Patient selection, bridging therapy and lymphodepletion

Michael D. Jain

4th Meeting on Innovative Immunotherapies for Lymphoid Malignancies

23 January 2026, Milan, Italy

MOFFITT CANCER CENTER

Conflicts of Interest

I have received funds for scientific advisory or consulting from:

- Kite/Gilead, J&J, Arcellx

I am the PI of investigator-initiated studies funded to my institution by:

- Kite/Gilead, Incyte, Lilly, BMS

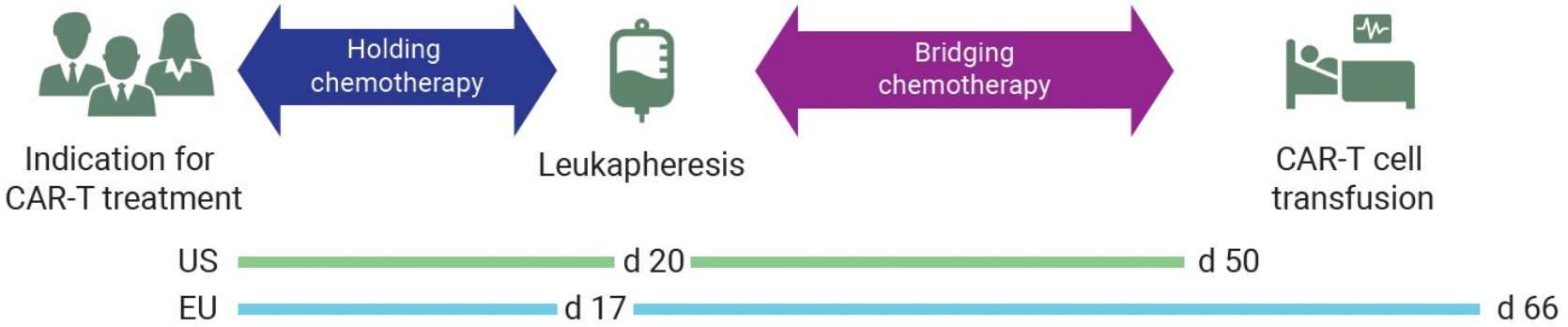
I have received honoraria for educational activities from:

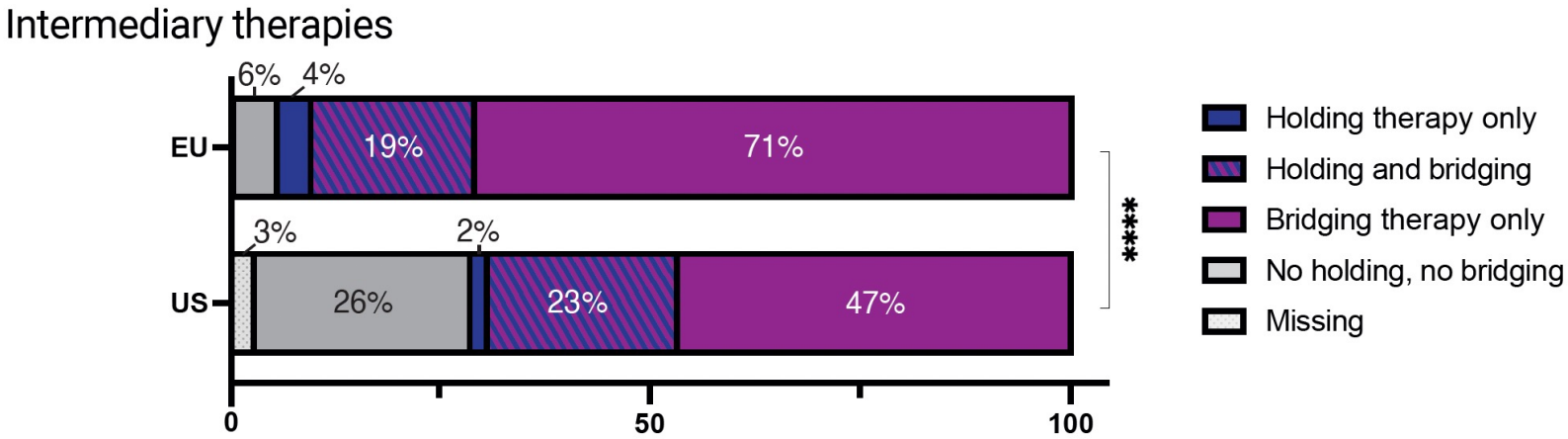
- PRIME Education, OncLive, Curio Science, Decera

Outline

1. Intermediary Therapies: Holding and Bridging
2. Systemic inflammation
3. Radiation bridging therapy
4. Lymphodepletion

