CAR-T for DLBCL: from second-line clinical trials to RWD

T-cell and NK-cell based immunotherapies for Lymphoid Malignancies, September 13th-14th, 2024

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MOFFITT CANCER CENTER

THIRD MEETING ON T-CELL AND NK-CELL BASED IMMUNOTHERAPIES FOR LYMPHOID MALIGNANCIES

Presidents
Paolo Corradini
Marco Ruella
Pier Luigi Zinzani

Disclosures of FREDERICK LOCKE

BOLOGNA, ROYAL HOTEL CARLTON
September 13-14, 2024

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

UNKNOWN

CAR-T for DLBCL: from second-line clinical trials to RWD

- Brief review of the randomized clinical trials in 2nd line
- Impact of Race and Ethnicity on CAR-T outcomes
- Tumor burden and its impact on CAR-T outcomes in 2nd line (MTV)
- Tumor features and their impact on CAR-T outcomes in 2nd line (Tumor immune contexture, CD19, myeloid cells, and SII)

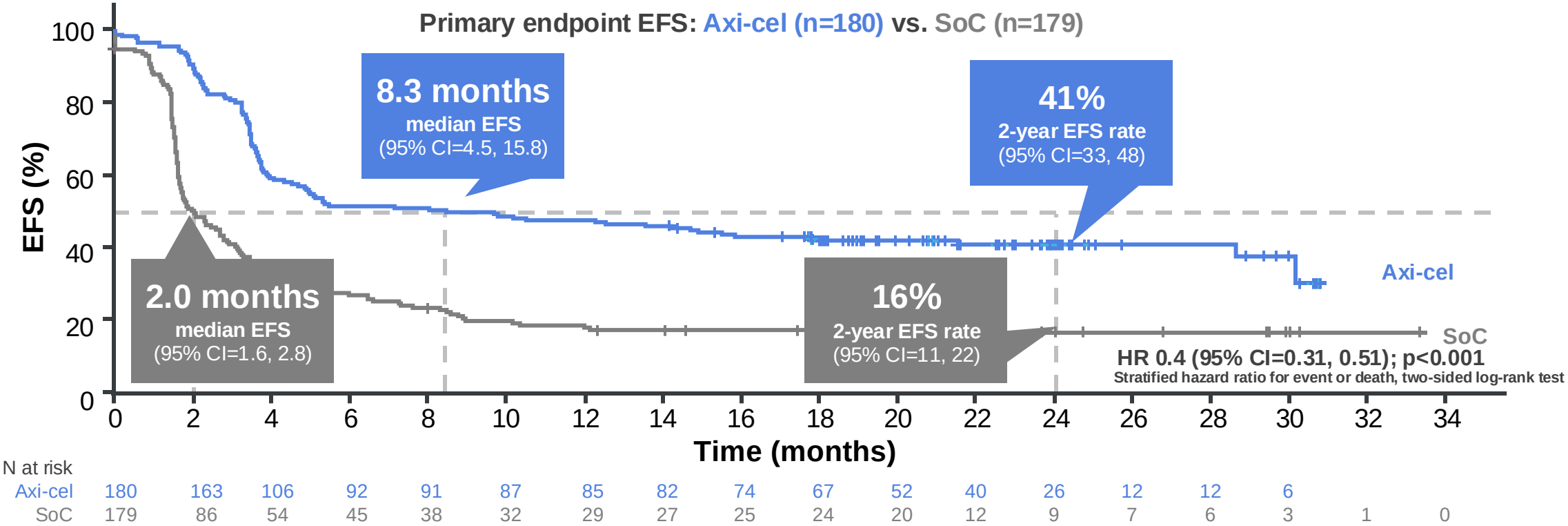
Randomized controlled trials leading to 2nd line indication of CAR-T for DLBCL

ZUMA-7: EFS improved with axi-cel compared to prior SOC

ZUMA-7

mFU: 24.9 months

Phase 3, randomised, multicentre trial of axi-cel vs. SoC (ASCT) as 2L treatment in patients with R/R LBCL (N=359)



Axi-cel demonstrated 2-year Event Free Survival rate of 41% in patients with R/R DLBCL showing statistical significance over SoC arm

Locke FL, *et al. N Engl J Med* 2022; 386:640–654.

ZUMA-7: Axi-cel improved OS compared to prior SOC

ZUMA-7

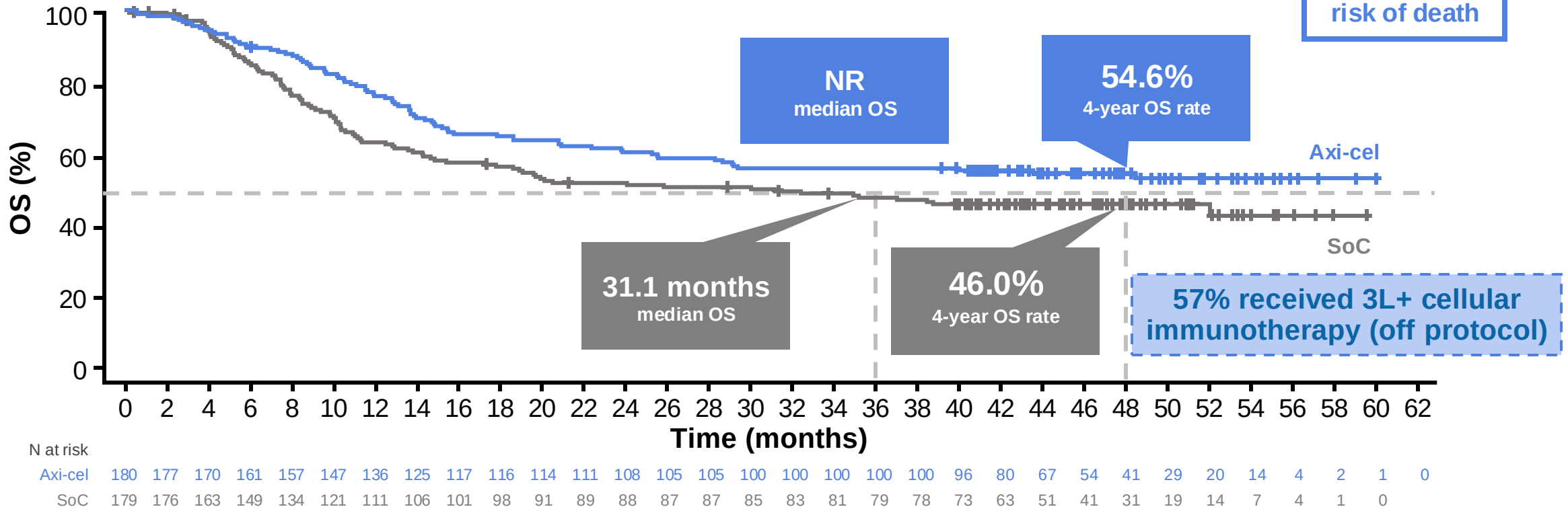
mFU: 47.2 months

OS: Axi-cel (n=180) vs. SoC (n=179)[1]

Stratified hazard ratio for death, one-sided log-rank test

HR 0.726 (95% CI=0.540, 0.977); p=0.0168

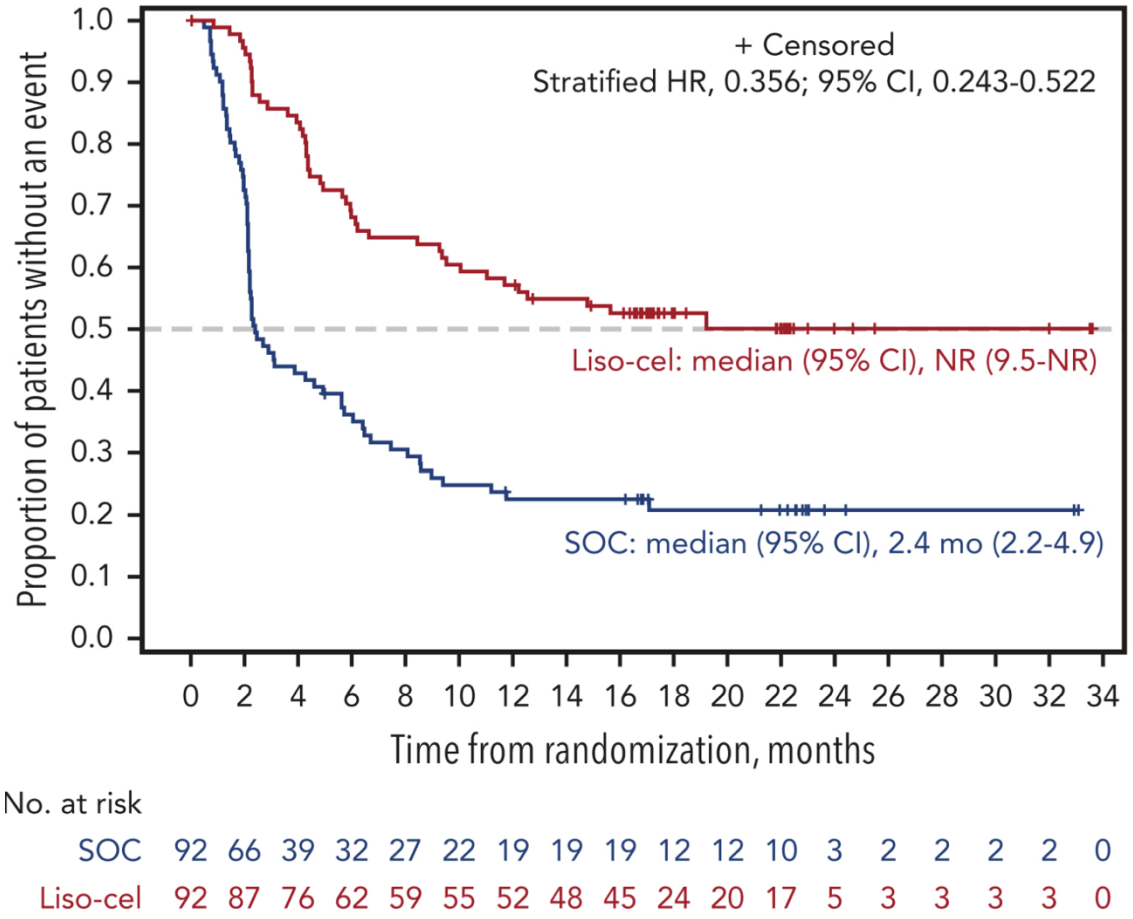
27% reduction in risk of death



Axi-cel demonstrated 54.6% 4-year OS rate, with median OS not reached at 47.2 months' median follow-up

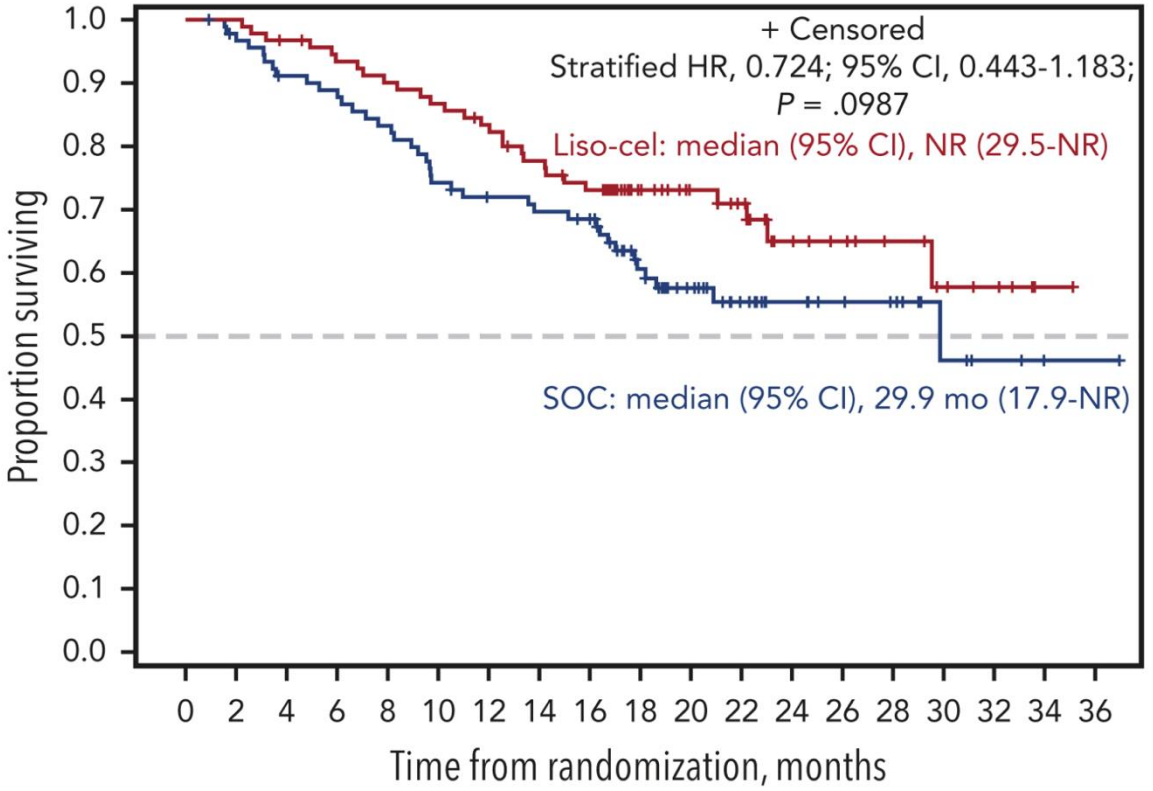
Westin JR, *et al.* ASCO 2023 (LBA107)
Westin JR, *et al.* NEJM 2023.

TRANSFORM: EFS improved with liso-cel compared to prior SOC



No. at risk

SOC	92	66	39	32	27	22	19	19	19	12	12	10	3	2	2	2	2	0
Liso-cel	92	87	76	62	59	55	52	48	45	24	20	17	5	3	3	3	3	0



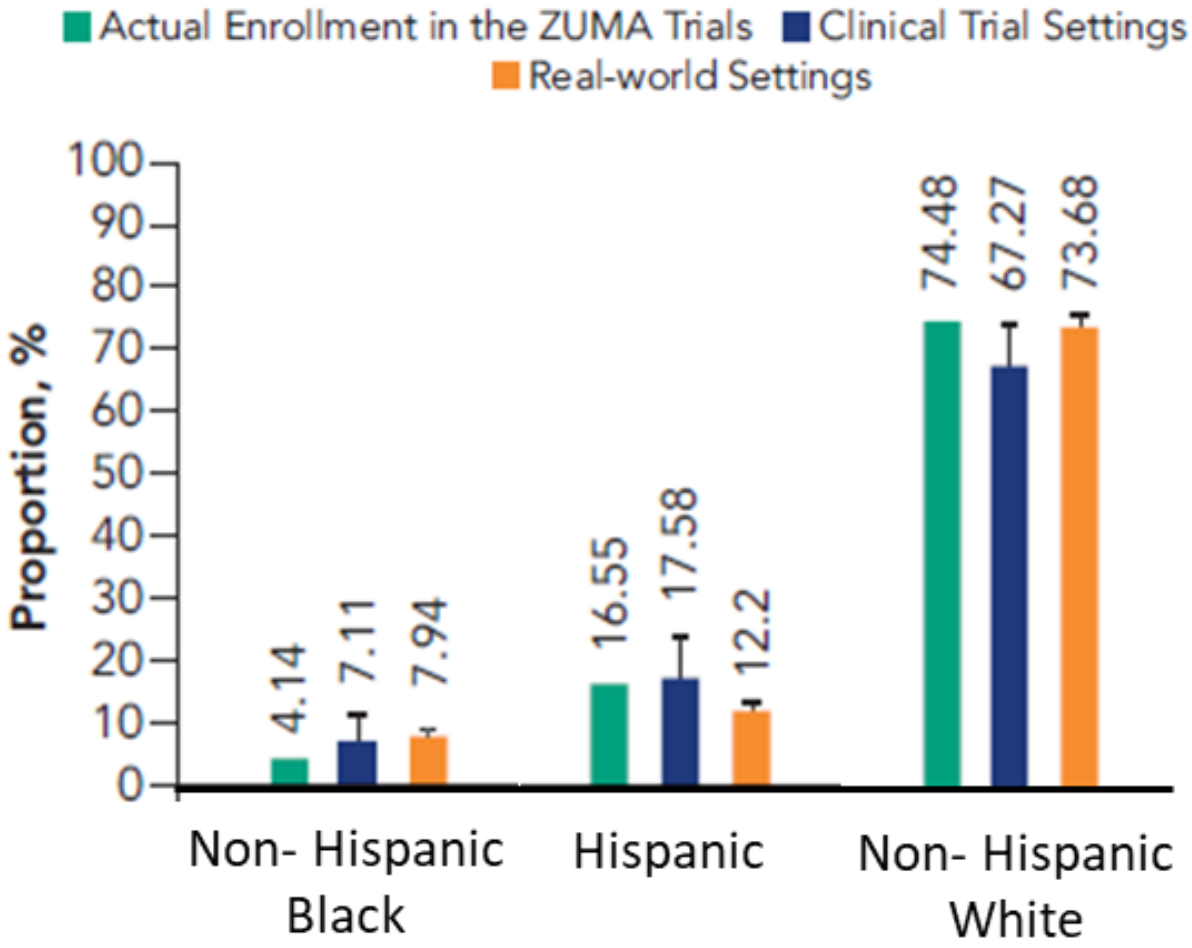
No. at risk

SOC	92	88	81	79	74	66	62	60	58	41	30	21	15	12	10	5	3	1	1
Liso-cel	92	92	88	84	81	78	74	68	63	43	34	30	16	13	10	7	5	1	0

Abramson J, *et al. Blood* 2023.

