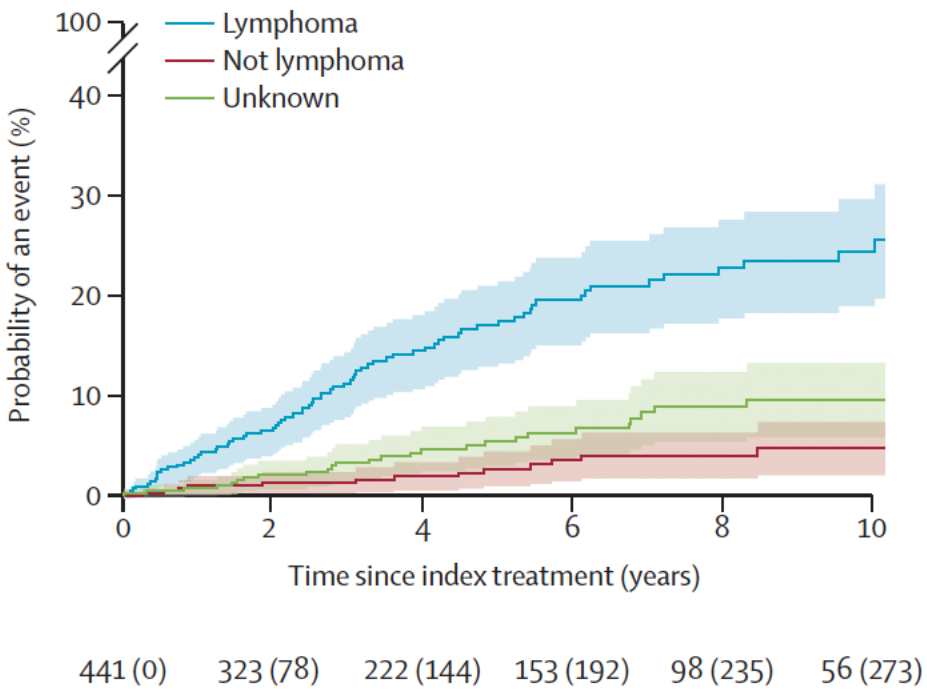
ZUMA-5: Cumulative Incidence of Lymphoma-Specific Death in FL



Neelapu et al. ASH 2024, Abstract 864

Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study

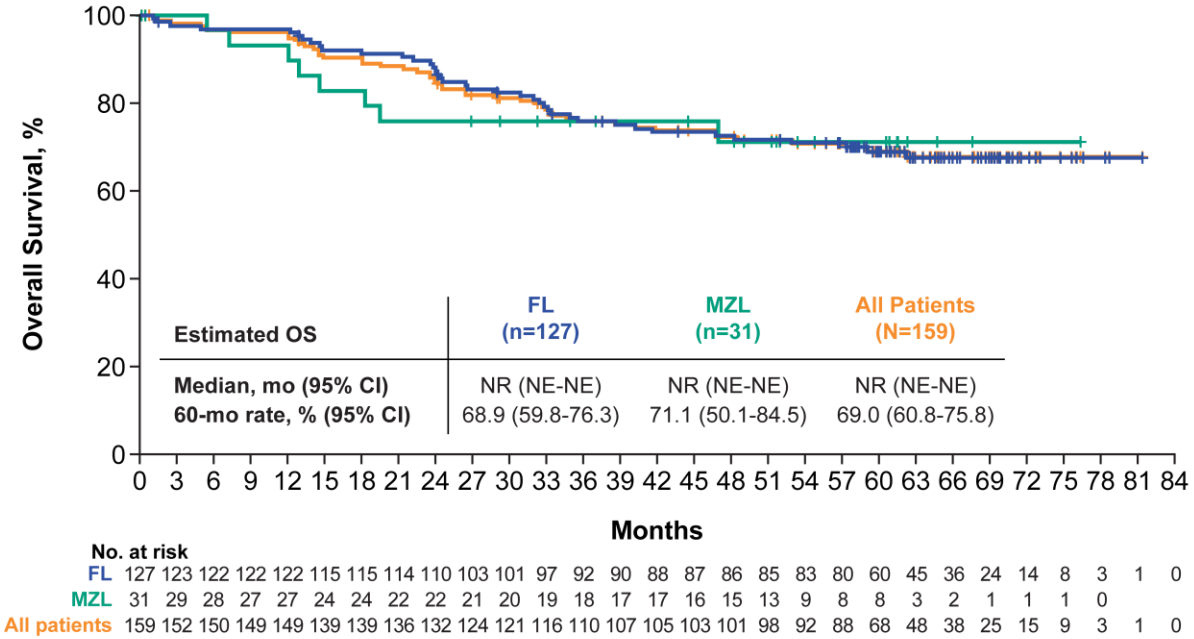
Carla Casulo, Melissa C Larson, Julianne J Lunde, Thomas M Habermann, Izidore S Lossos, Yucai Wang, Loretta J Nastoupil, Christopher Strouse, Dai Chihara, Peter Martin, Jonathon B Cohen, Brad S Kahl, W Richard Burack, Jean L Koff, Yong Mun, Anthony Masaquel, Mei Wu, Michael C Wei, Ashwini Shewade, Jia Li, James Cerhan, Christopher R Flowers, Brian K Link, Matthew J Maurer