Intermediary therapies before CAR T: Disease-Holding and Bridging

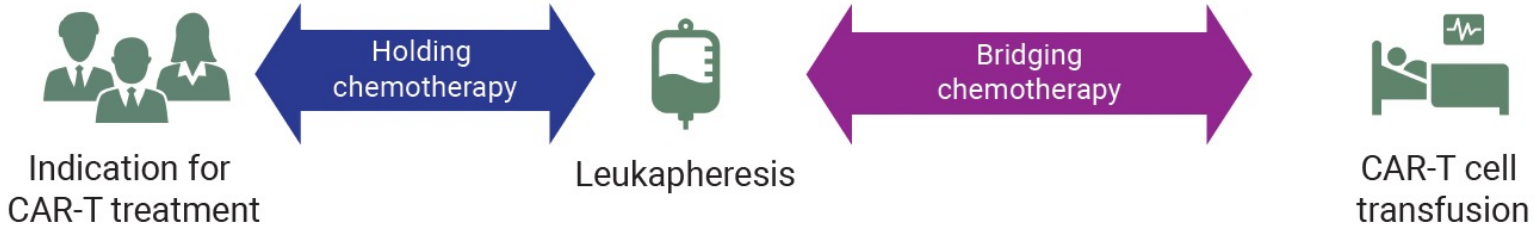




Bucklein et al. Hemasphere 2023

Intermediary therapies before CAR T: Disease-Holding and Bridging

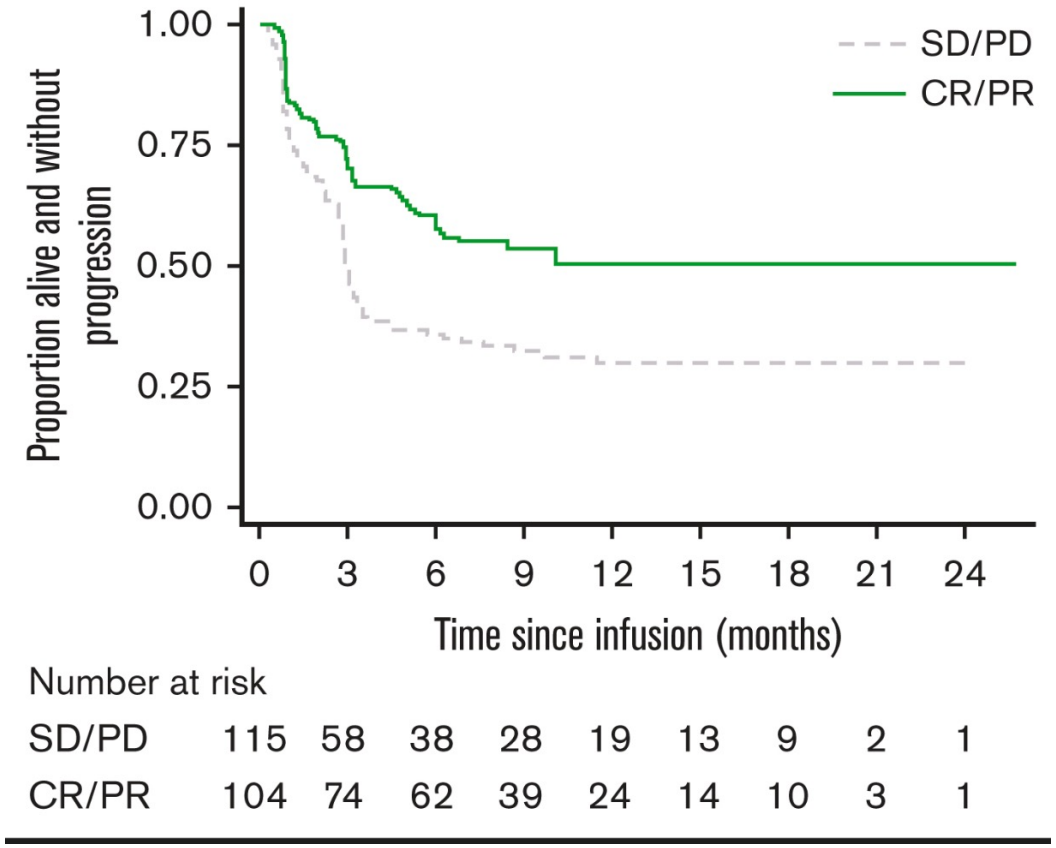
N=152 patients with 2L therapy (n=143 axi-cel; n=11 liso-cel)
Moffitt, Stanford, City of Hope, Miami, Kansas, Maryland