Impact of Race and Ethnicity on CAR-T outcomes

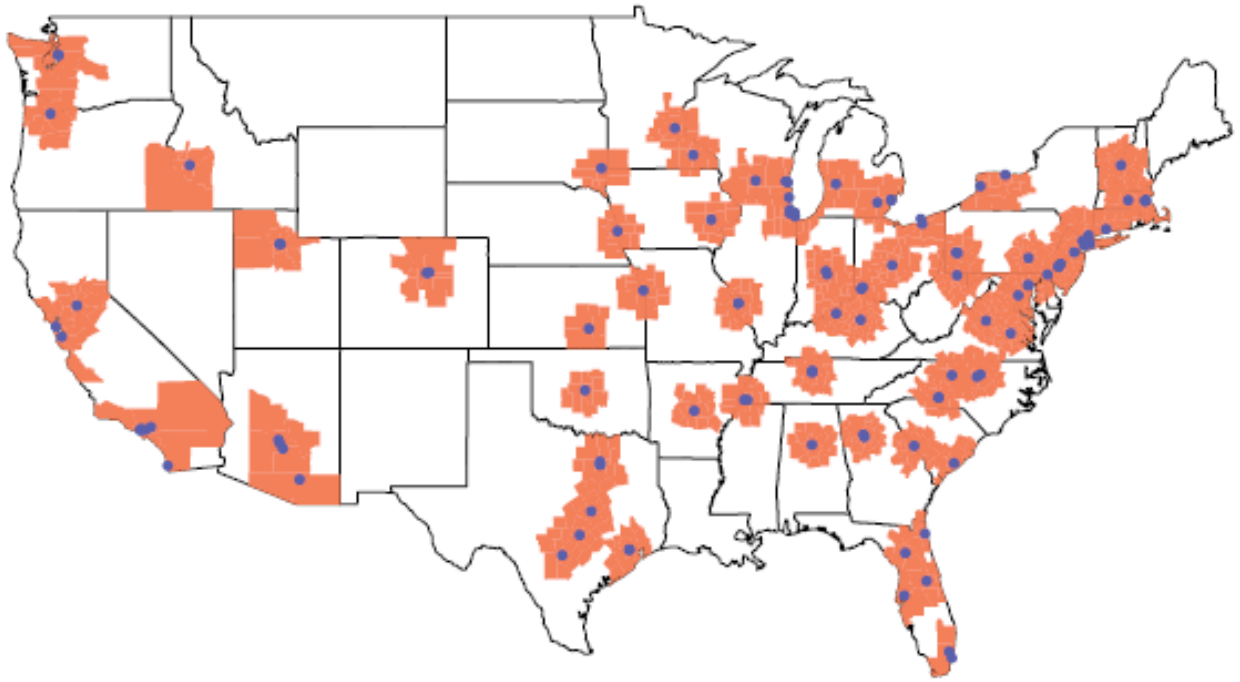
In the US, there is underrepresentation of minoritized patients that receive axi-cel for LBCL



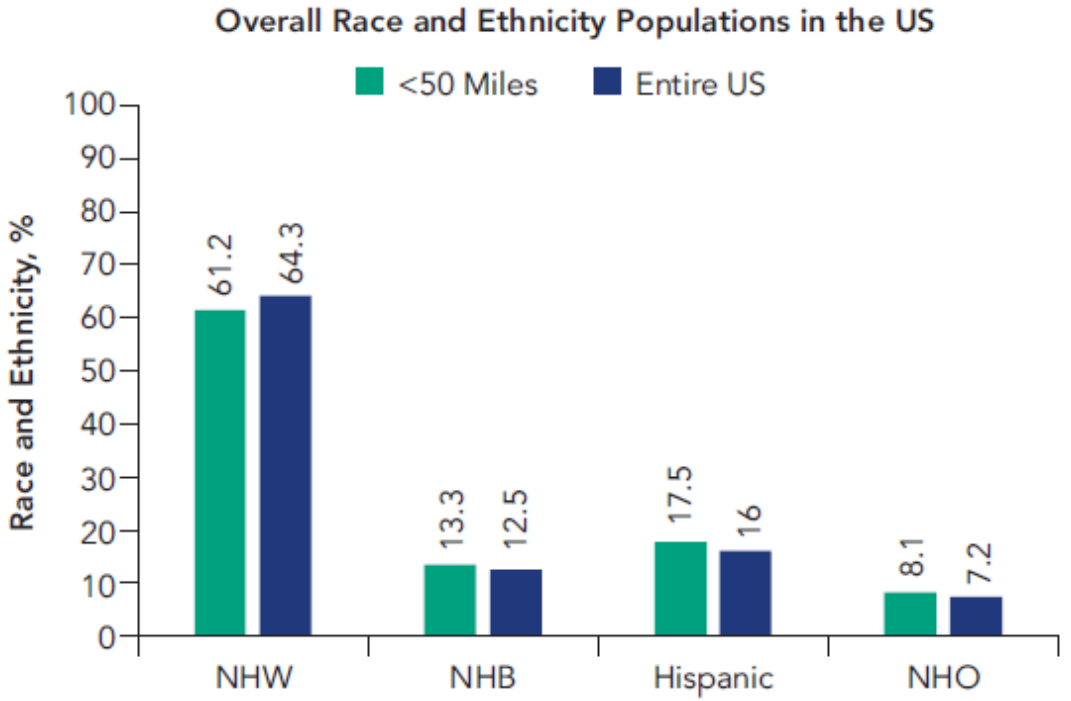
Goldfinger M, et al. ASH 2022. #4284.

In the US, underrepresentation cannot be explained by proximity to treatment center

Figure 2. Populations Within 50 Miles of Any Commercial ATC[a]



[a]Commercial ATCs (for axicabtagene ciloleucel or brexucabtagene autoleucel) with counties within 50 miles.

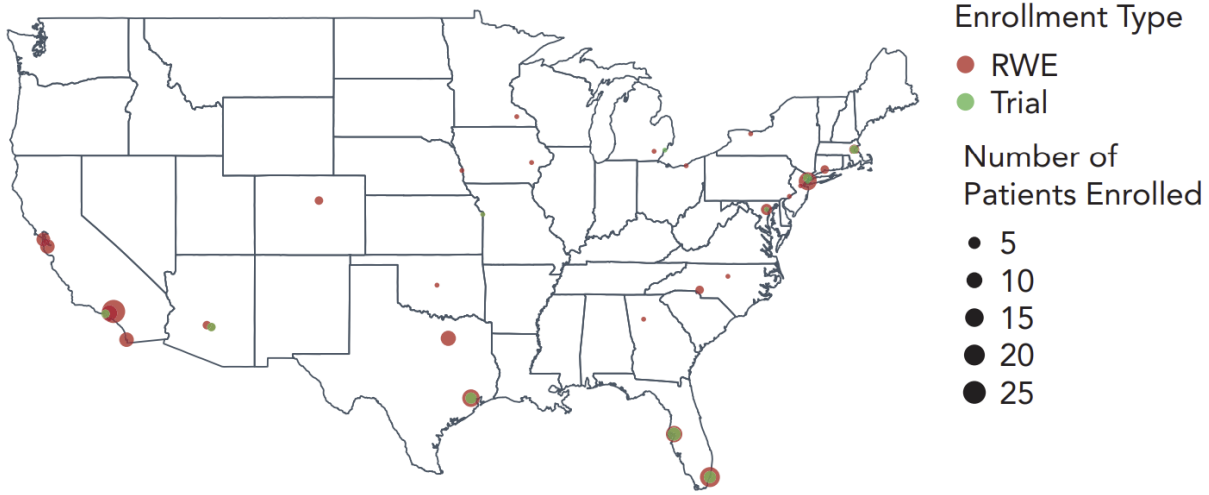


Goldfinger M, et al. ASH 2022. #4284.

Treatment Location and Incidence of Hispanic and Black DLBCL patients on ZUMA trials or in CIBMTR Real World Registry

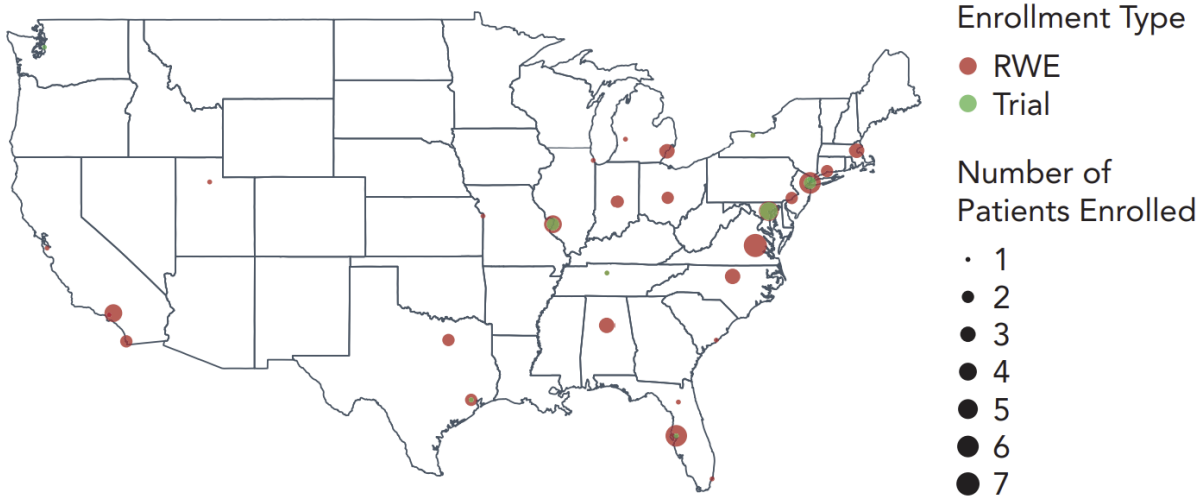
Hispanic patients

(11.8%, n = 152 from CIBMTR;
10.5%, n = 19 from ZUMA-1, n = 10 from ZUMA-7)



Non-Hispanic Black patients

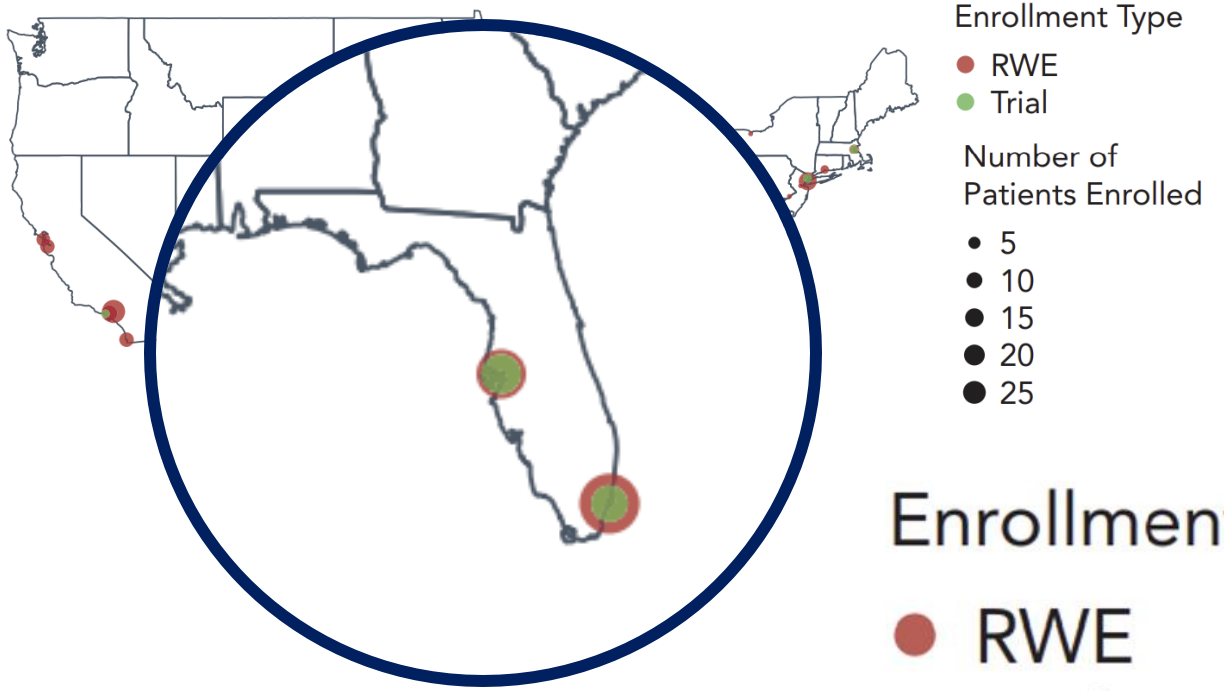
(5.3%, n = 68 from CIBMTR;
5.5%, n = 5 from ZUMA-1 and n = 10 from ZUMA-7)



Locke FL, et al. Blood 2024. Jun 27;143(26):2722-2734.

Axi-cel treatment likelihood appears to differ between ZUMA trials and SOC for Hispanic and Black DLBCL patients

Hispanic patients
(11.8%, n = 152 from CIBMTR;
10.5%, n = 19 from ZUMA-1, n = 10 from ZUMA-7)



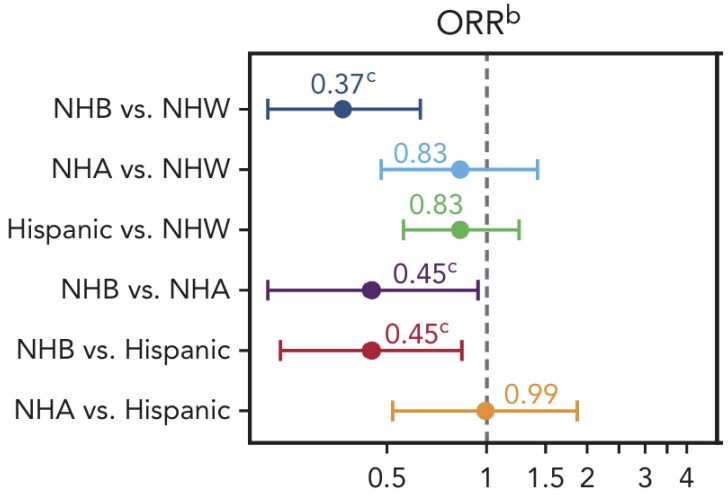
Non-Hispanic Black patients
(5.3%, n = 68 from CIBMTR;
5.5%, n = 5 from ZUMA-1 and n = 10 from ZUMA-7)

Enrollment Type
RWE
Trial

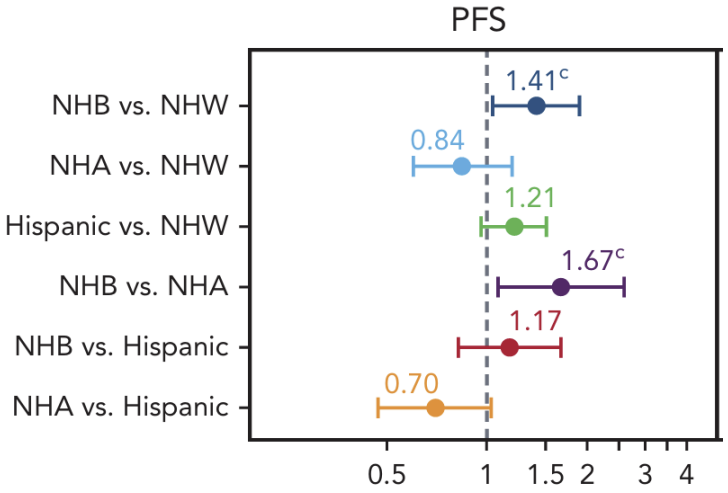
Locke FL, et al. Blood 2024. Jun 27;143(26):2722-2734.