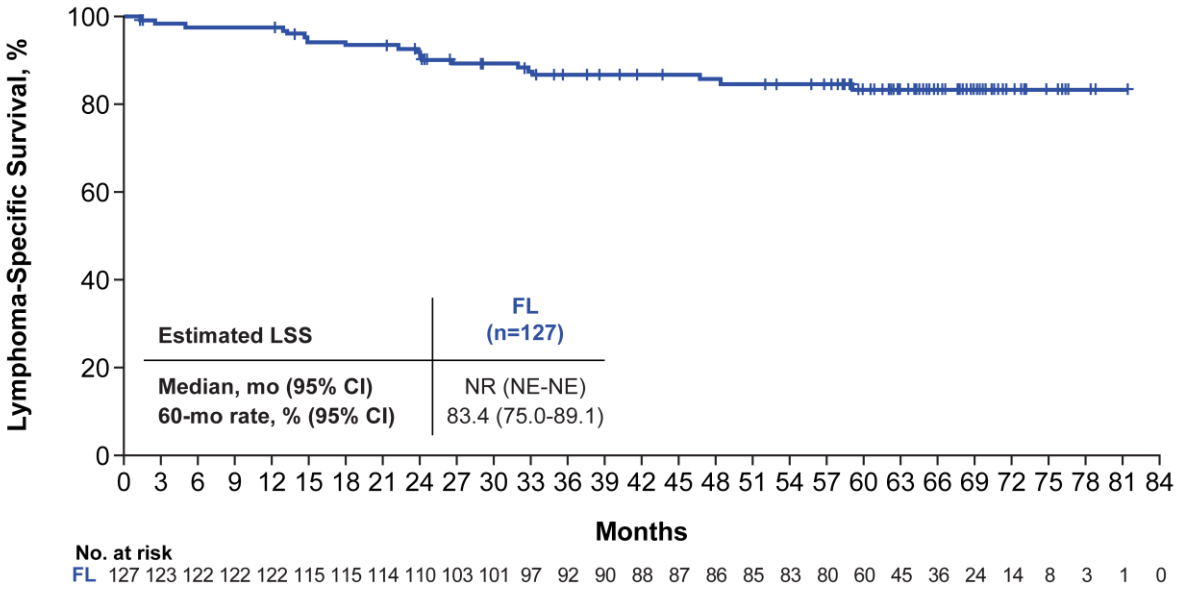
Casulo C et al. *Lancet Haematol* 2022 Apr;9(4):e289-e300