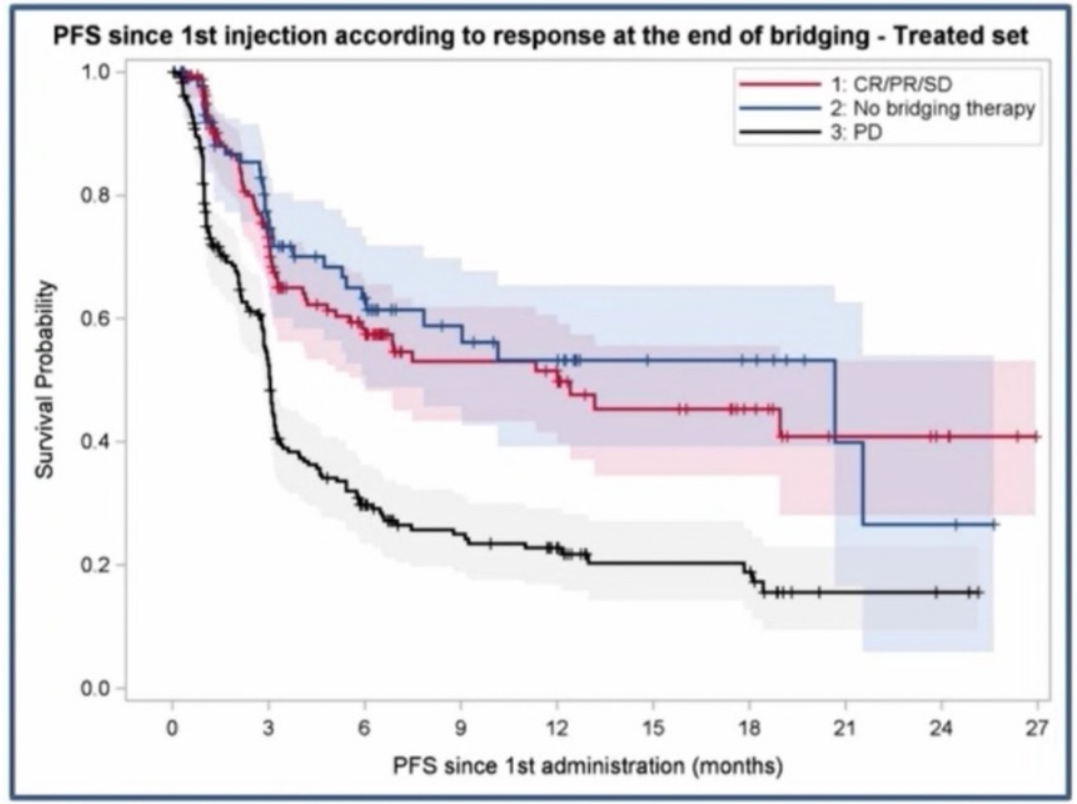


Holding	Bridging	N	%
No	No	32	21%
No	Yes	65	43%
Yes	No	14	9%
Yes	Yes	41	27%

Dahiya et al. ASH 2023

Responding to intermediary therapies is good in lymphoma

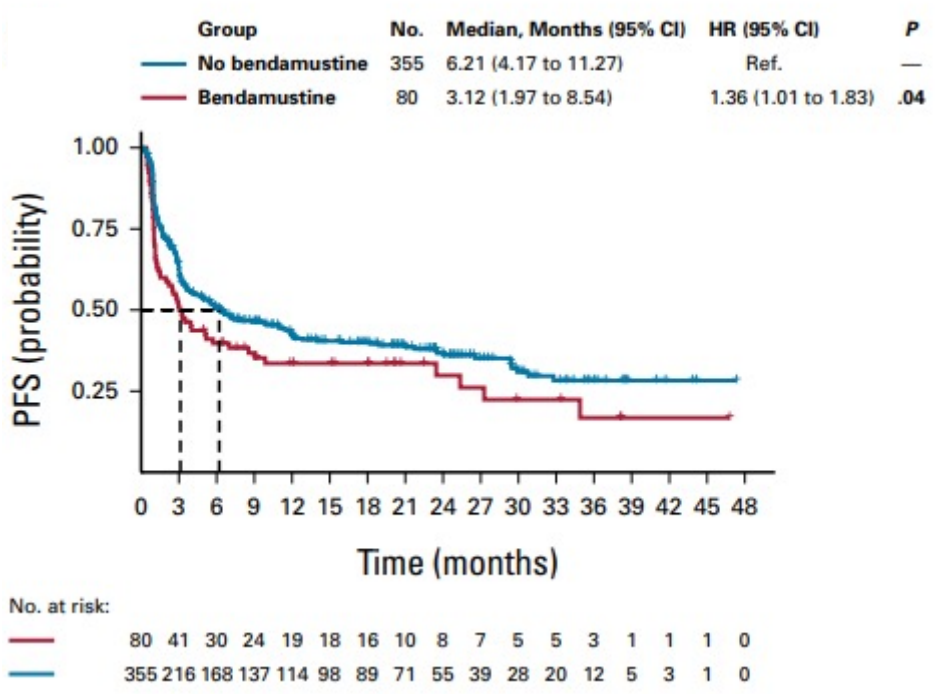




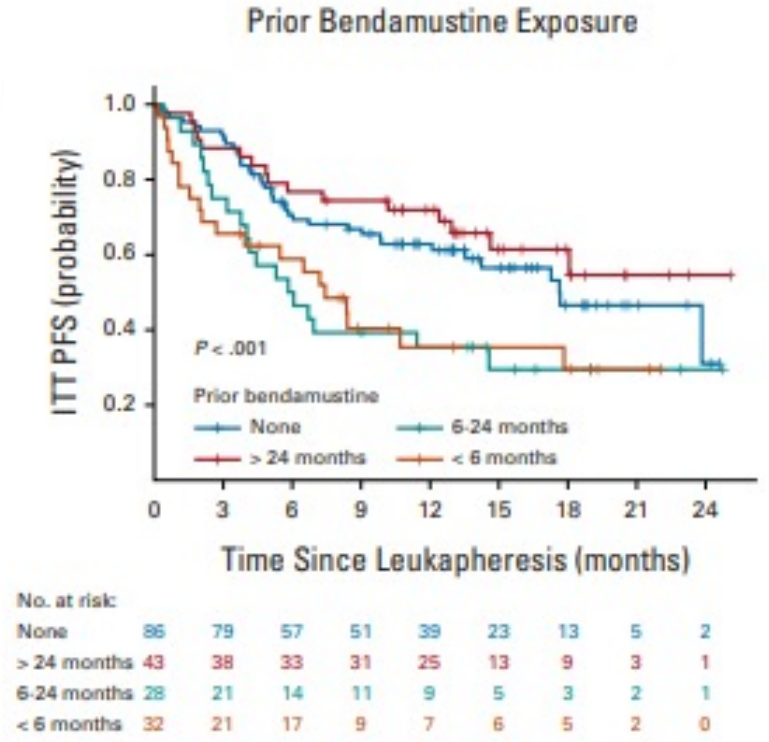
Roddie et al. Blood Adv. 2023 – UK experience axi-cel/tisa-cel

DESCAR-T registry Le Gouill et al. EHA 2021

Caution: bendamustine before apheresis is bad



Iacoboni et al. J. Clin. Oncol. 2024 (DLBCL)