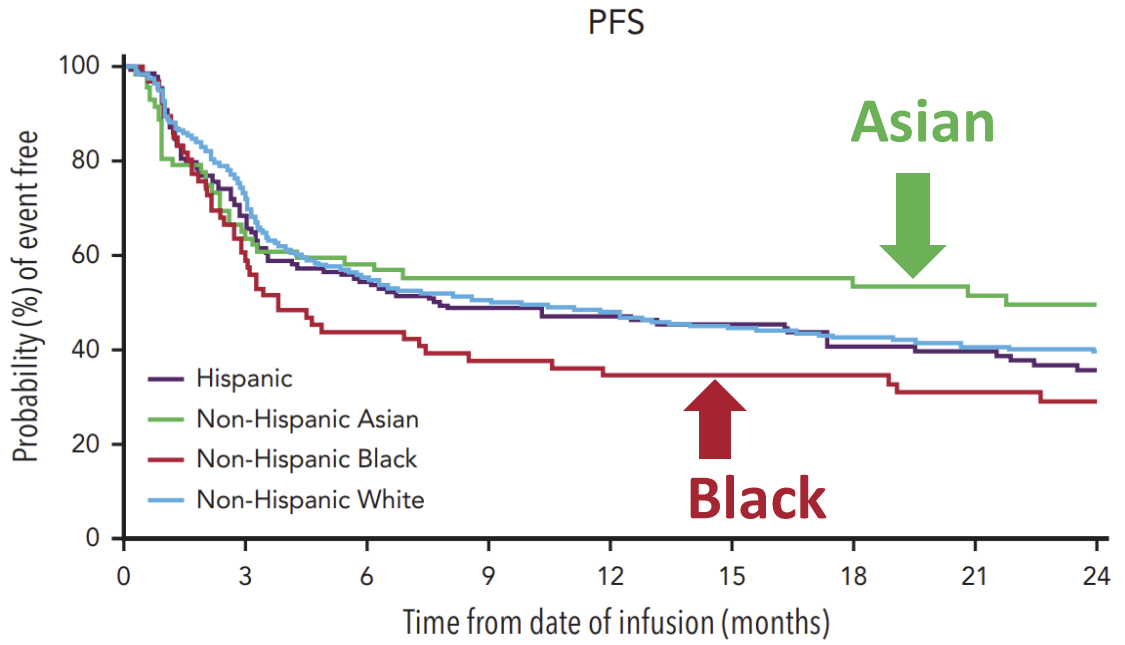
Race and ethnicity have some association with axi-cel efficacy and safety outcomes

ORR Odds Ratio



PFS Hazzard Ratio





Patients at risk									
Hispanic	144	97	76	67	61	49	43	40	31
Non-Hispanic Asian	72	46	42	39	36	29	28	27	17
Non-Hispanic Black	67	39	29	24	22	20	20	17	13
Non-Hispanic White	952	677	505	455	403	323	301	278	223

Locke FL, et al. Blood 2024. Jun 27;143(26):2722-2734.

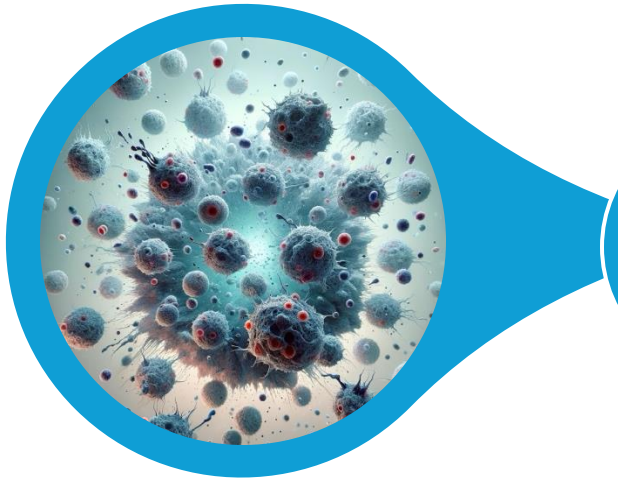
Tumor burden and its impact on CAR-T outcomes in the 2nd line (MTV)

Factors Influencing Efficacy of CAR-T in DLBCL

Locke et al, Blood Advances. 2020.
Dean et al, Blood Advances. 2020.
Frank et al. JCO 2020.
Kimmel et al, Proc. B. 2021.
Plaks et al, Blood. 2021.
Dean et al, Blood Advances. 2023.
Locke et al. Nat. Med. 2024

Tumor and TME

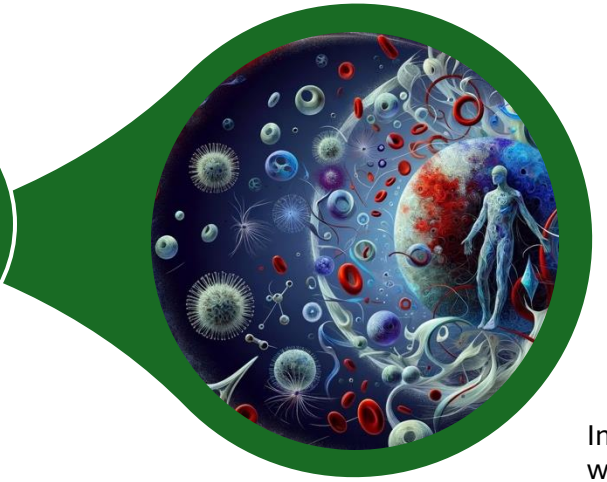
Locke et al, Mol. Therapy. 2016.
Neelapu et al, NEJM. 2017.
Locke et al, Lancet Onc. 2019.
Locke et al. NEJM. 2022.
Neelapu et al, Blood. 2023.
Westin et al. NEJM. 2023.



CAR-T product

Frank et al. JCO 2020.
Jain et al, Blood. 2021.
Jain et al. Blood. 2022.
Scholler et al, Nat. Med. 2022.
Jacobson et al. TCT. 2022.
Faramand et al. Bl. Can. Disc. 2024.

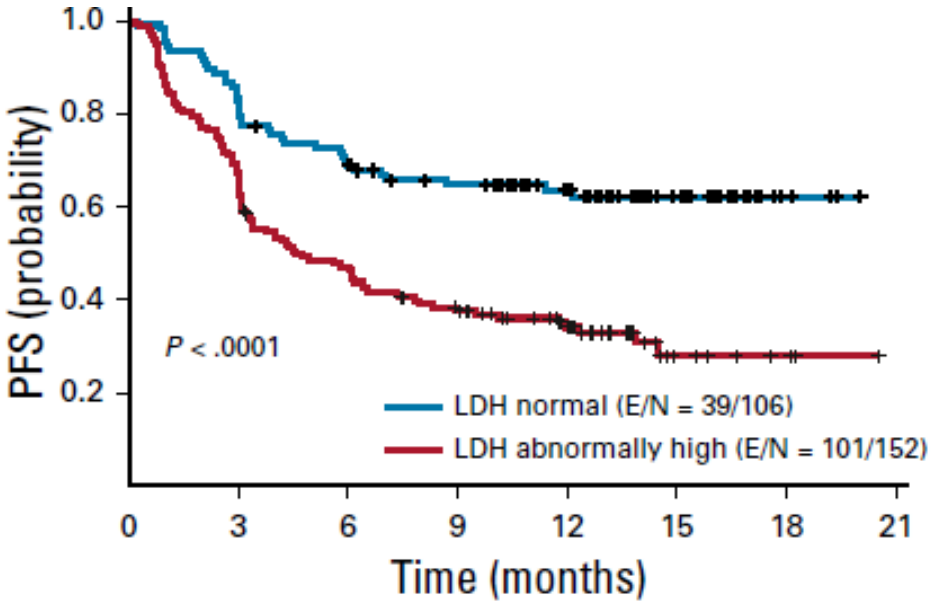
Systemic Immunity



Images created with ChatGPT

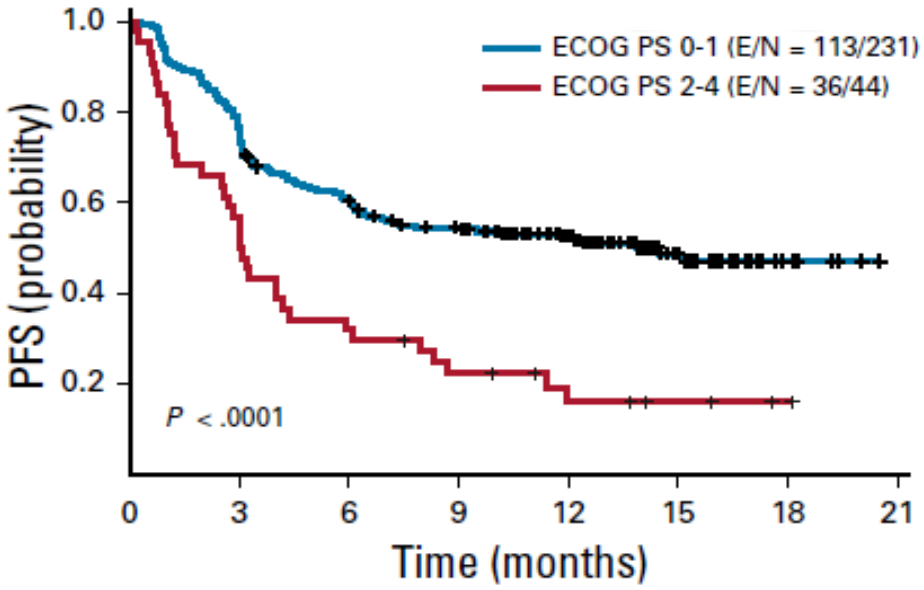
3rd or later line: High LDH and ECOG PS Associated With Lower Durable Response Rates

Elevated LDH



No. at risk:								
LDH normal	106	85	72	62	48	24	4	0
LDH abnormally high	152	100	70	53	32	7	3	0

ECOG 2 +



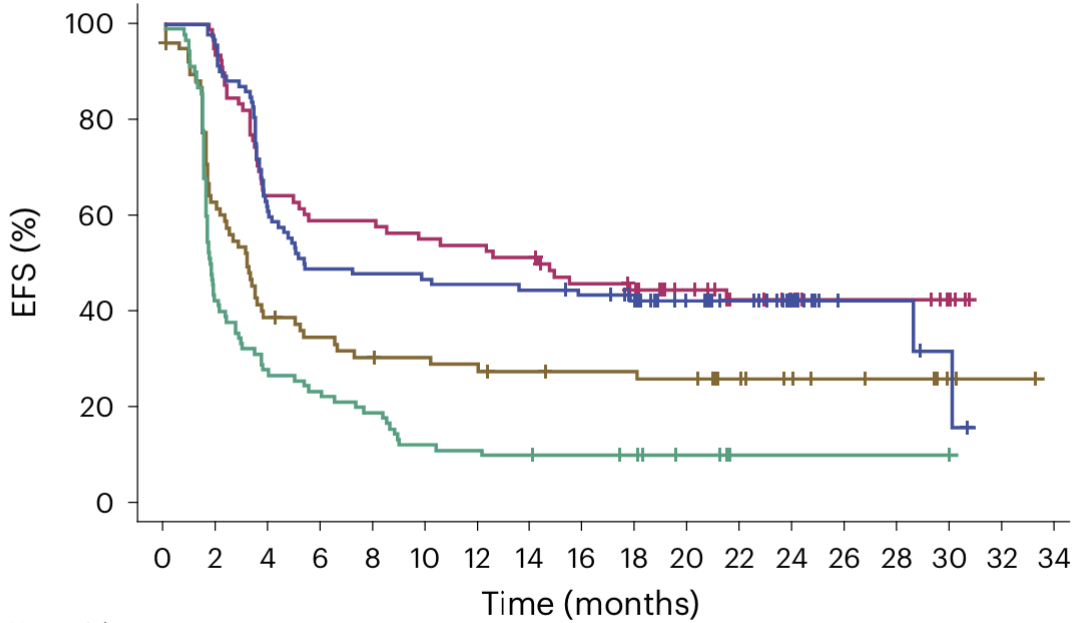
No. at risk:								
ECOG PS 0-1	231	172	137	115	82	31	6	0
ECOG PS 2-4	44	25	14	9	5	3	1	0

Nastoupil, Jain. JCO. 2020;38:3119.

U.S. CAR-T Lymphoma CONSORTIUM

ZUMA-7: LDH is not associated with EFS after axi-cel

	LDH elevated (axi-cel versus SOC)	LDH normal (axi-cel versus SOC)	Axi-cel LDH (elevated versus normal)	SOC LDH (elevated versus normal)
Unstratified HR (95% CI)	0.324 (0.228, 0.459)	0.496 (0.333, 0.739)	1.108 (0.745, 1.648)	1.556 (1.102, 2.195)
Unstratified *P* value	2.50×10^{-10}	0.0006	0.6132	0.0119



No. at risk																		
Axi-cel, LDH elevated	92	88	55	45	44	43	42	41	39	35	26	21	12	4	4	2		
Axi-cel, LDH normal	78	73	50	46	46	43	42	40	34	31	25	18	14	8	8	4		
SOC, LDH elevated	90	38	24	20	17	11	10	9	8	7	4	1	1	1	1	1		
SOC, LDH normal	78	46	29	25	21	21	19	18	17	17	16	11	8	6	5	2	1	0

Locke F, et al, Nature Medicine 2024.

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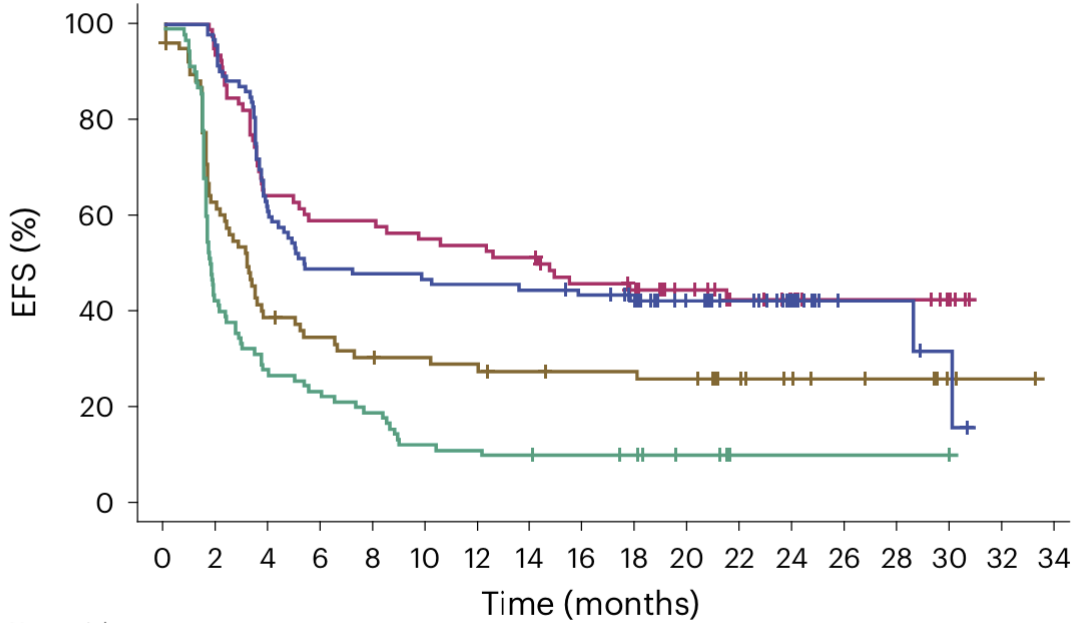
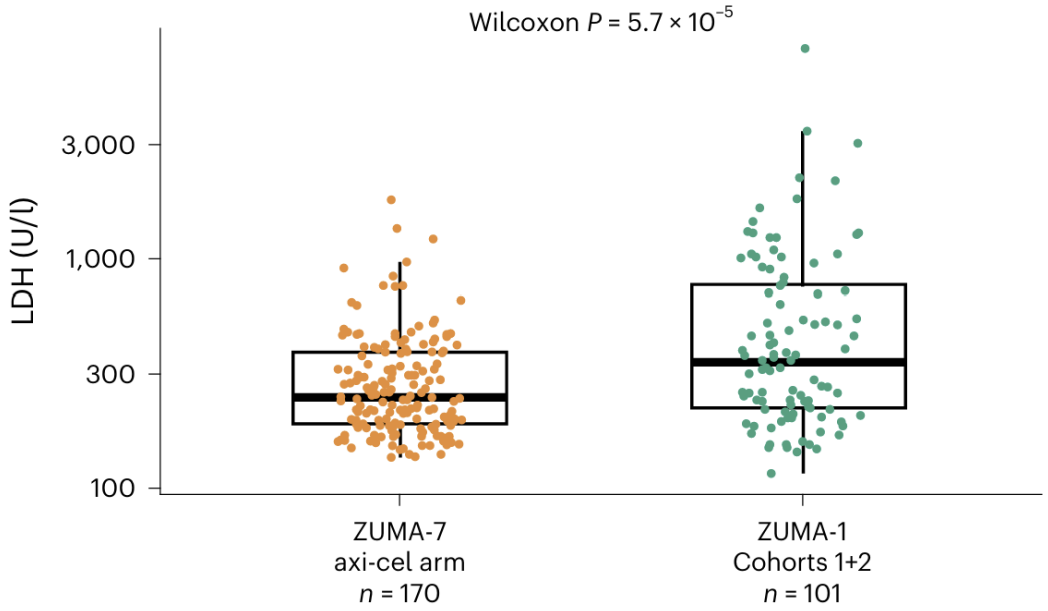