ZUMA-5: OS and Lymphoma-specific survival

Overall Survival



Lymphoma-Specific Survival

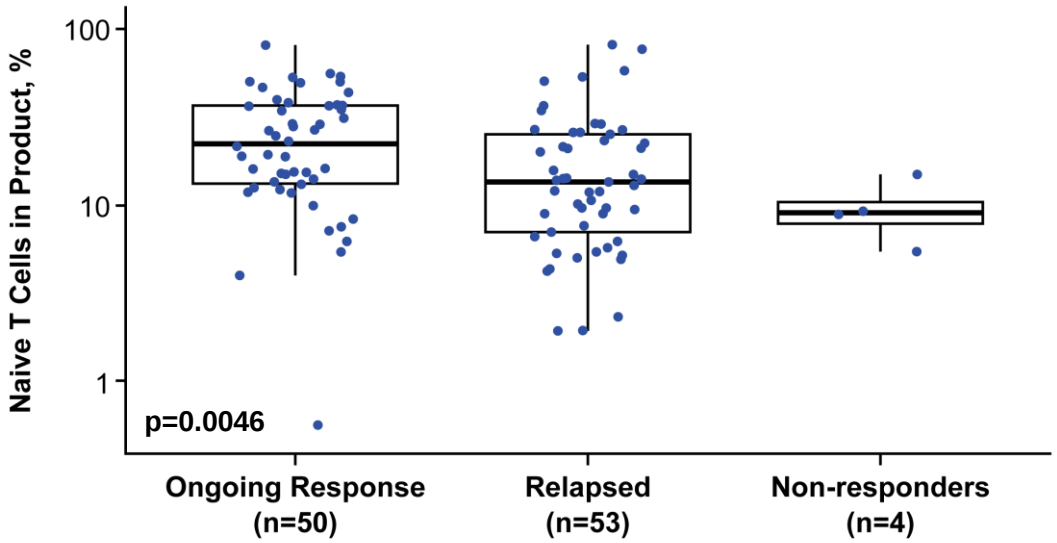


- Median lymphoma-specific survival in FL was not reached (95% CI, NE-NE)
- 60-month lymphoma-specific survival in FL was 83.4%

Neelapu et al. ASH 2024, Abstract 864

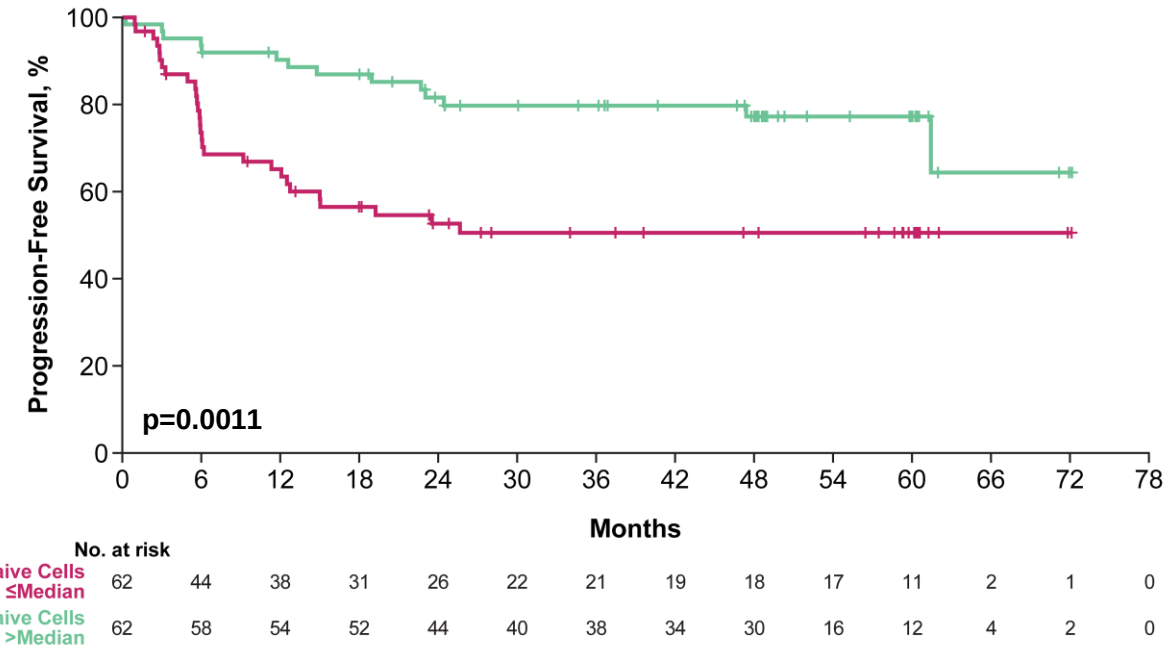
ZUMA-5: Impact of naïve T cells in product in FL