Y. Wang et al. J. Clin. Oncol. 2023 (MCL)

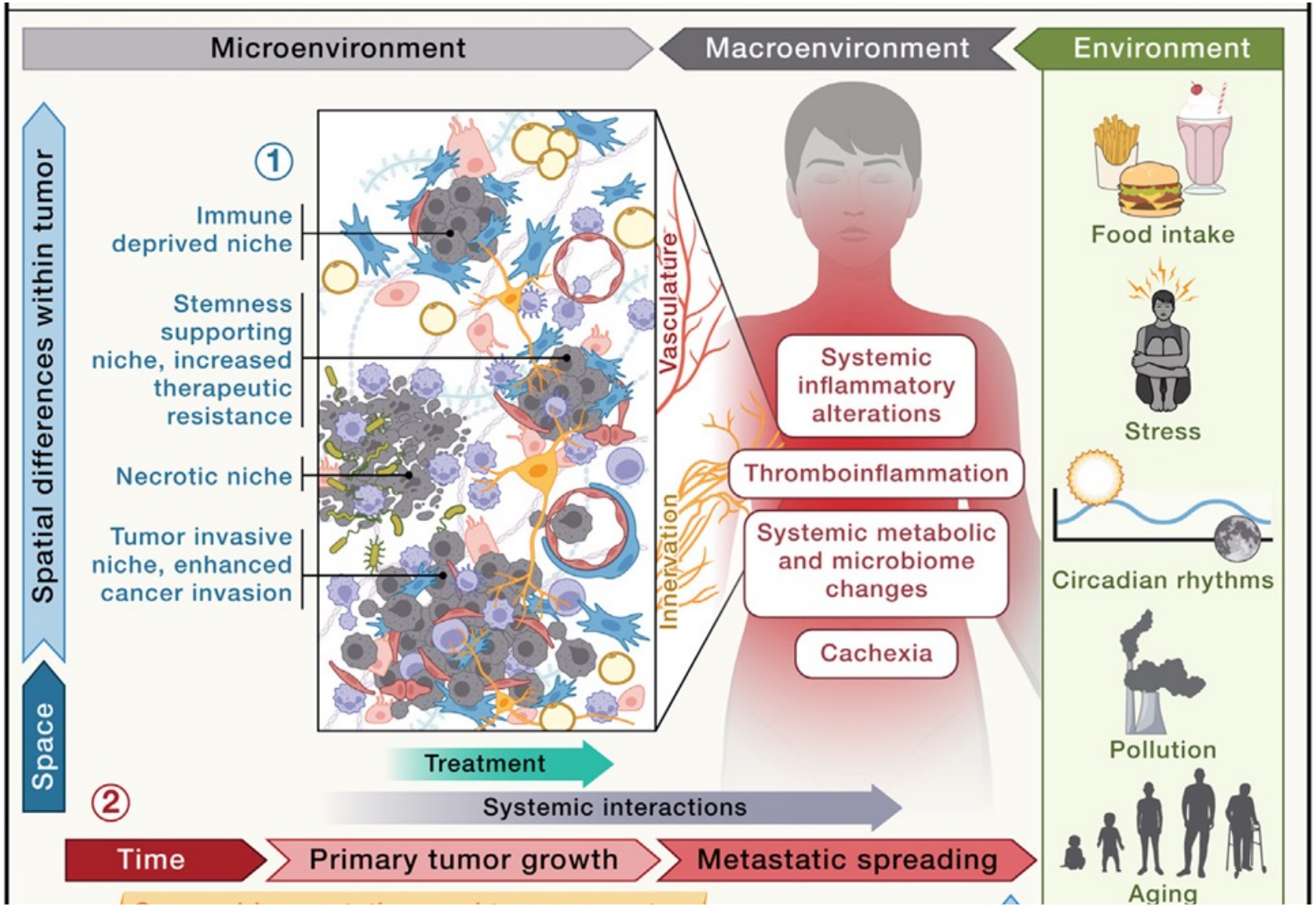
Summary: Intermediary Therapies

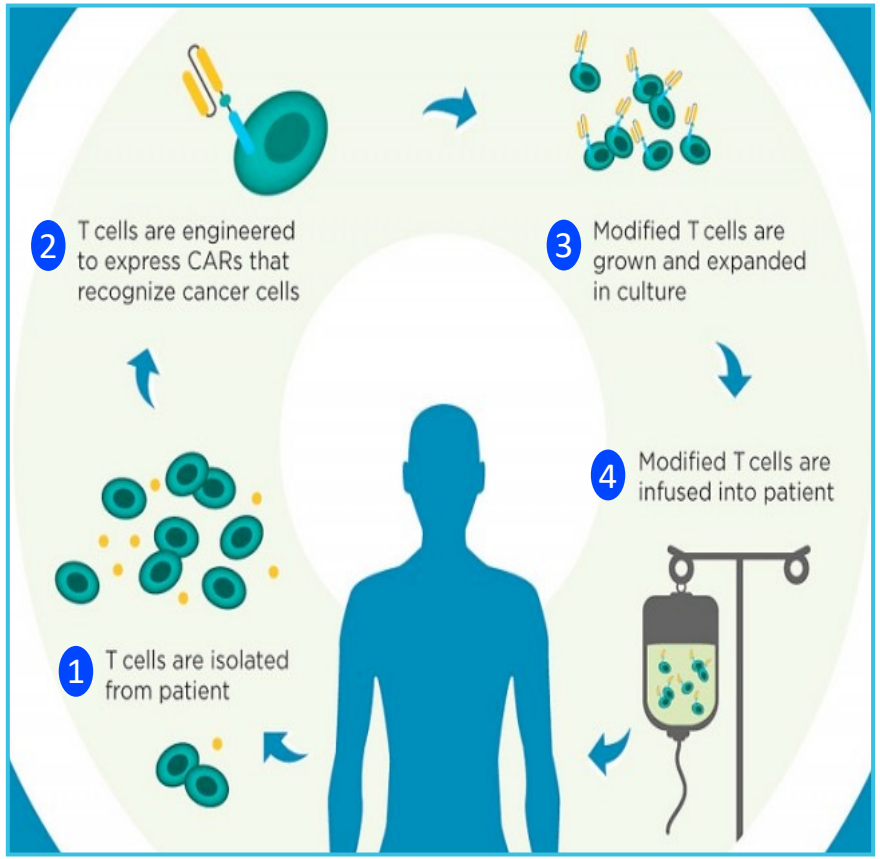
- Holding and bridging therapies are widely used and profoundly affect the outcome of CAR T – should be considered as part of the treatment plan!
- Holding differs from bridging because it may affect the quality of T cells collected at apheresis (e.g. bendamustine)
- The optimal bridging therapy reduces tumor burden without causing toxicity

Outline

1. Intermediary Therapies: Holding and Bridging
2. Systemic inflammation
3. Radiation bridging therapy
4. Lymphodepletion

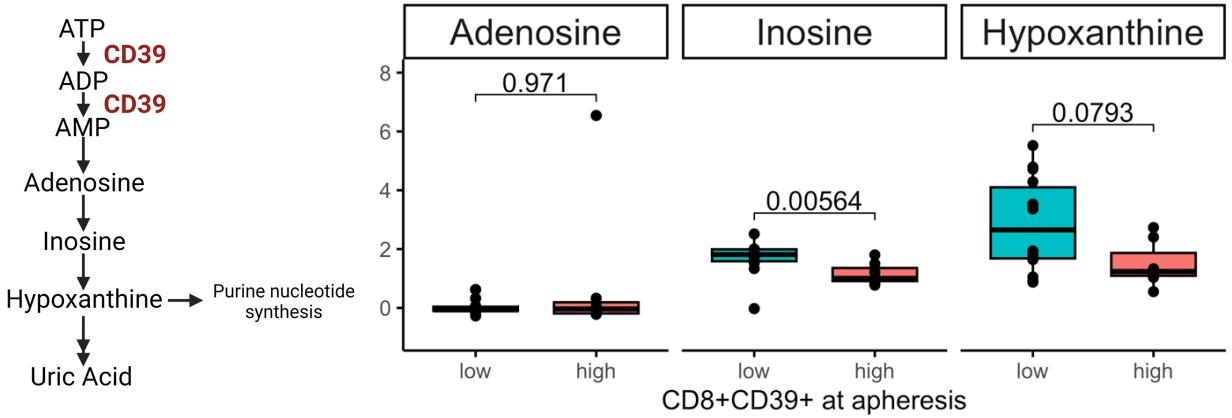
Cancer is a systemic inflammatory disease



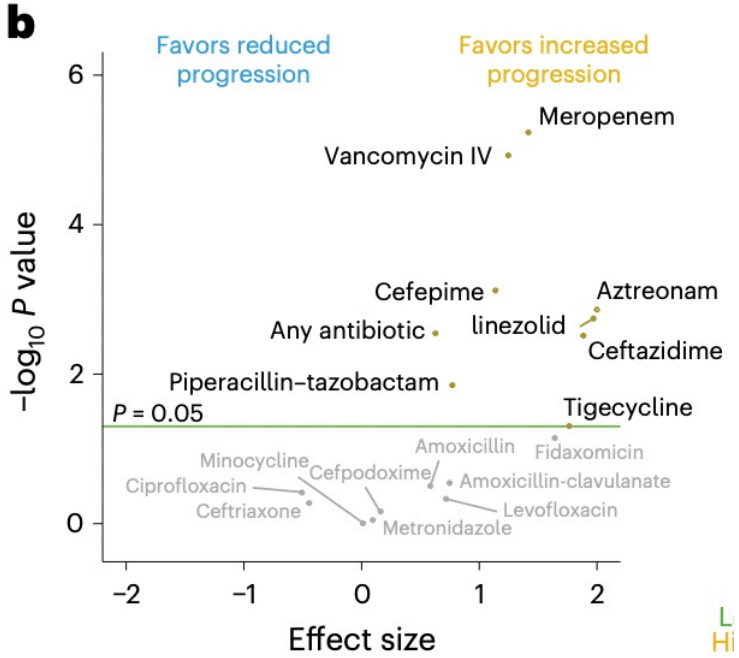


Swanton et al. Cell 2024

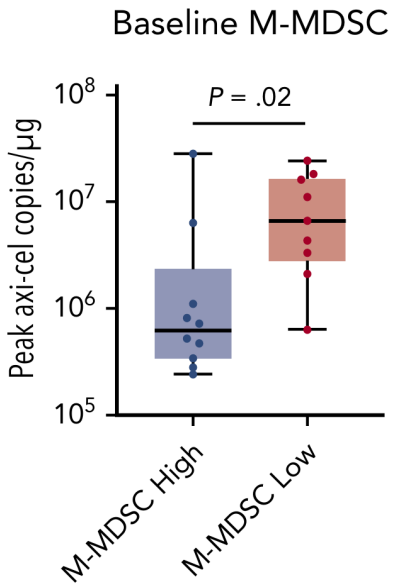
CAR T cells in an immunometabolic macroenvironment