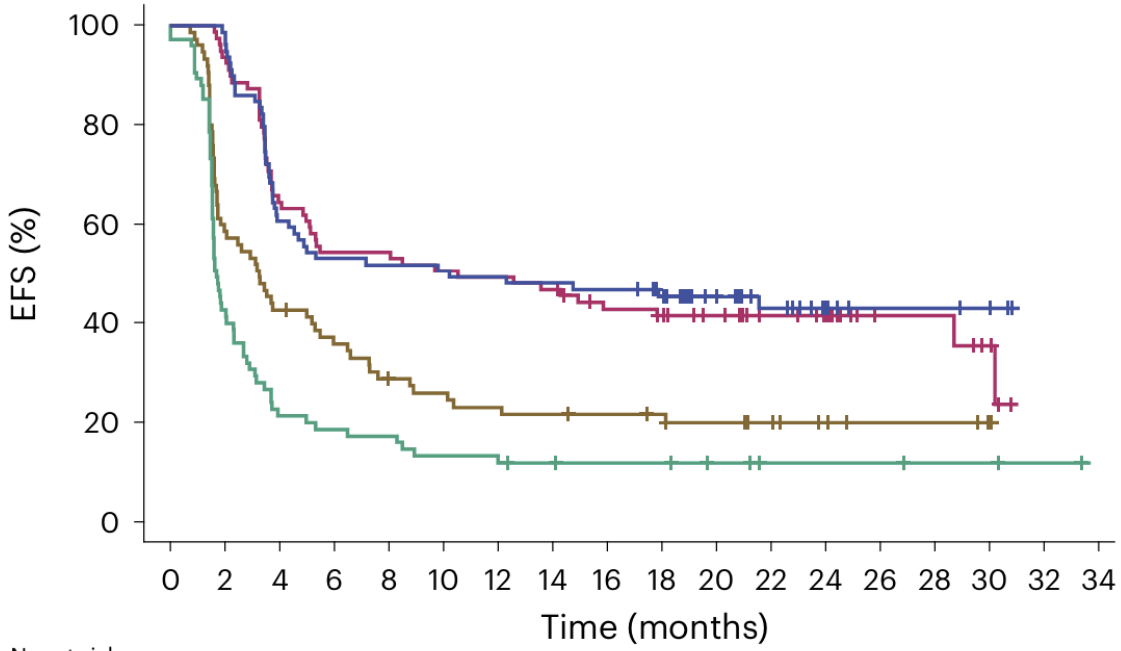
No. at risk																	
Axi-cel, LDH elevated	92	88	55	45	44	43	42	41	39	35	26	21	12	4	4	2	
Axi-cel, LDH normal	78	73	50	46	46	43	42	40	34	31	25	18	14	8	8	4	
SOC, LDH elevated	90	38	24	20	17	11	10	9	8	7	4	1	1	1	1	1	
SOC, LDH normal	78	46	29	25	21	21	19	18	17	17	16	11	8	6	5	2	1	0



Locke F, et al, Nature Medicine 2024.

ZUMA-7: CT scan SPD is not associated with EFS after axi-cel

	SPD high (axi-cel versus SOC)	SPD low (axi-cel versus SOC)	Axi-cel SPD (high versus low)	SOC SPD (high versus low)
Unstratified HR (95% CI)	0.291 (0.198, 0.430)	0.484 (0.329, 0.712)	0.930 (0.617, 1.400)	1.516 (1.065, 2.159)
Unstratified *P* value	4.74×10^{-10}	0.0002	0.7265	0.0210



No. at risk																	
Axi-cel, SPD high	79	78	48	42	41	40	39	38	37	33	22	17	8	5	5	2	
Axi-cel, SPD low	79	74	51	43	43	40	39	37	31	29	25	20	17	7	7	4	
SOC, SPD high	75	32	16	14	13	10	9	8	7	7	5	3	3	3	2	2	1	0
SOC, SPD low	75	44	32	26	20	18	16	15	14	13	11	8	5	3	3	1	

Locke F, et al, Nature Medicine 2024.

ZUMA-7: CT scan SPD is not associated with EFS after axi-cel

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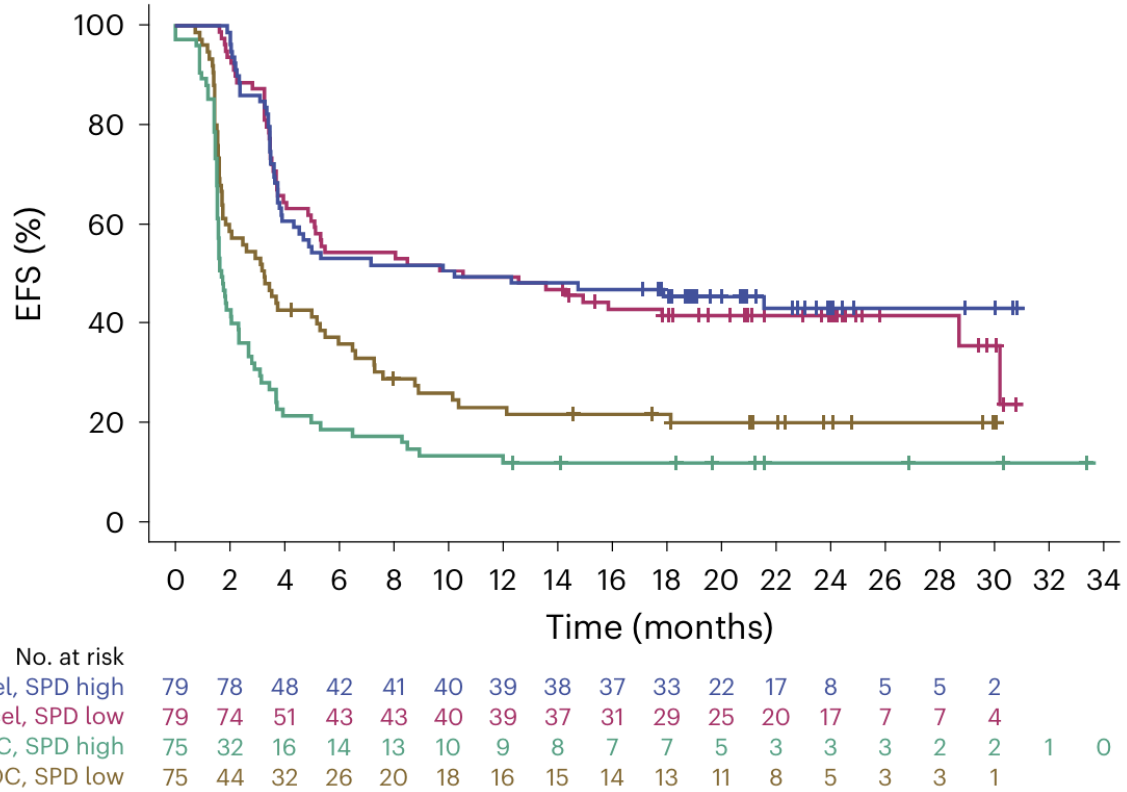
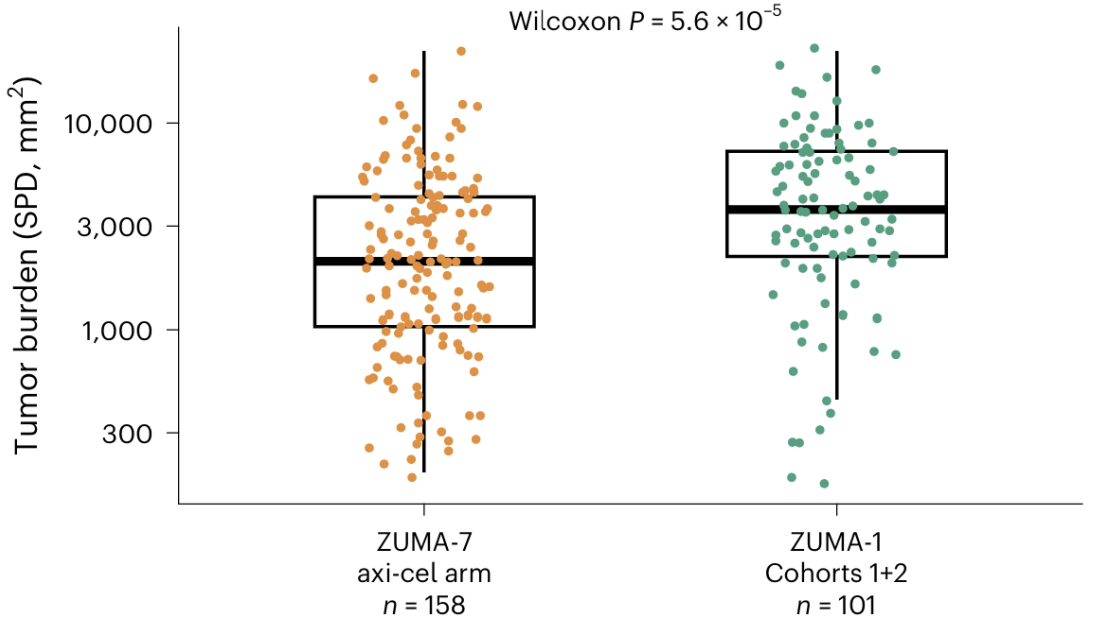
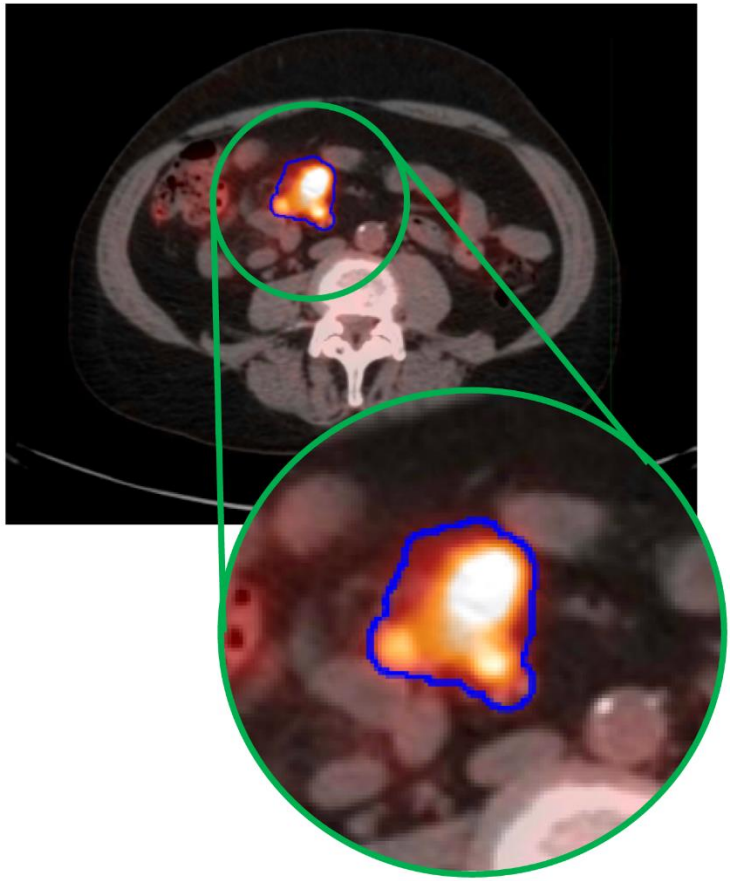
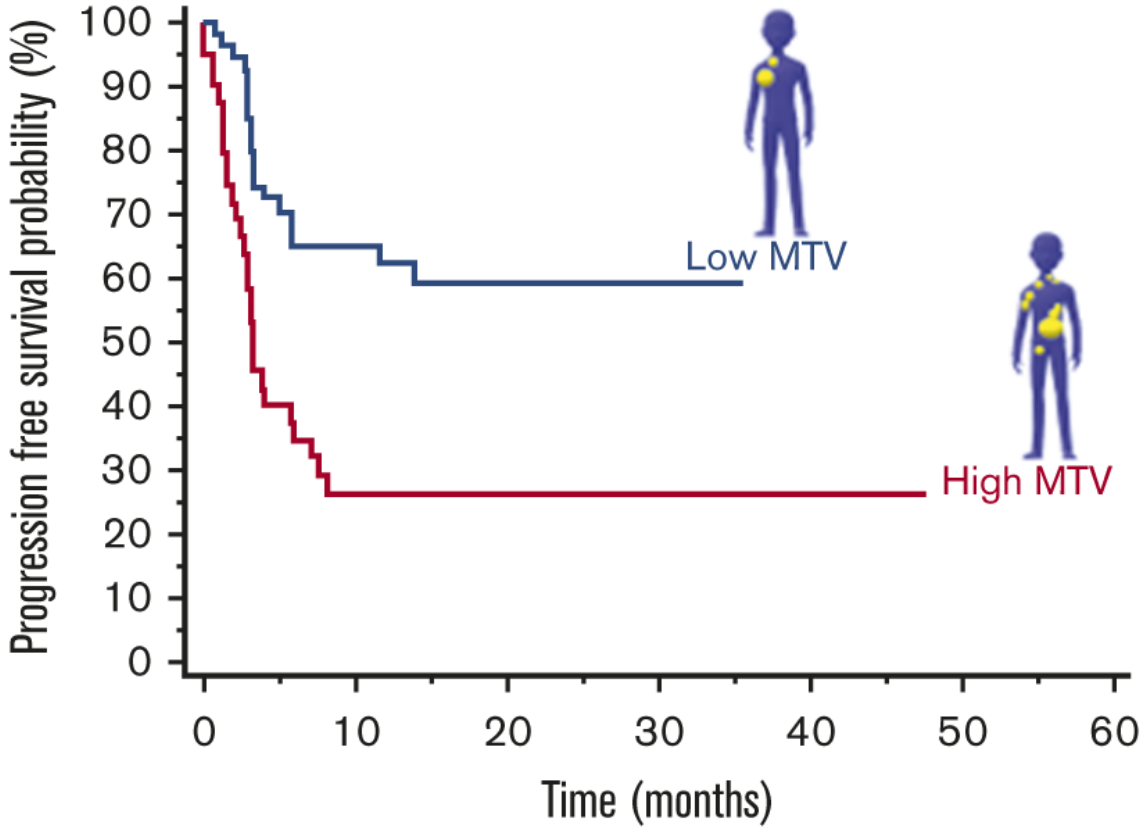




Locke F, et al, Nature Medicine 2024.