Naive T Cells in Product



	Ongoing Response (n=50)	Relapsed (n=53)	Non-responders (n=4)
Median cells, %	22.3	13.5	9.0

PFS by Median Naive T Cells in Product



No. at risk

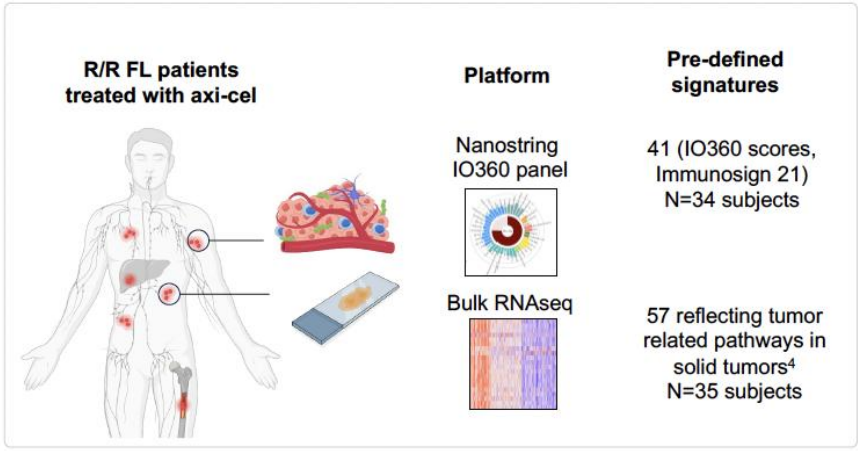
% Naive Cells ≤Median	62	44	38	31	26	22	21	19	18	17	11	2	1	0
% Naive Cells >Median	62	58	54	52	44	40	38	34	30	16	12	4	2	0

- Among patients with FL, a higher percentage of naive T cells (CCR7+CD45RA+) in axi-cel product, indicative of naive phenotype, was associated with ongoing response at 60 months and longer PFS

Neelapu et al. ASH 2024, Abstract 864

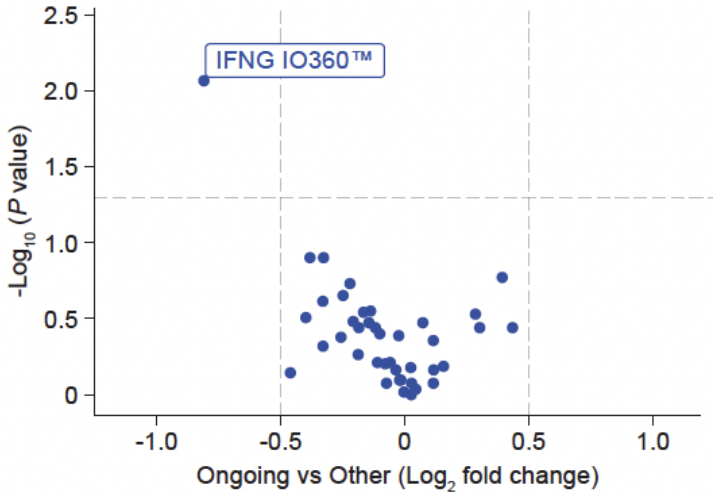
IFN signaling in the TME was associated with inferior PFS after axi-cel in r/r FL (ZUMA-5)