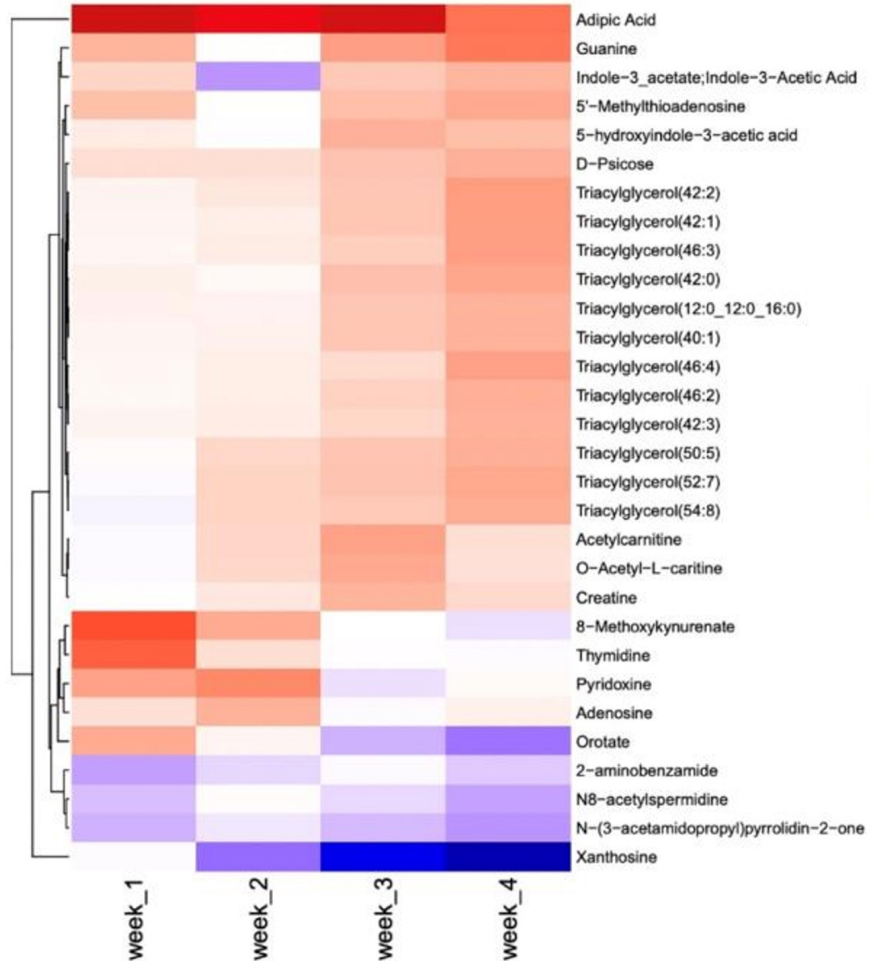
Jain, Locke unpublished



Stein-Thoeringer et al. Nat. Med. 2023

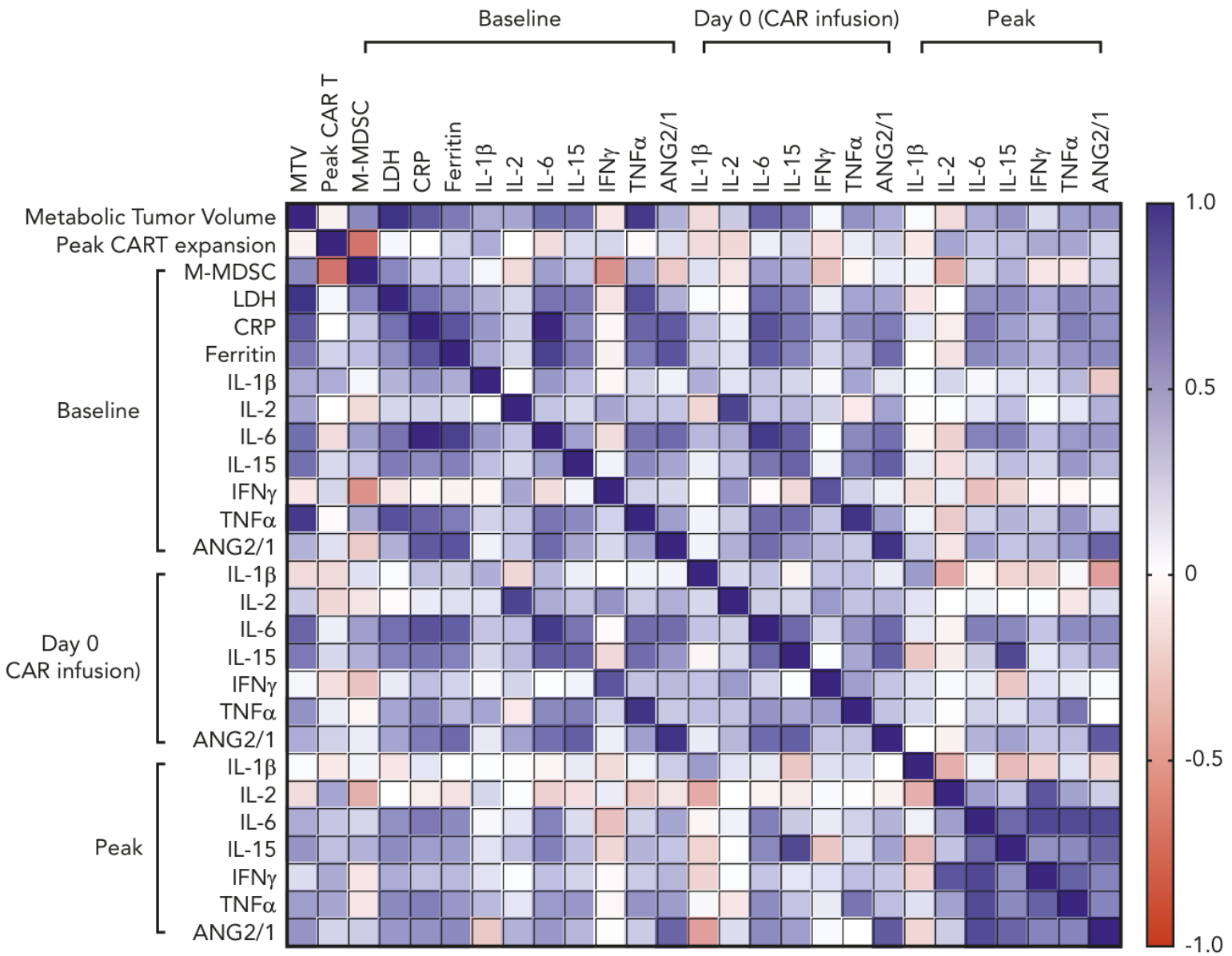


Jain et al. Blood 2021



Jhaveri et al. Clin. Cancer Res. 2025

Inflammation after CAR T is an exacerbation of baseline



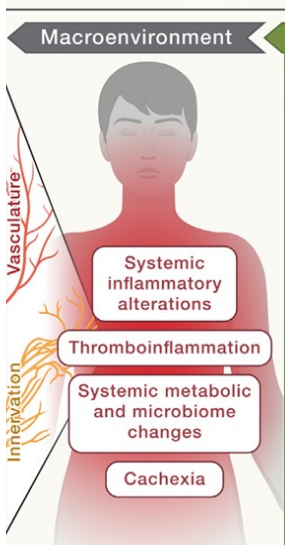
Blue = positive correlation

Red = negative correlation

Jain et al. Blood 2021

Systemic Inflammation Leads to Worse CRS and ICANS

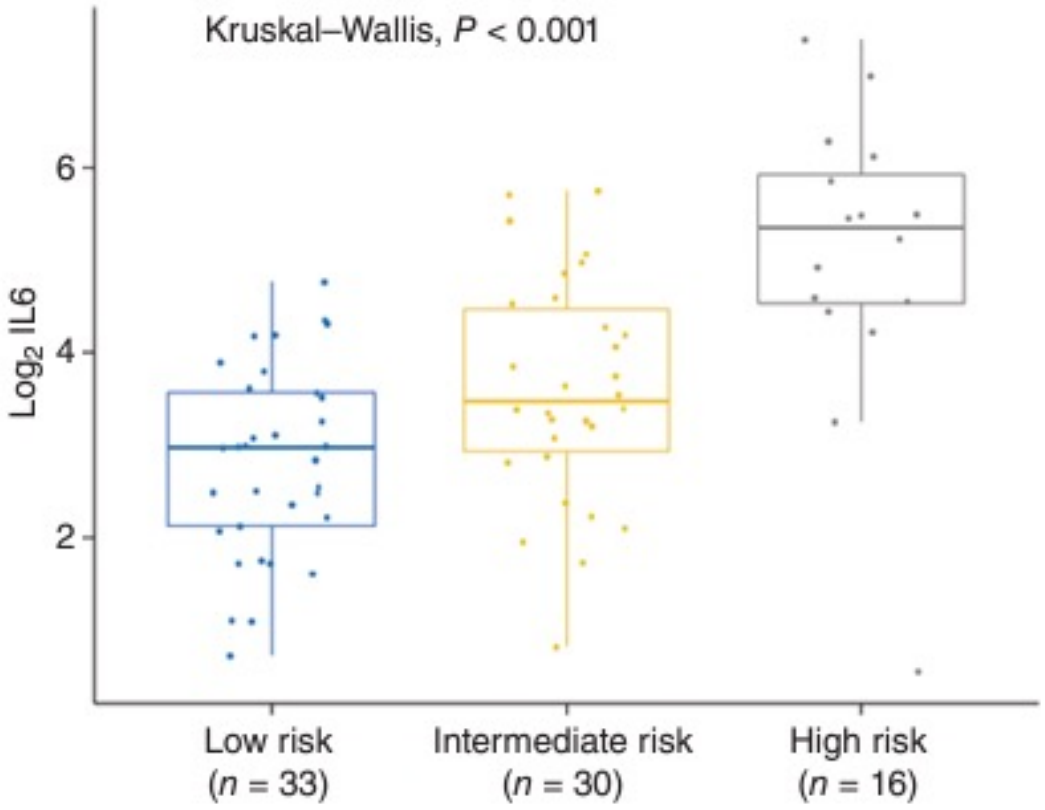
Low Risk: Ferritin <400, CRP<4
Intermediate: Either high ferritin or CRP
High risk: Both high ferritin and CRP



	All patients (*n* = 136)	Low risk (*n* = 62)	Intermediate risk (*n* = 47)	High risk (*n* = 27)	*P* value[a]
CRS					