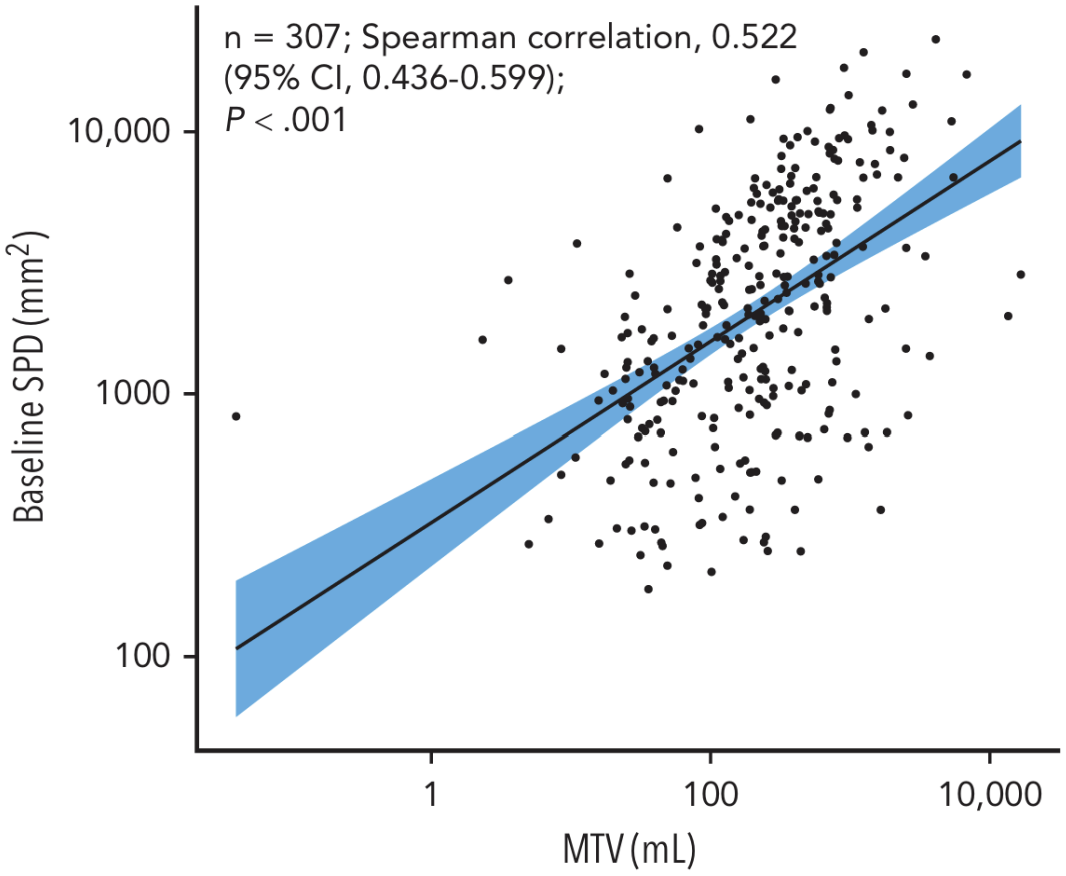
Moffitt RWE 3rd or later line: Higher Metabolic Tumor Volume (MTV) associates with lower durable response rates

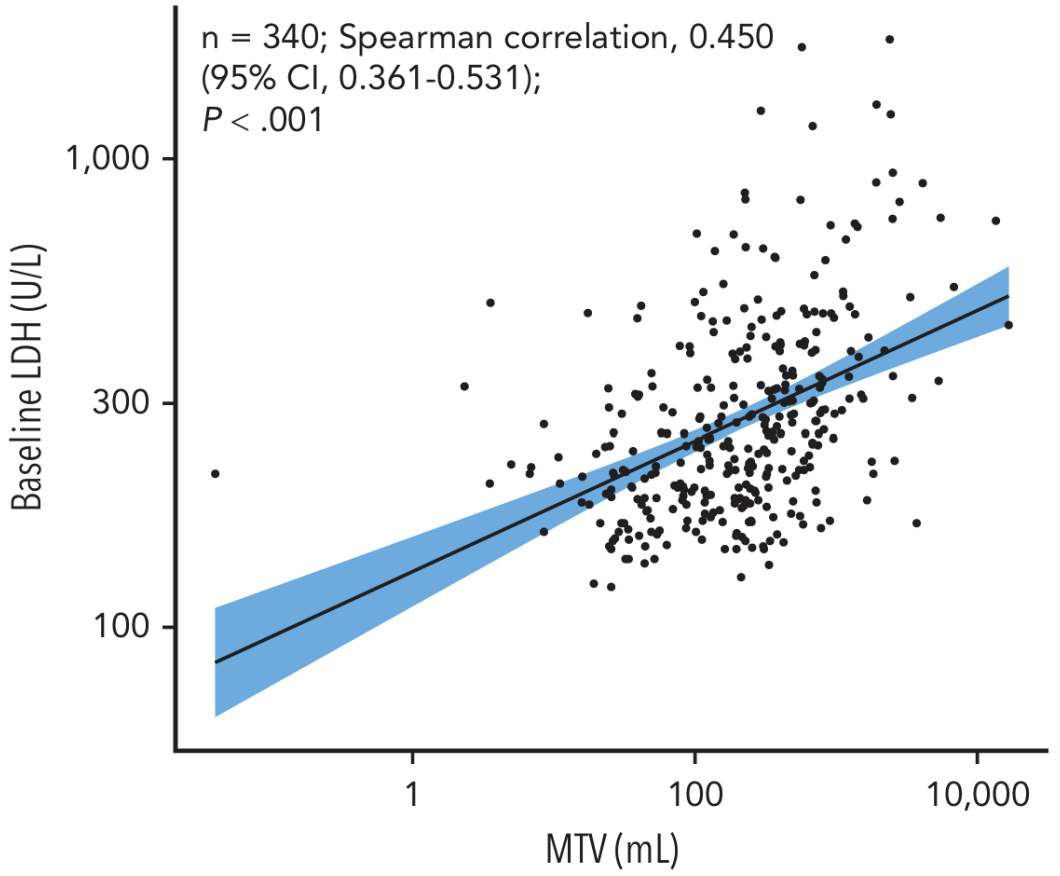




Dean E, et al, Blood Advances 2020

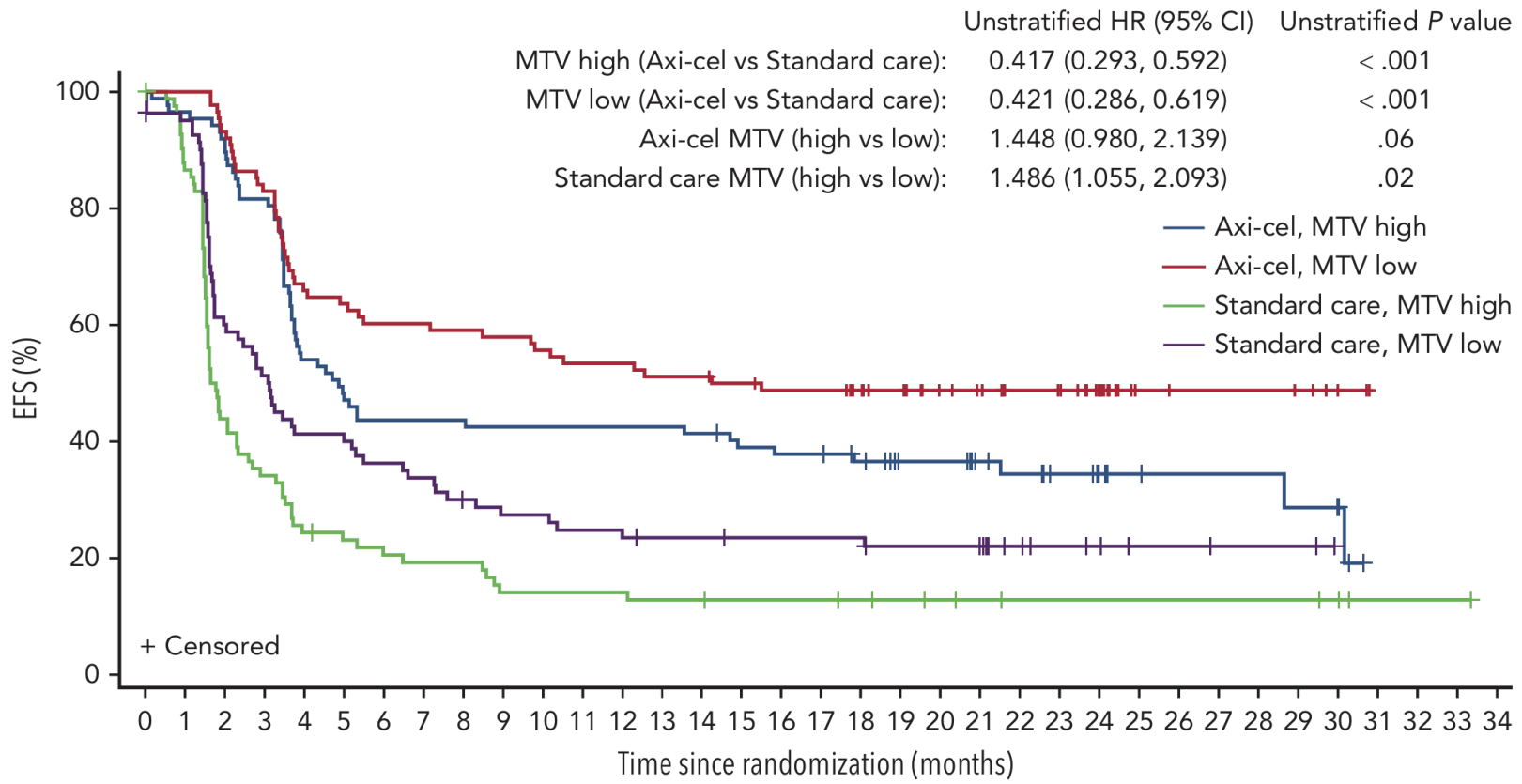
ZUMA-7: MTV provides granular information about tumor burden not captured by CT scan or LDH





Locke F, et al, Blood. 2024.

ZUMA-7: MTV is associated with EFS after axi-cel



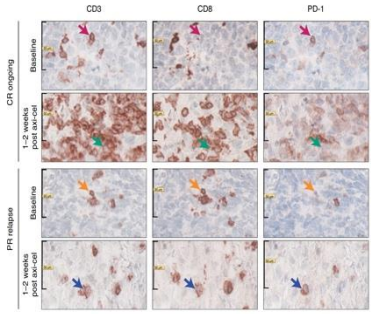
Patients at risk

Axi-cel, MTV high	87	84	80	71	47	41	38	38	38	37	37	37	37	37	36	33	32	32	29	22	22	18	16	13	9	7	6	6	6	5	4	0
Axi-cel, MTV low	88	88	82	73	58	56	53	53	52	51	49	47	47	45	45	43	41	41	38	35	30	28	24	23	17	7	6	6	6	5	2	0
Standard care, MTV high	83	71	36	28	20	18	16	15	15	11	11	11	11	10	10	9	9	9	8	7	6	5	4	4	4	4	4	4	4	4	3	1	1	1	0
Standard care, MTV low	82	76	48	41	33	32	29	27	23	21	21	19	18	17	17	16	16	16	16	14	14	13	8	6	5	3	3	2	2	2	0				

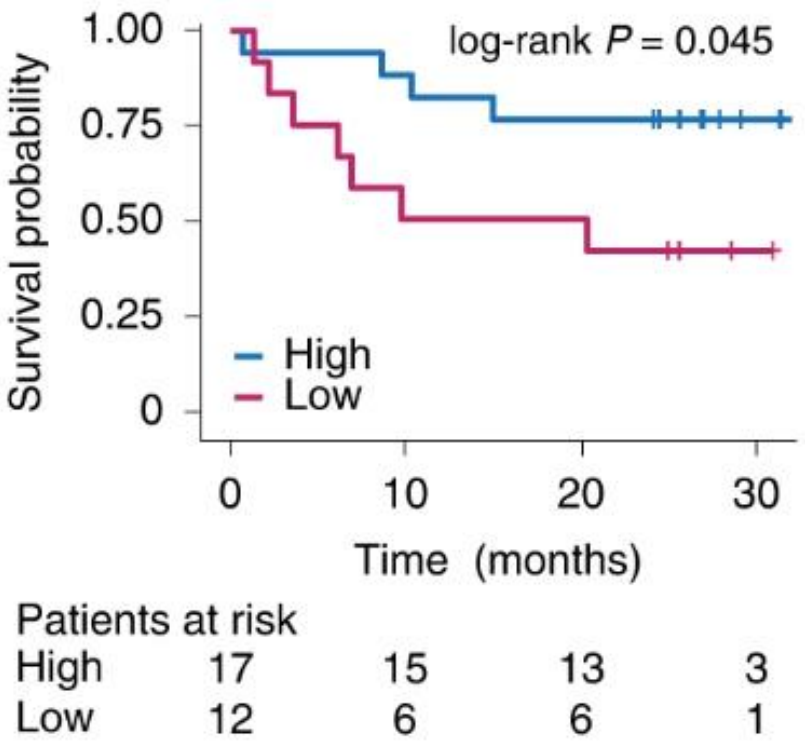
Locke F, et al, Blood. 2024.

Tumor features and their impact on CAR-T outcomes in 2nd line (Tumor immune contexture, CD19, myeloid cells, and SII)

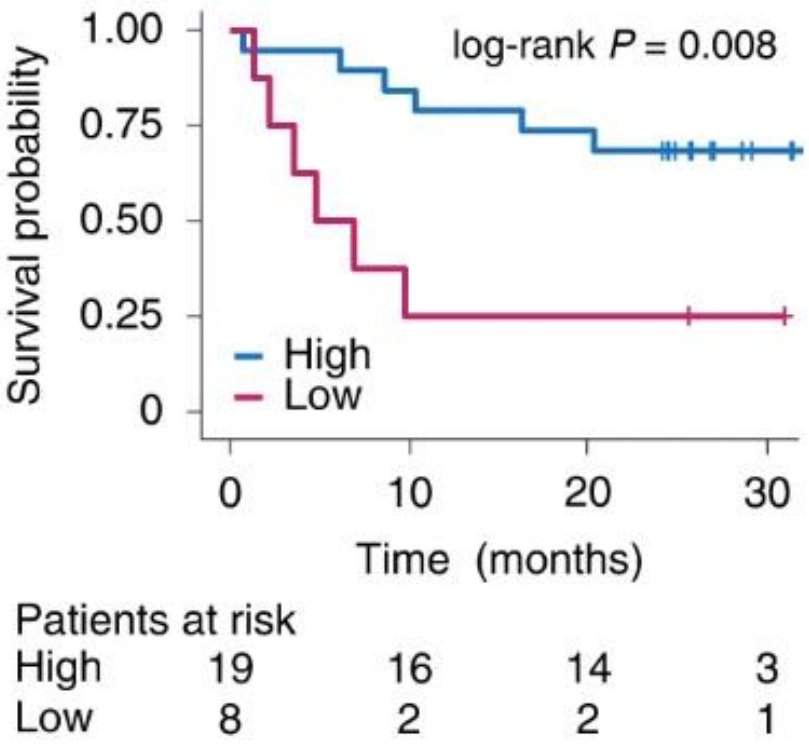
ZUMA-1: Survival after CAR T cell therapy is higher in patients with pre-treatment LBCL exhibiting T cell immune infiltration

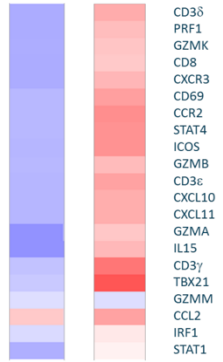


Immunoscore
(IHC derived Immune Contexture)



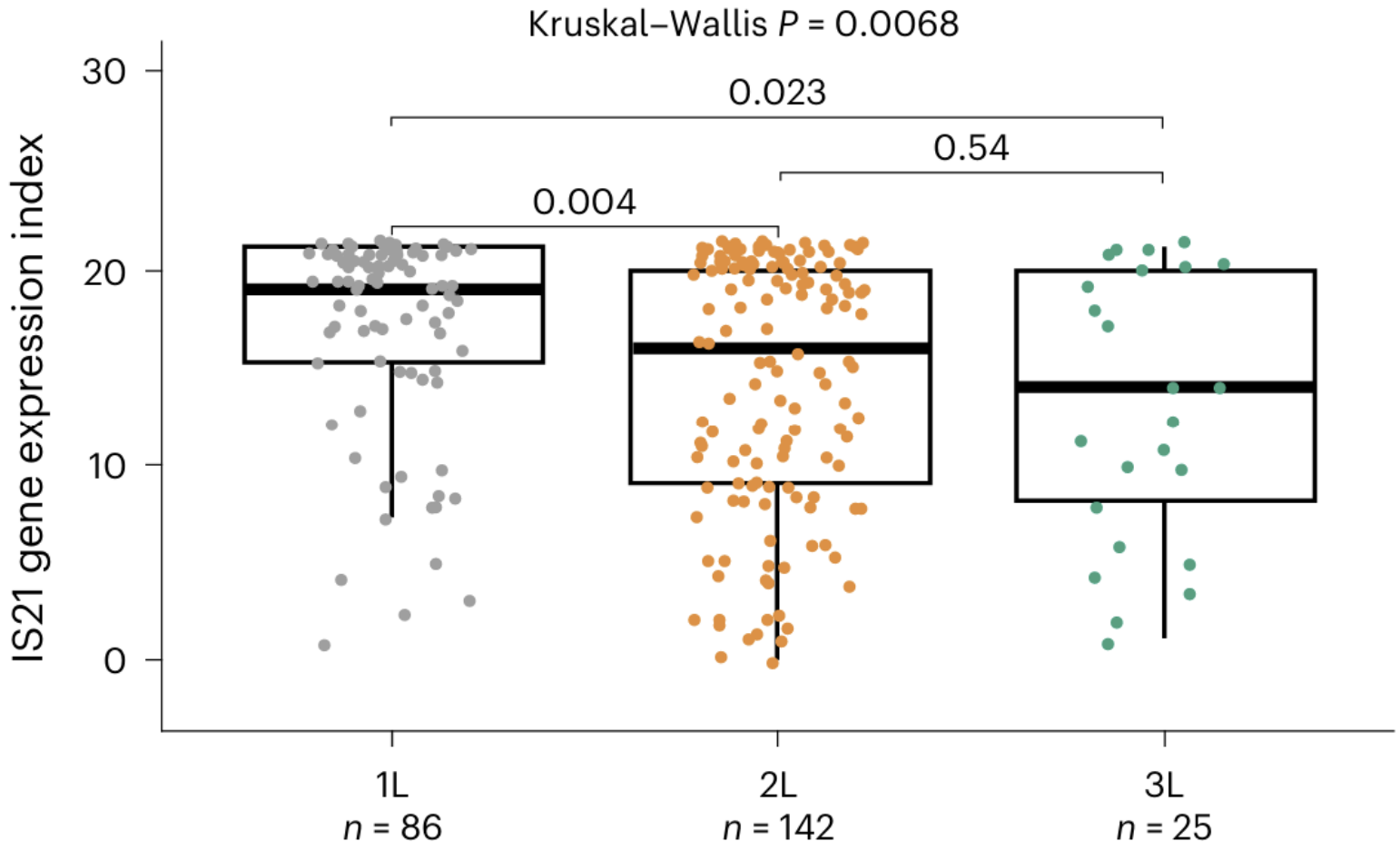
Immunosign 21
(Nanostring derived Immune Contexture)