Pre-treatment tumor profiling

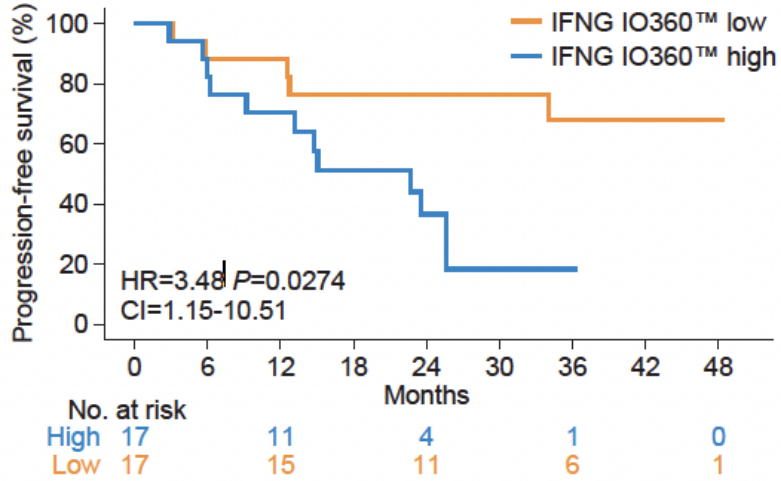


R/R, relapsed/refractory; 30 subjects were overlapping in nanostring and RNAseq analysis;

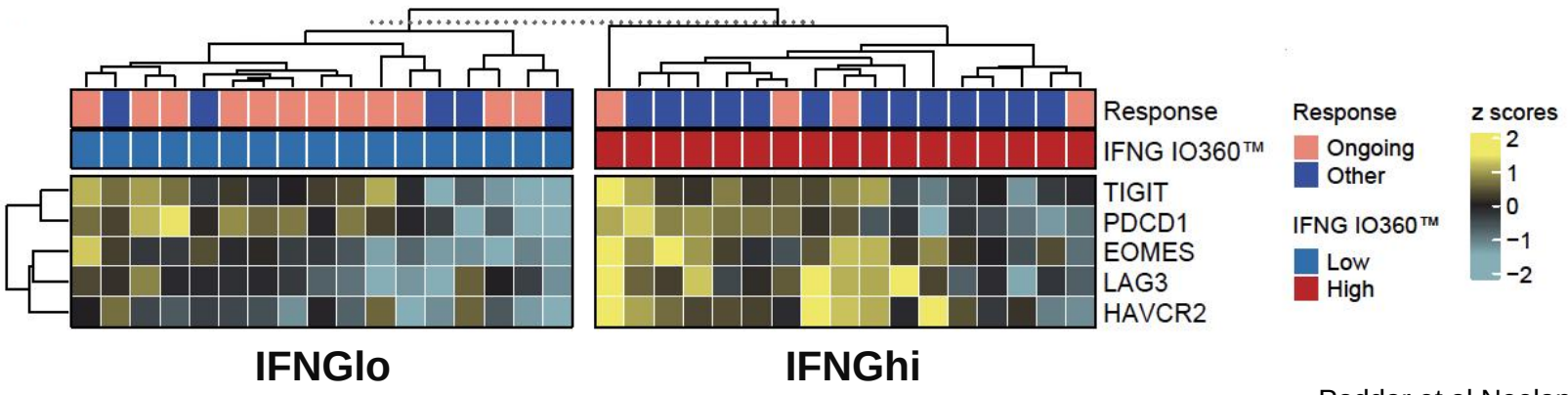
GES association with relapse



IFNG GES association with PFS



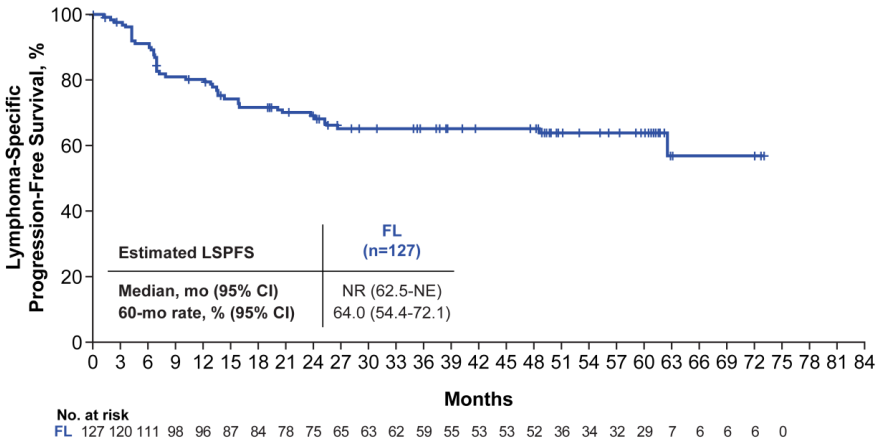
High LAG3, TIM3, and EOMES in IFNGhi tumors