CRS all grades, *n* (%)	126 (93)	59 (95)	44 (94)	23 (85)	0.30
Grade ≥3 CRS, *n* (%)	14 (10)	1 (1.6)	6 (13)	7 (26)	0.001
Grade 5 CRS, *n* (%)	3 (2)	0	1 (2)	2 (7)	0.09
Use of tocilizumab, *n* (%)	71 (52)	28 (45)	26 (55)	17 (63)	0.26
Use of steroids, *n* (%)	66 (49)	24 (39)	22 (47)	20 (74)	0.01
ICANS					
ICANS all grades, *n* (%)	83 (61)	33 (53)	29 (62)	21 (78)	0.09
Grade ≥3 ICANS, *n* (%)	38 (28)	10 (16)	14 (30)	14 (52)	0.002

Faramand et al. Blood Cancer Discovery 2024

Systemic Inflammation Leads to Poor Efficacy



Low Risk: Ferritin <400, CRP<4
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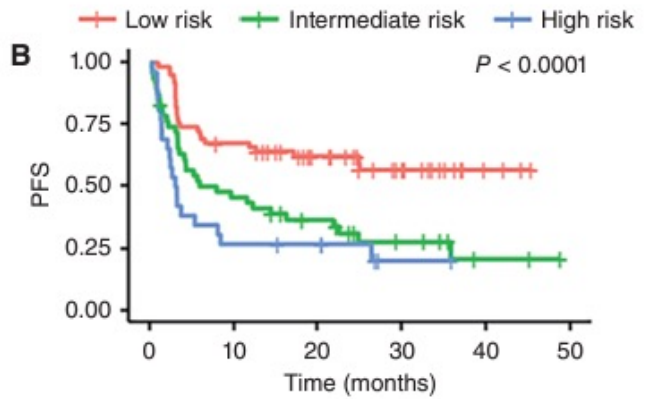
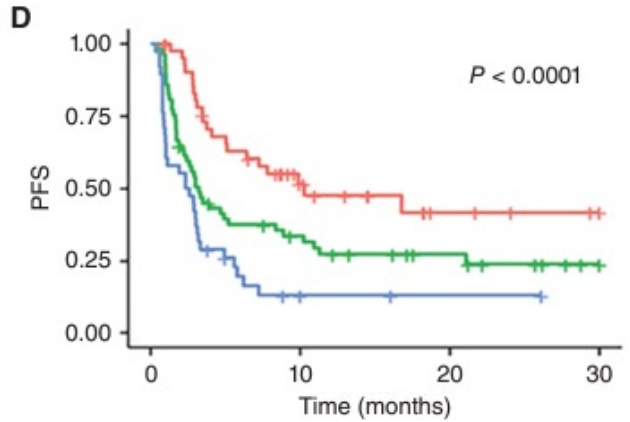
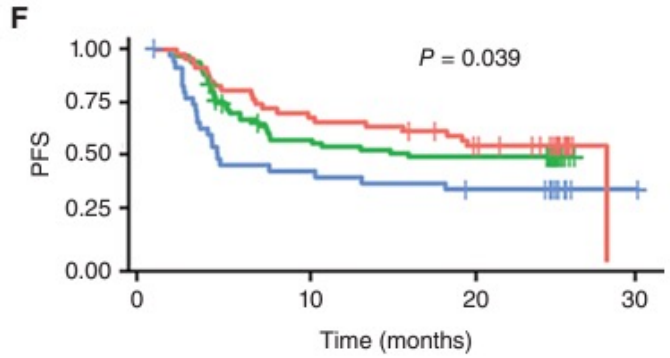
Faramand et al. Blood Cancer Discovery 2024