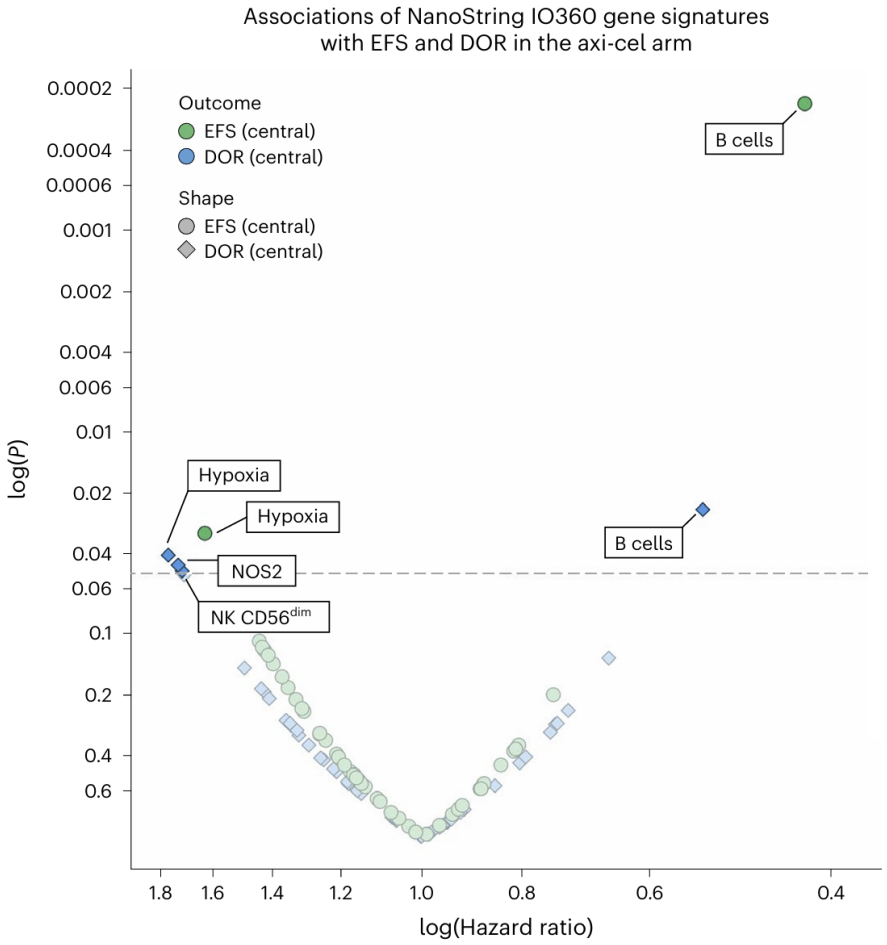
Scholler N, et al, Nature Medicine 2022.

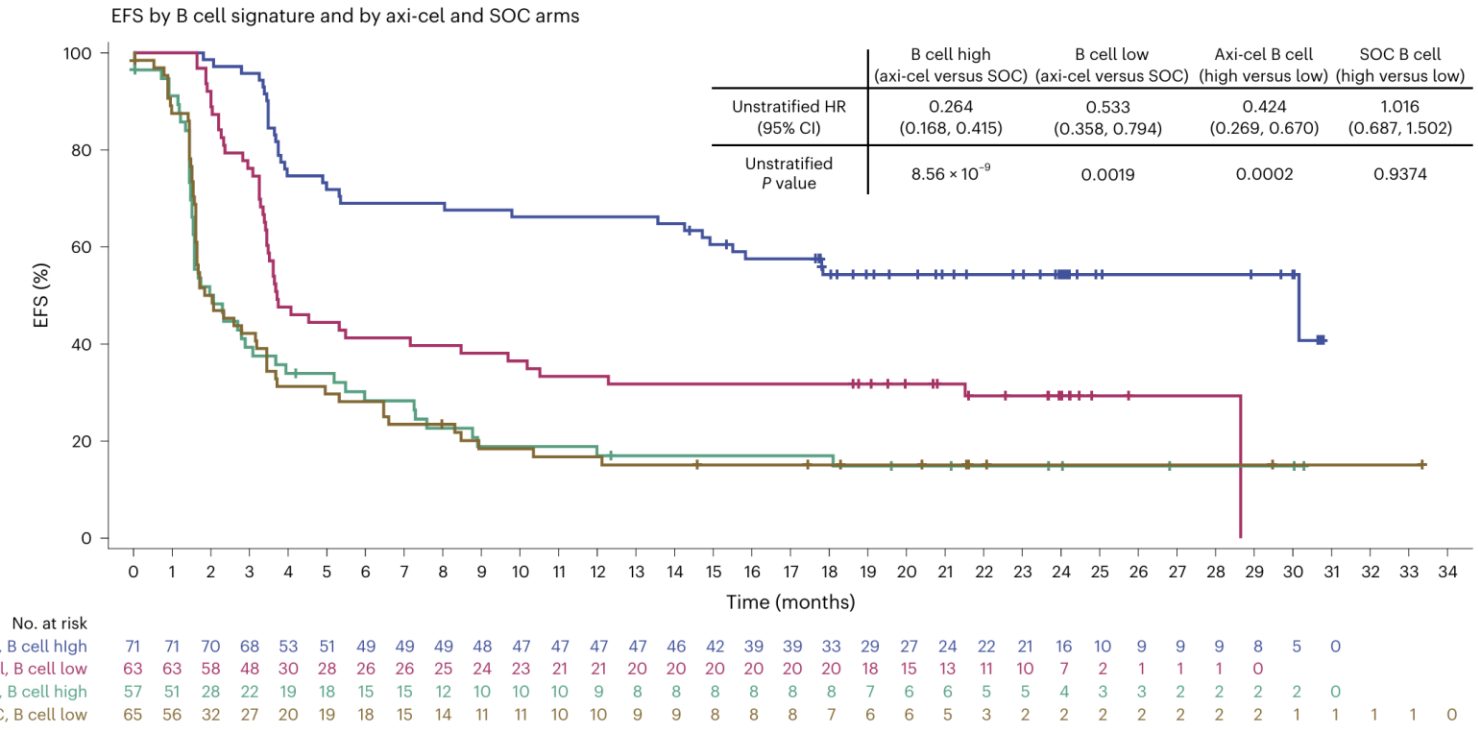
LBCL immune contexture is different depending upon the number of prior lines of therapy



Locke F, et al, Nature Medicine 2024.

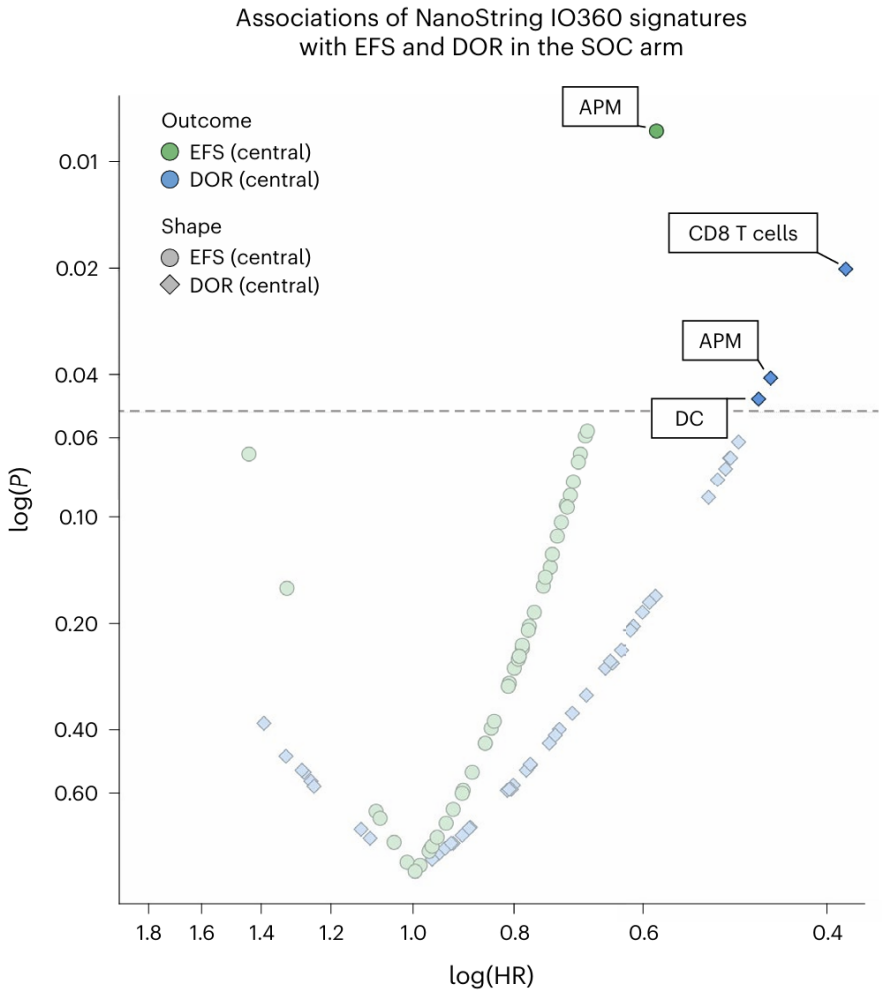
ZUMA-7: LBCL biopsies prior to axi-cel treatment demonstrate that higher B cell signature (Nanostring IO360) expression associates with longer EFS and DOR

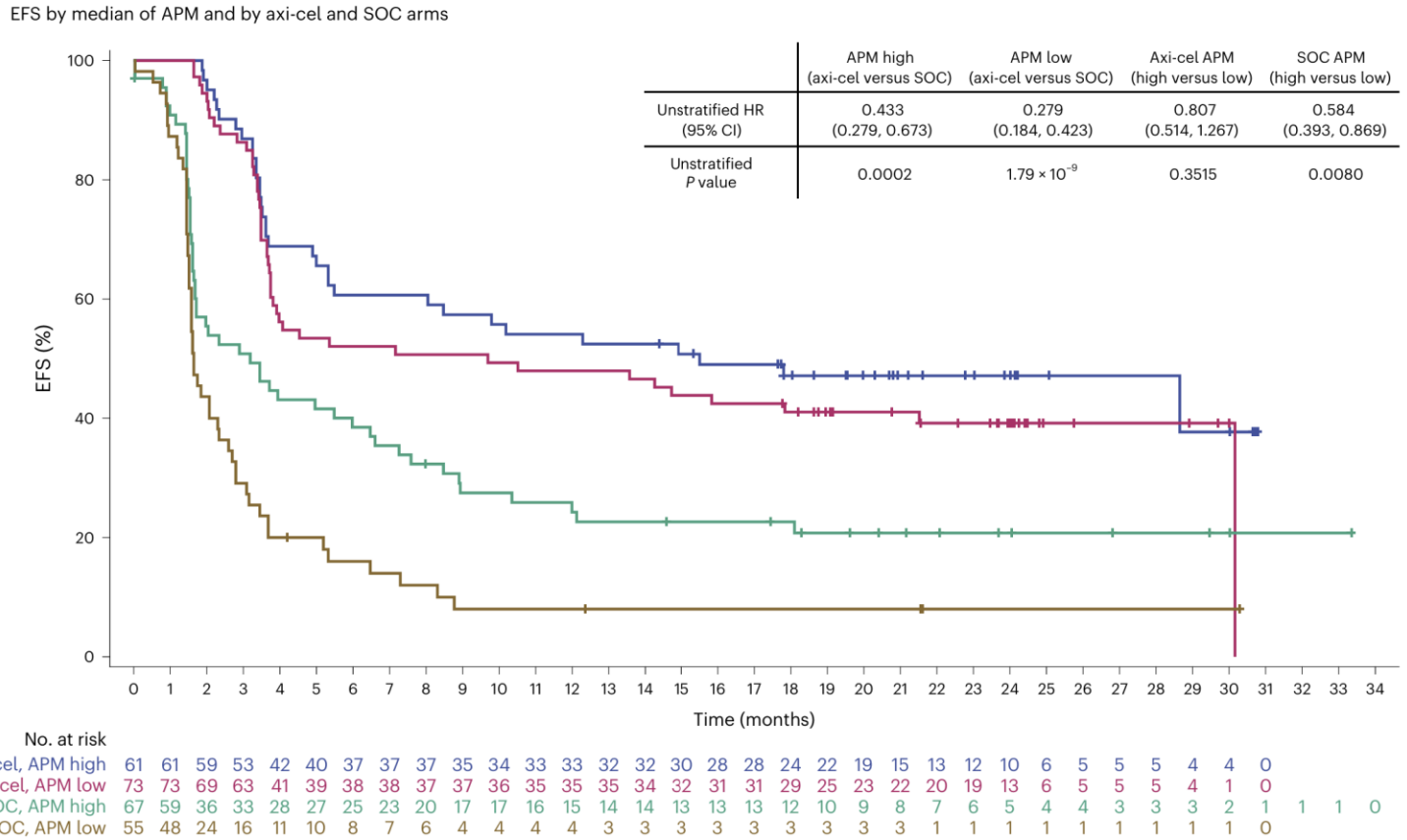




Locke F, et al, Nature Medicine 2024.

ZUMA-7: LBCL biopsies prior to SOC treatment demonstrate that higher Antigen Presentation Machinery signature expression associates with longer EFS and DOR