Poddar et al Neelapu, *ASH* 2024, Abstract 4368

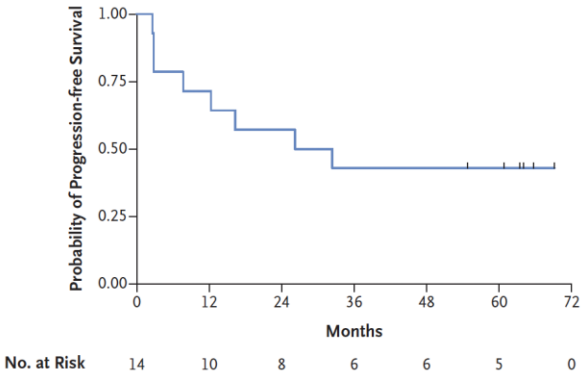
How many R/R FL can we cure with CAR T cells?

ZUMA-5: Lymphoma-Specific PFS



Neelapu et al. ASH 2024, Abstract 864

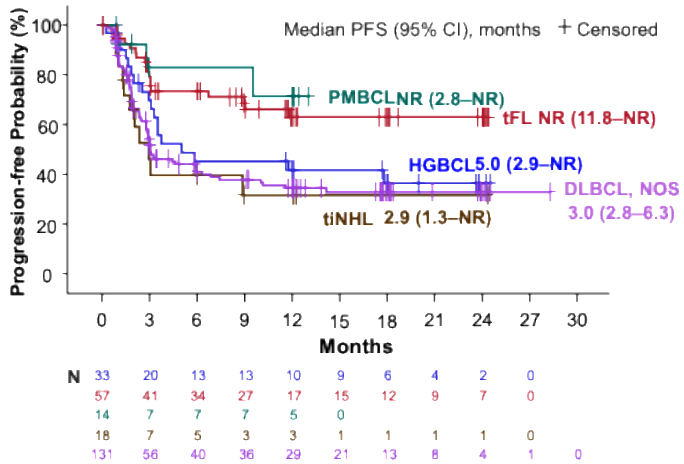
U Penn / CTL019: FL PFS



Chong EA et al. *N Engl J Med*. 2021 Feb 18;384(7):673-674

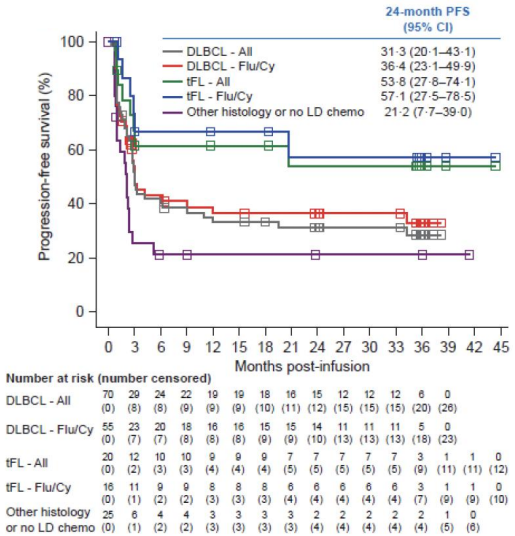
Cure in FL ~60%

TRANSCEND tFL PFS



Abramson et al. ASH 2019, Abstract 241

JULIET tFL PFS



Schuster SJ et al, *Lancet Oncol* 2021 Oct;22(10):1403-1415

Thank you for your attention!

Email: sneelapu@mdanderson.org