Moffitt standard of care axi-cel

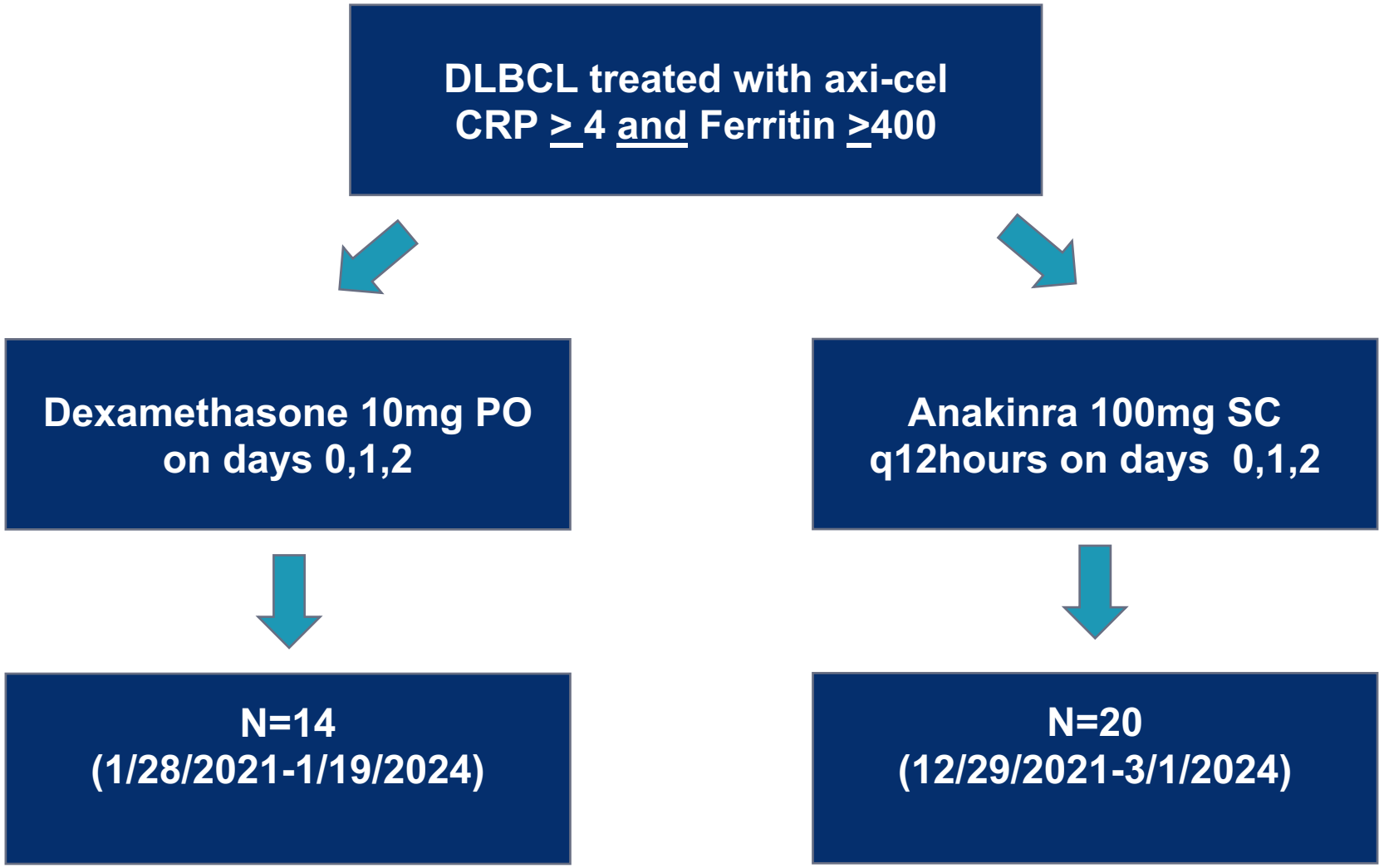


Europe standard of care axi-cel



ZUMA-1 trial axi-cel

Can we improve outcomes for inflamed patients?



Rawan Faramand

Can we improve outcomes for inflamed patients?

Baseline Characteristics	No prophy (n=27)	Dex (n=14)	Anakinra (n=20)	P value
Age	65	65	62	0.74
Female Sex	44%	21%	20%	0.14
Advanced Stage	93%	93%	90%	0.94
ECOG 2+	48%	50%	50%	0.94
IPI at apheresis	4	4	4	0.53
Prior lines of therapy	3	2	2	0.05
Baseline CRP	8.1	6.0	7.1	0.63
Baseline Ferritin	1193	1557.5	1584.8	0.40
Baseline LDH	470	457	375	0.78

Moffitt Axi-cel Patients

High risk: Both high ferritin >400 and CRP > 4

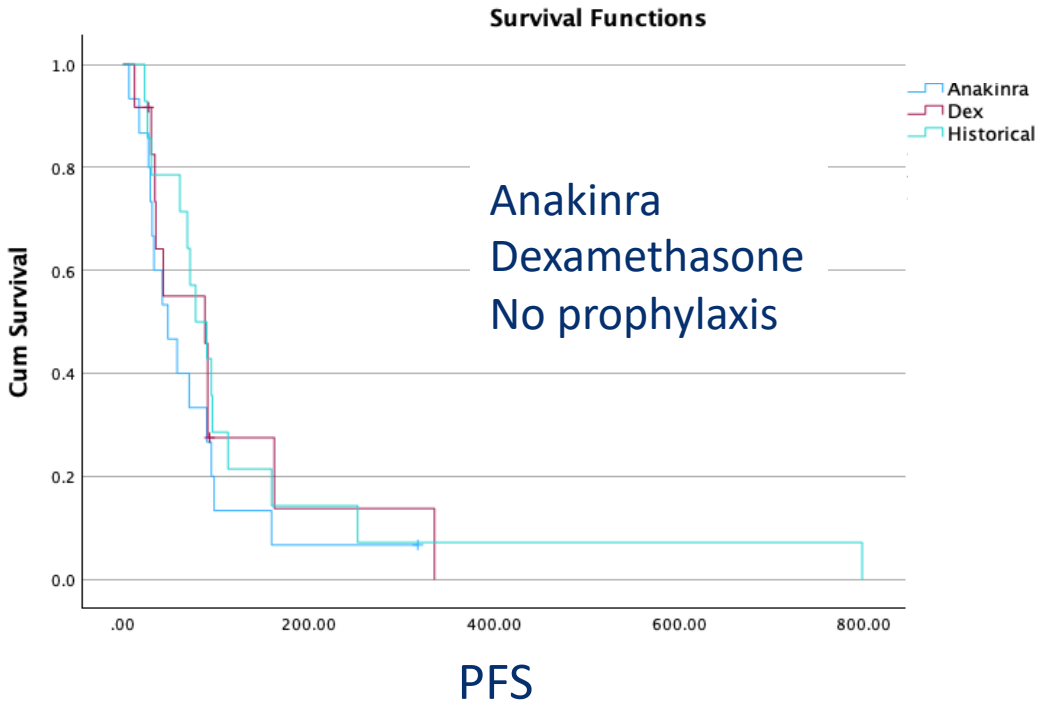
Can we improve outcomes for inflamed patients?

Toxicity Outcomes	No prophy (n=27)	Dex (n=14)	Anakinra (n=20)	P value
CRS – all grades	85%	93%	85%	0.08
CRS – grade 3+	26%	0%	15%	0.1
ICANS – all grades	78%	70%	64%	0.3
ICANS – grade 3+	52%	36%	45%	0.6
Severe infections	30%	29%	45%	0.5

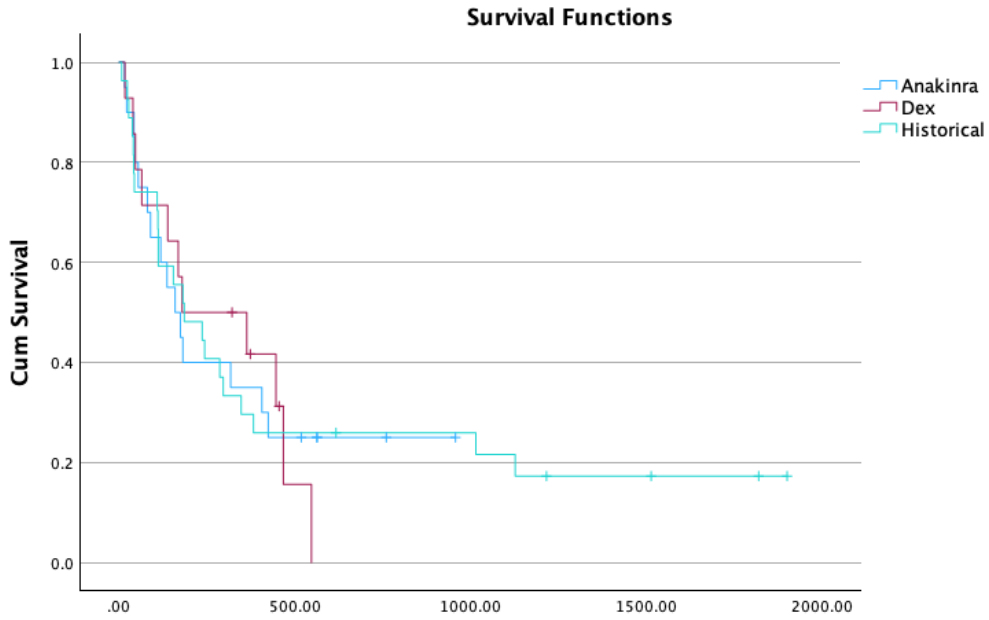
Moffitt Axi-cel Patients

High risk: Both high ferritin >400 and CRP > 4

Can we improve outcomes for inflamed patients?