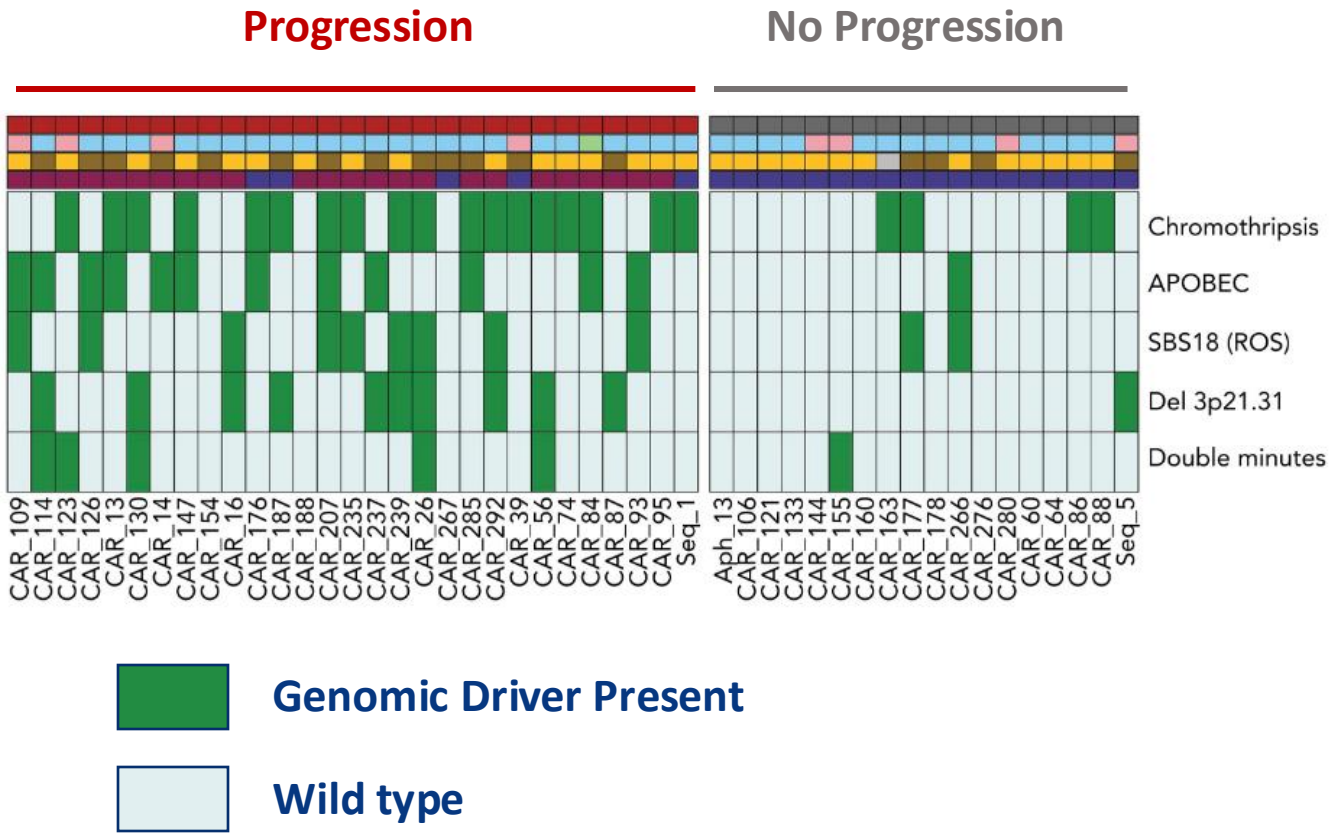


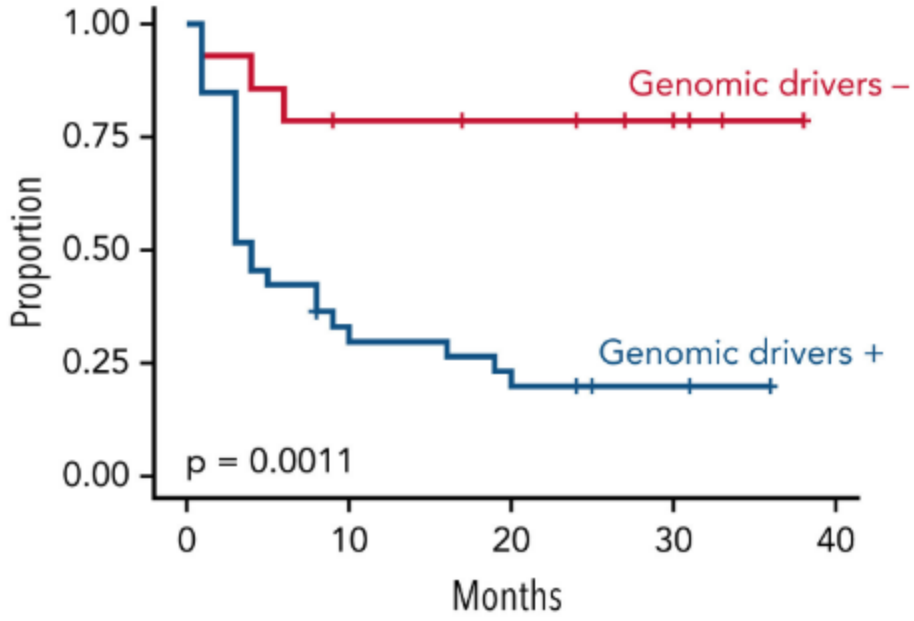


	APM high (axi-cel versus SOC)	APM low (axi-cel versus SOC)	Axi-cel APM (high versus low)	SOC APM (high versus low)
Unstratified HR (95% CI)	0.433 (0.279, 0.673)	0.279 (0.184, 0.423)	0.807 (0.514, 1.267)	0.584 (0.393, 0.869)
Unstratified *P* value	0.0002	1.79×10^{-9}	0.3515	0.0080

Locke F, et al, Nature Medicine 2024.

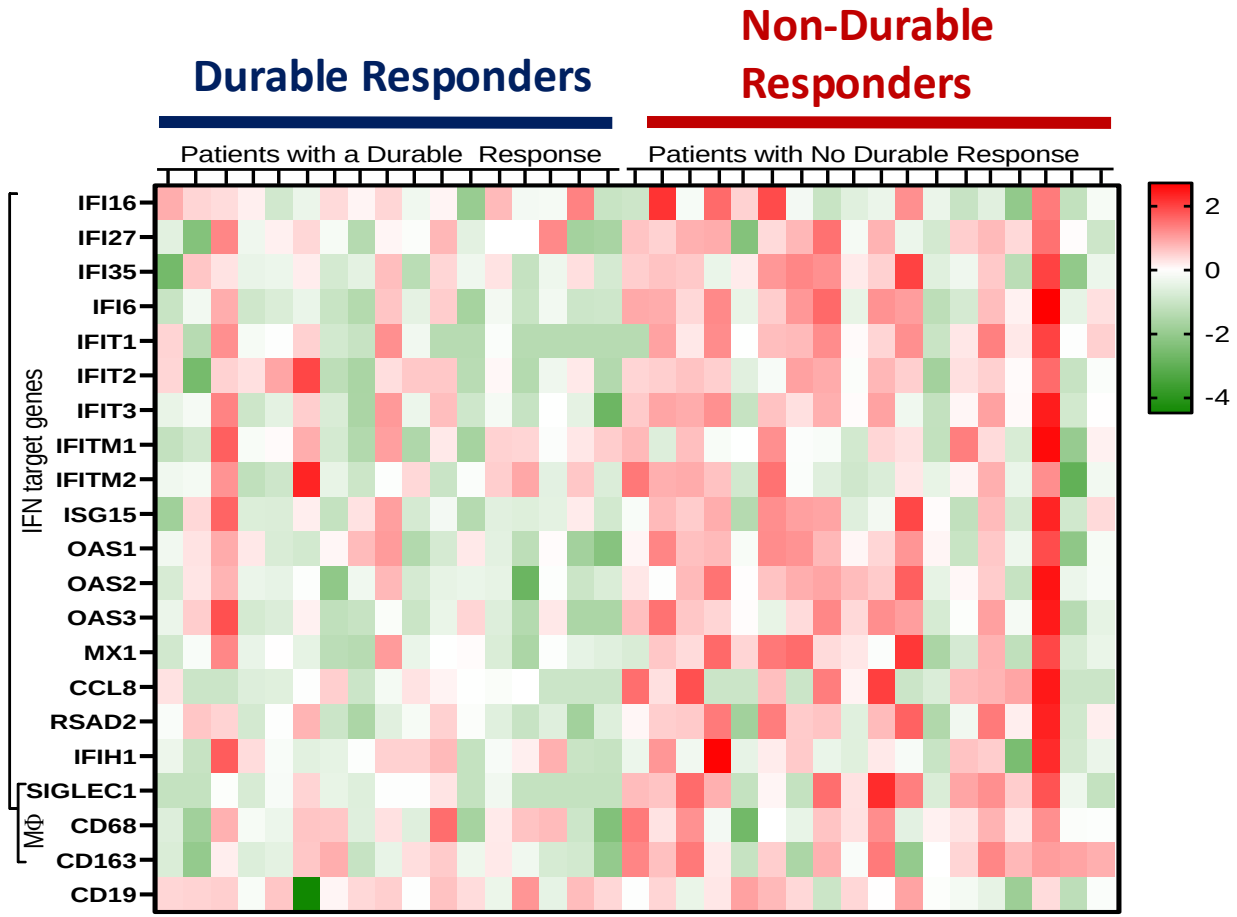
Moffitt/Miami: Genomic Complexity, identified by pre-treatment LBCL tumor Whole Genome Sequencing, is associated with worse CAR T cell efficacy

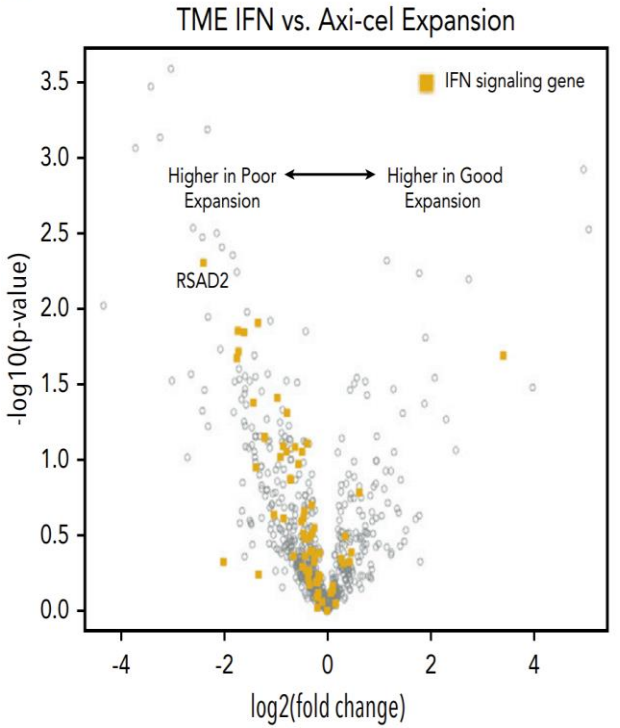




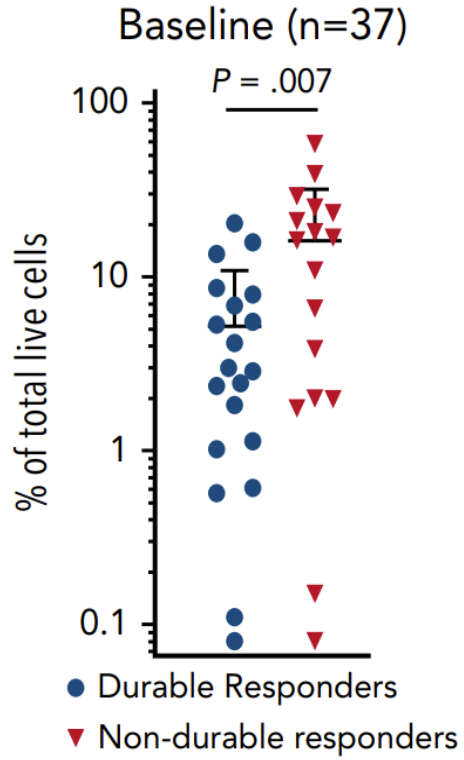
Jain M, Zicchedu B, et al, Blood 2022.

Moffitt RWE: Tumor IFN signaling and suppressive myeloid cells associate with poor CAR-T expansion and a failure to achieve durable response following axi-cel





M-MDSC numbers in blood before CAR-T



Jain M , Zhao H, et al. Blood 2021.

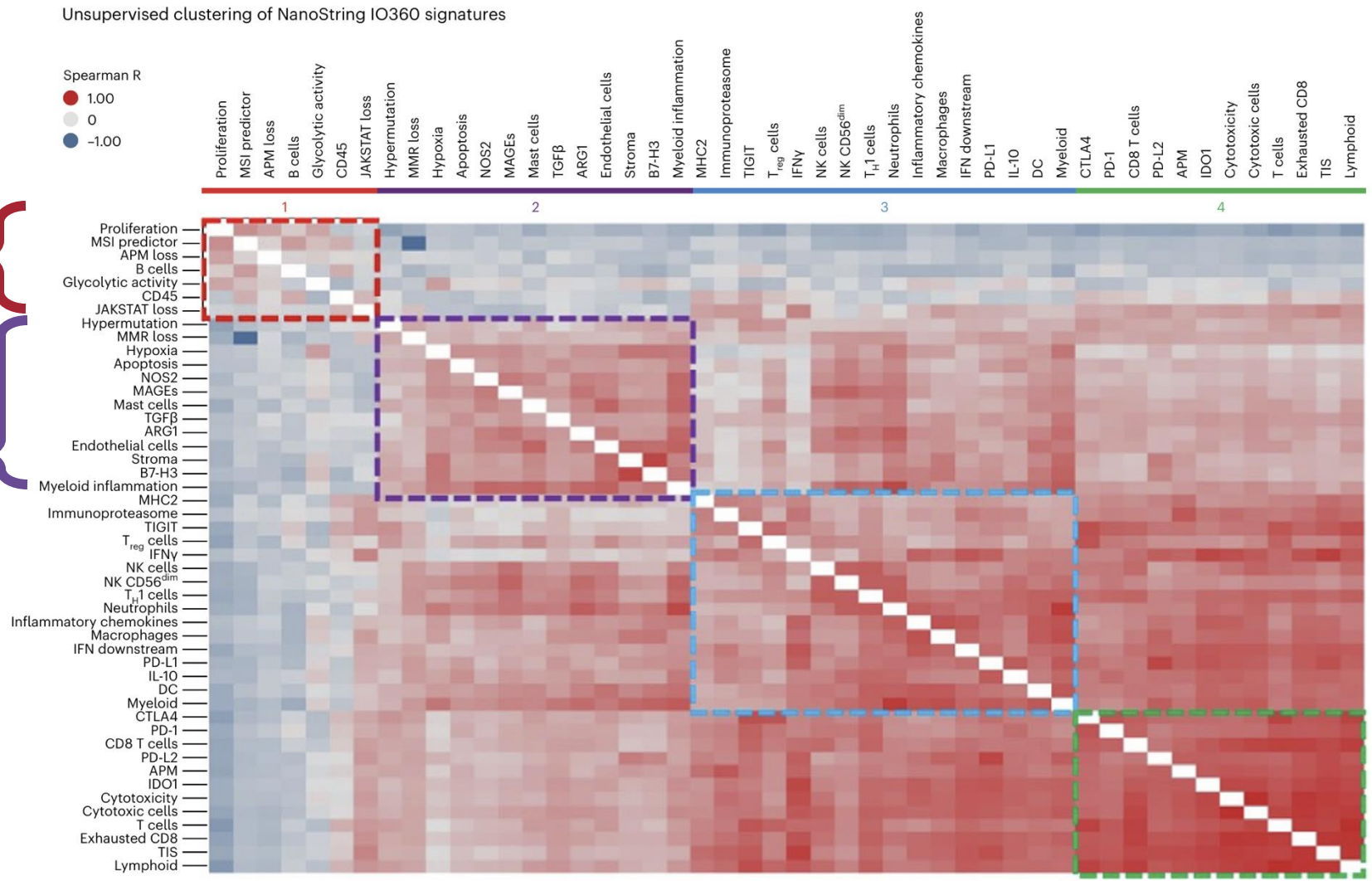
ZUMA-7: Unsupervised clustering of pre-treatment LBCL gene expression pathways (Nanostring IO360) identified a B cell Proliferative Index (BPI) and a Stromal Immunosuppressive Index (SII)

BPI

Nanostring 360 gene signatures making up BPI

Nanostring 360 gene signatures making up SII

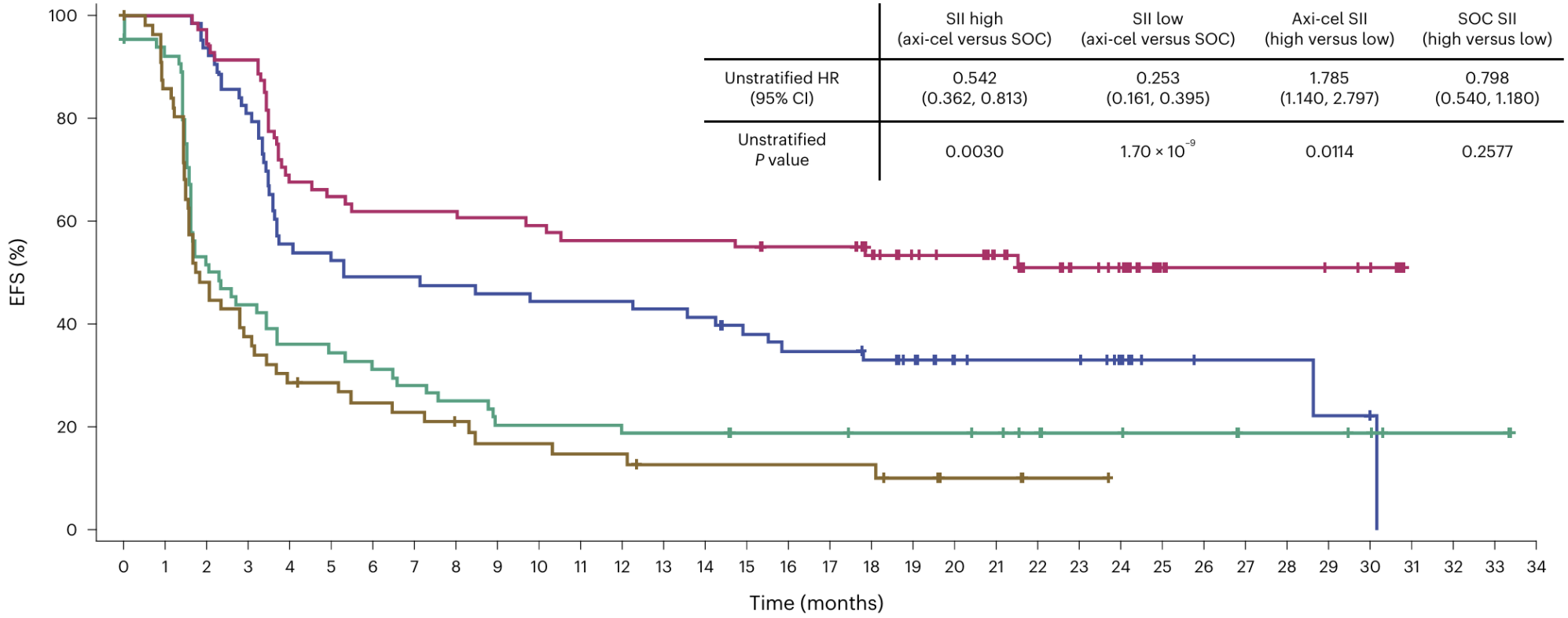
SII



Locke F, et al, Nature Medicine 2024.

ZUMA-7: LBCL Nanostring gene set derived SII gene score associates with EFS after axi-cel treatment

b EFS by median of SII and by axi-cel and SOC arms



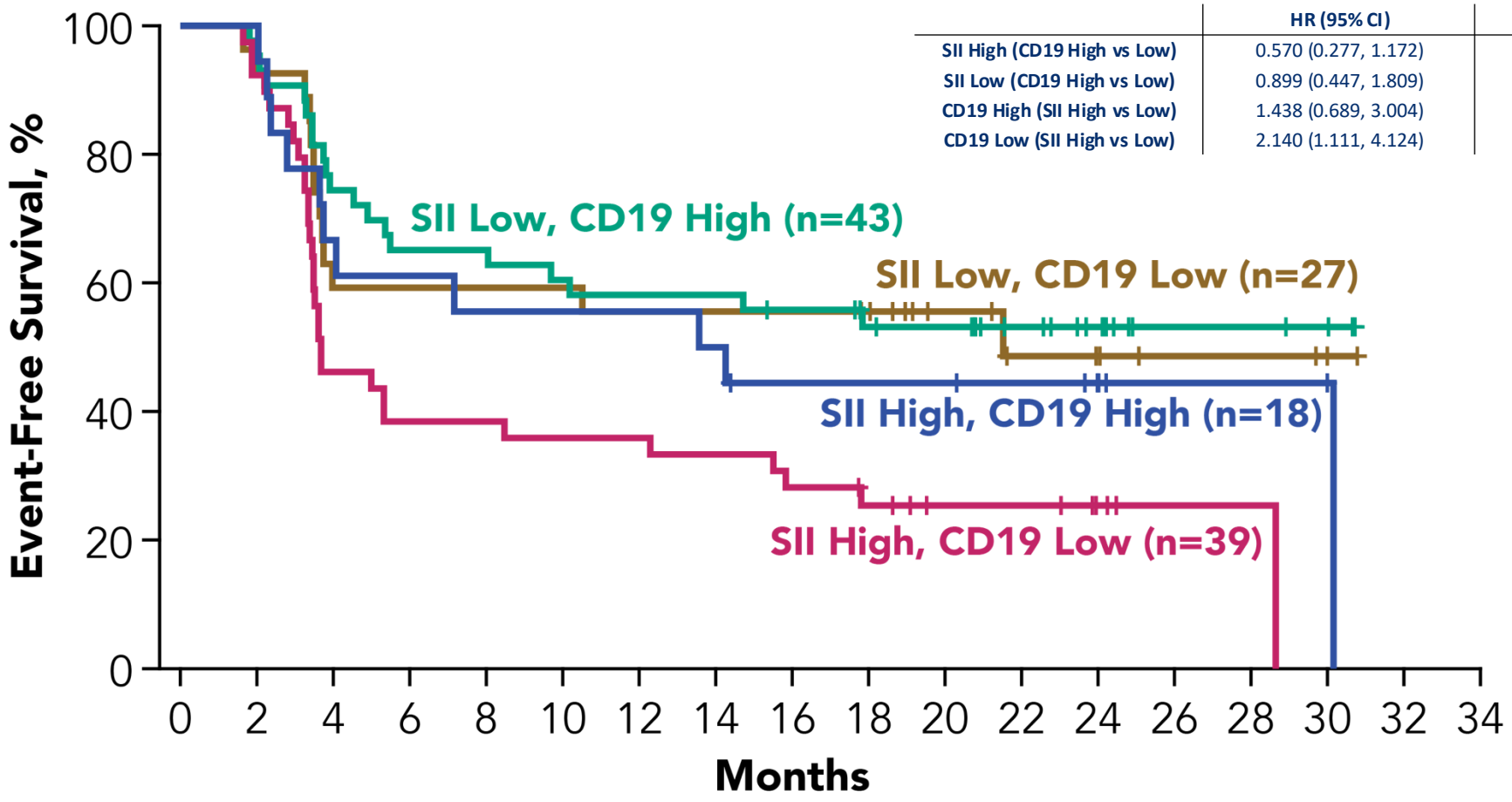
	SII high (axi-cel versus SOC)	SII low (axi-cel versus SOC)	Axi-cel SII (high versus low)	SOC SII (high versus low)
Unstratified HR (95% CI)	0.542 (0.362, 0.813)	0.253 (0.161, 0.395)	1.785 (1.140, 2.797)	0.798 (0.540, 1.180)
Unstratified *P* value	0.0030	1.70×10^{-9}	0.0114	0.2577

No. at risk

Axi-cel, SII high	63	63	59	51	35	33	31	31	30	29	28	28	28	27	26	23	21	21	19	17	14	13	13	13	8	4	3	3	3	2	1	0
Axi-cel, SII low	71	71	69	65	48	46	44	44	44	43	42	40	40	40	40	39	38	38	34	30	28	24	20	18	15	8	7	7	7	6	4	0
SOC, SII high	65	59	33	28	23	22	20	18	16	13	13	13	12	12	12	11	11	11	10	10	10	9	7	6	6	5	5	4	4	4	3	1	1	1	0
SOC, SII low	57	48	27	21	16	15	13	12	10	8	8	7	7	5	5	5	5	5	5	3	2	2	1	1	0									

Locke F, et al, Nature Medicine 2024.

ZUMA-7: Unfavorable outcomes are associated with the presence of both low CD19 expression and high SII scores



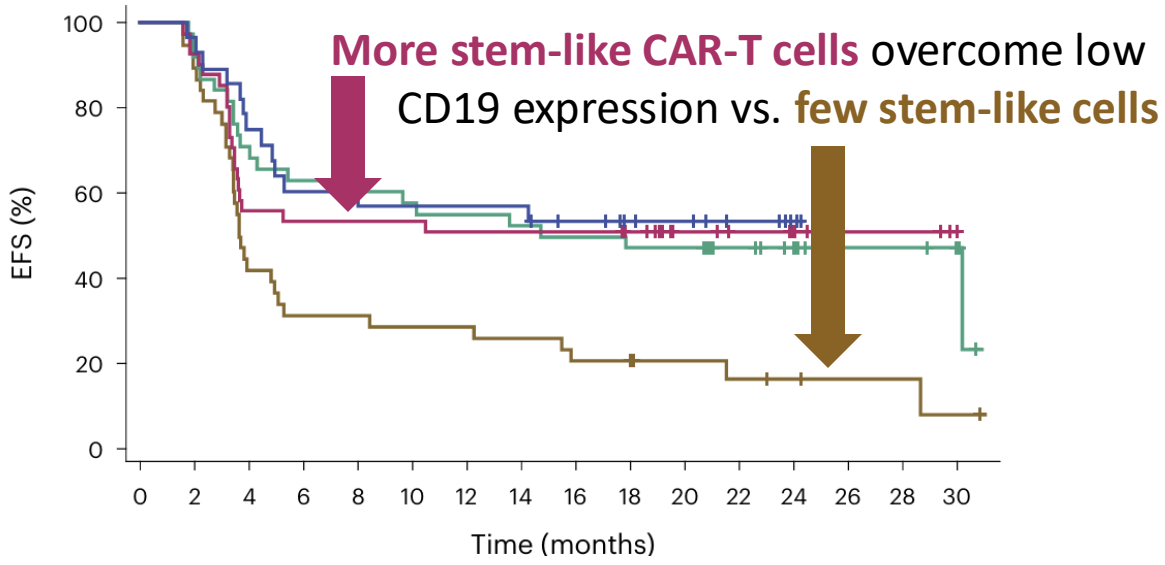
	HR (95% CI)	*P* value
SII High (CD19 High vs Low)	0.570 (0.277, 1.172)	.1264
SII Low (CD19 High vs Low)	0.899 (0.447, 1.809)	.7660
CD19 High (SII High vs Low)	1.438 (0.689, 3.004)	.3334
CD19 Low (SII High vs Low)	2.140 (1.111, 4.124)	.0230

Locke F, et al, Nature Medicine 2024.

ZUMA-7: Both low CD19 expression and high SII scores may be overcome by a more favorable CAR-T product

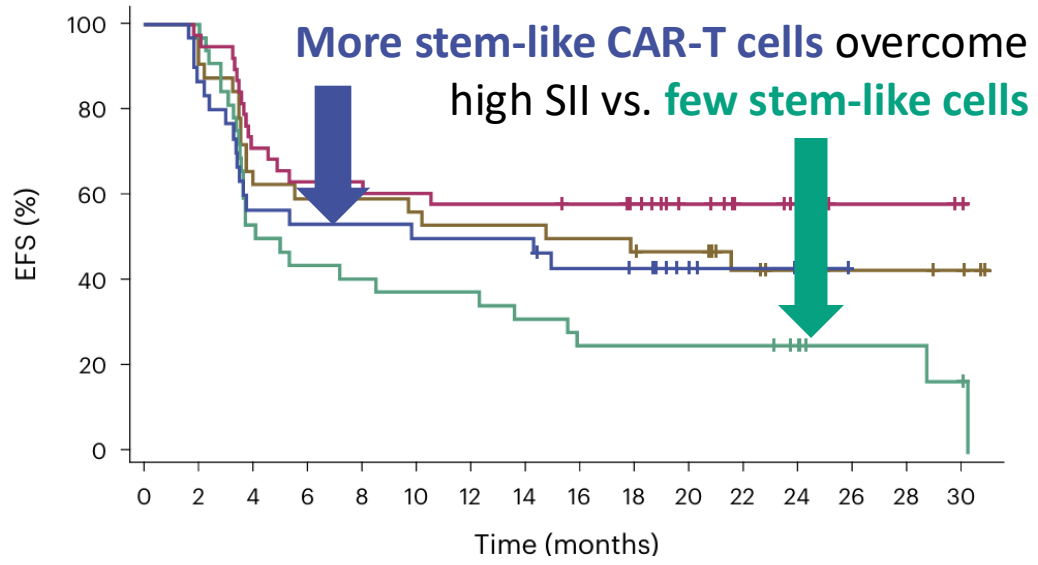
EFS in axi-cel arm by median of $CCR7^{+}CD45RA^{+}$ T cells axi-cel product and baseline CD19 protein (H-Score as assessed by IHC) In tumor

	CD19 high ($CCR7^{+}CD45RA^{+}$ T cells high versus low)	CD19 low ($CCR7^{+}CD45RA^{+}$ T cells high versus low)
Unstratified HR (95% CI)	0.856 (0.425, 0.721)	0.478 (0.272, 0.837)
Unstratified *P* value	0.6619	0.0099



EFS in axi-cel arm by median of $CCR7^{+}CD45RA^{+}$ T cells axi-cel product and median of SII In tumor

	SII high ($CCR7^{+}CD45RA^{+}$ high versus low)	SII low ($CCR7^{+}CD45RA^{+}$ high versus low)
Unstratified HR (95% CI)	0.724 (0.388, 1.350)	0.709 (0.362, 1.391)
Unstratified *P* value	0.3096	0.3177



Locke F, et al, Nature Medicine 2024.

Factors Influencing Efficacy of CAR-T in DLBCL

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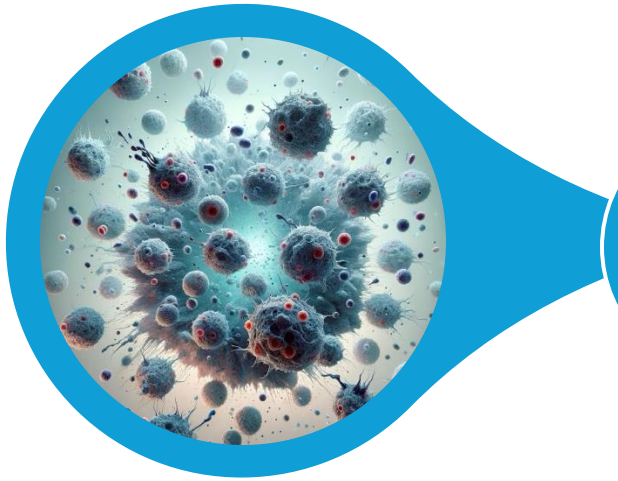

CAR-T product

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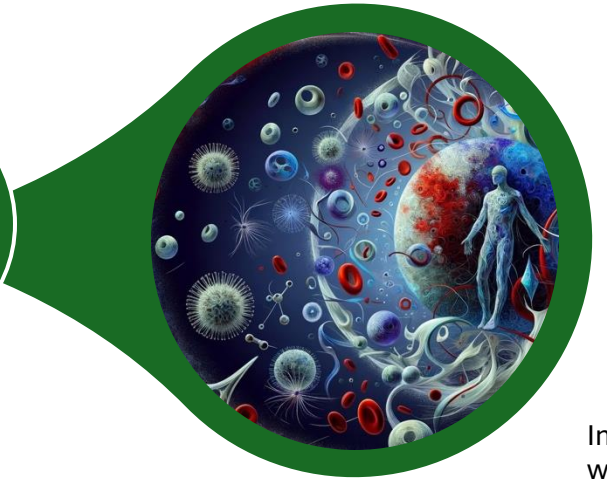
Systemic Immunity



Images created with ChatGPT

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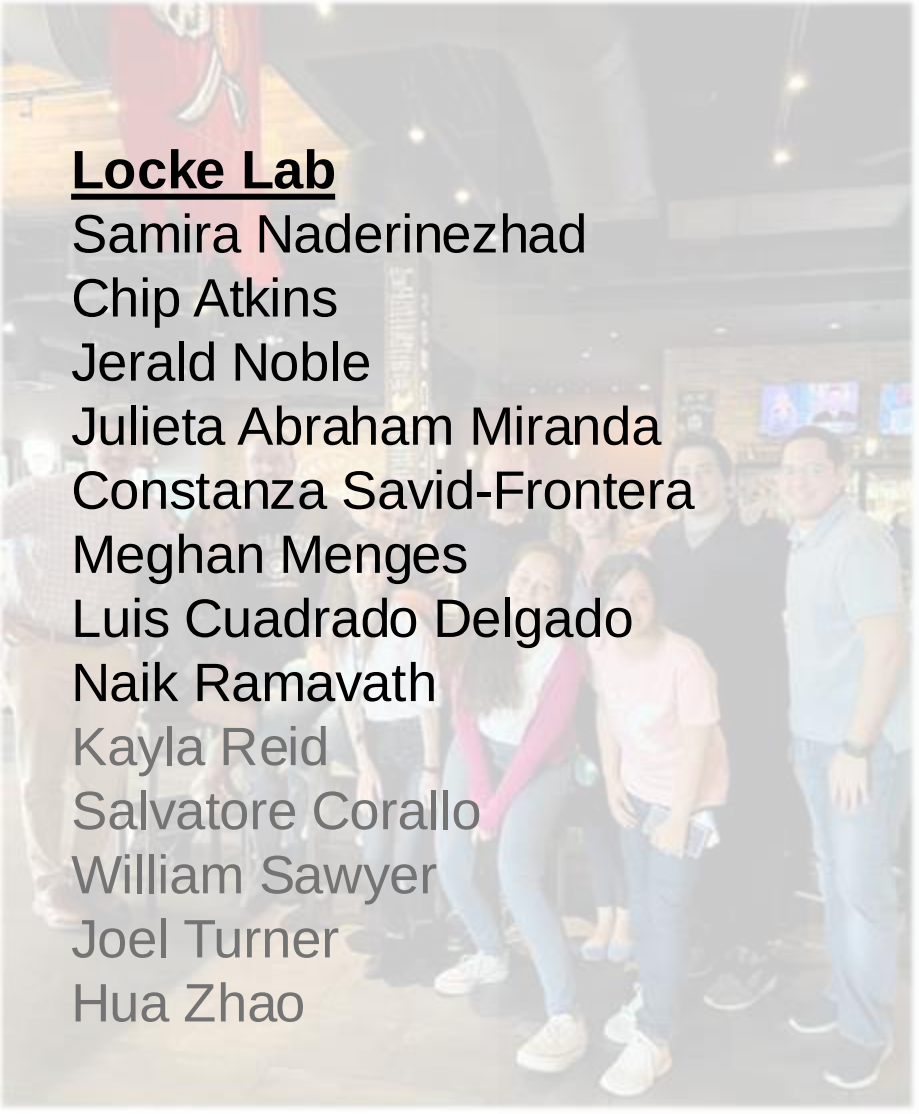

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Thank you!

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