PFS



OS

Moffitt Axi-cel Patients

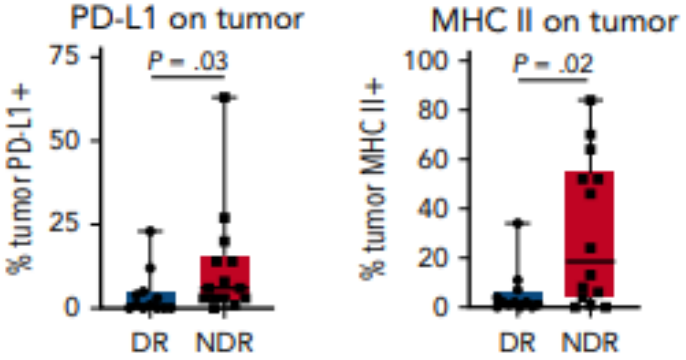
High risk: Both high ferritin >400 and CRP > 4

Can we improve outcomes for inflamed patients?

- Prophylaxis may improve rates of severe CRS/ICANS
- Prophylaxis does not improve or worsen the poor PFS/OS

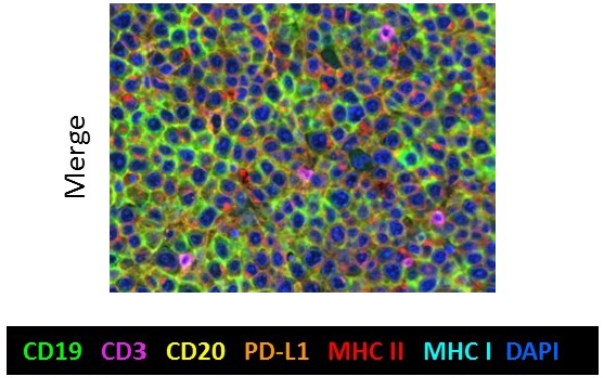
Chronic Tumor Interferon Signaling and CAR T Outcomes

Immune Checkpoints in the TME

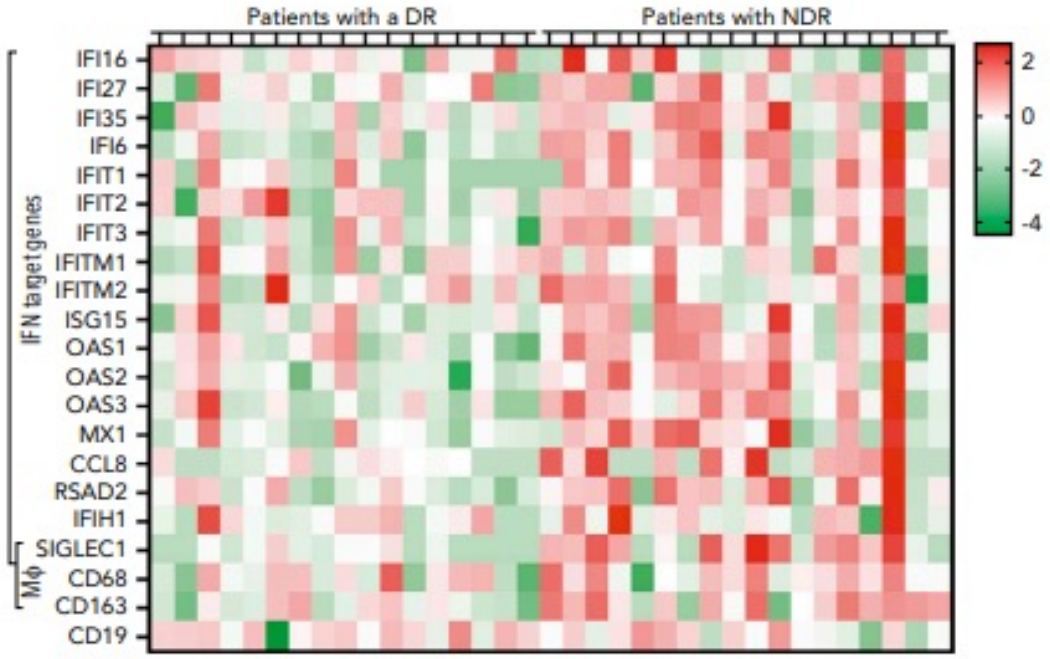


DR – durable response; NDR – no durable response

Immunofluorescence on FFPE



Chronic Tumor IFN in the TME

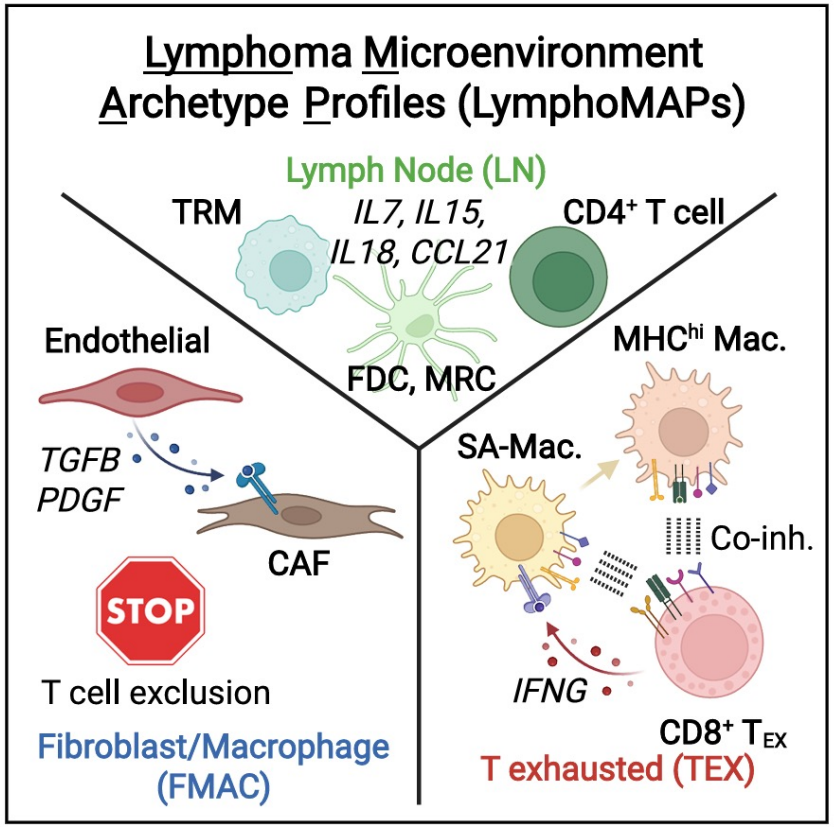


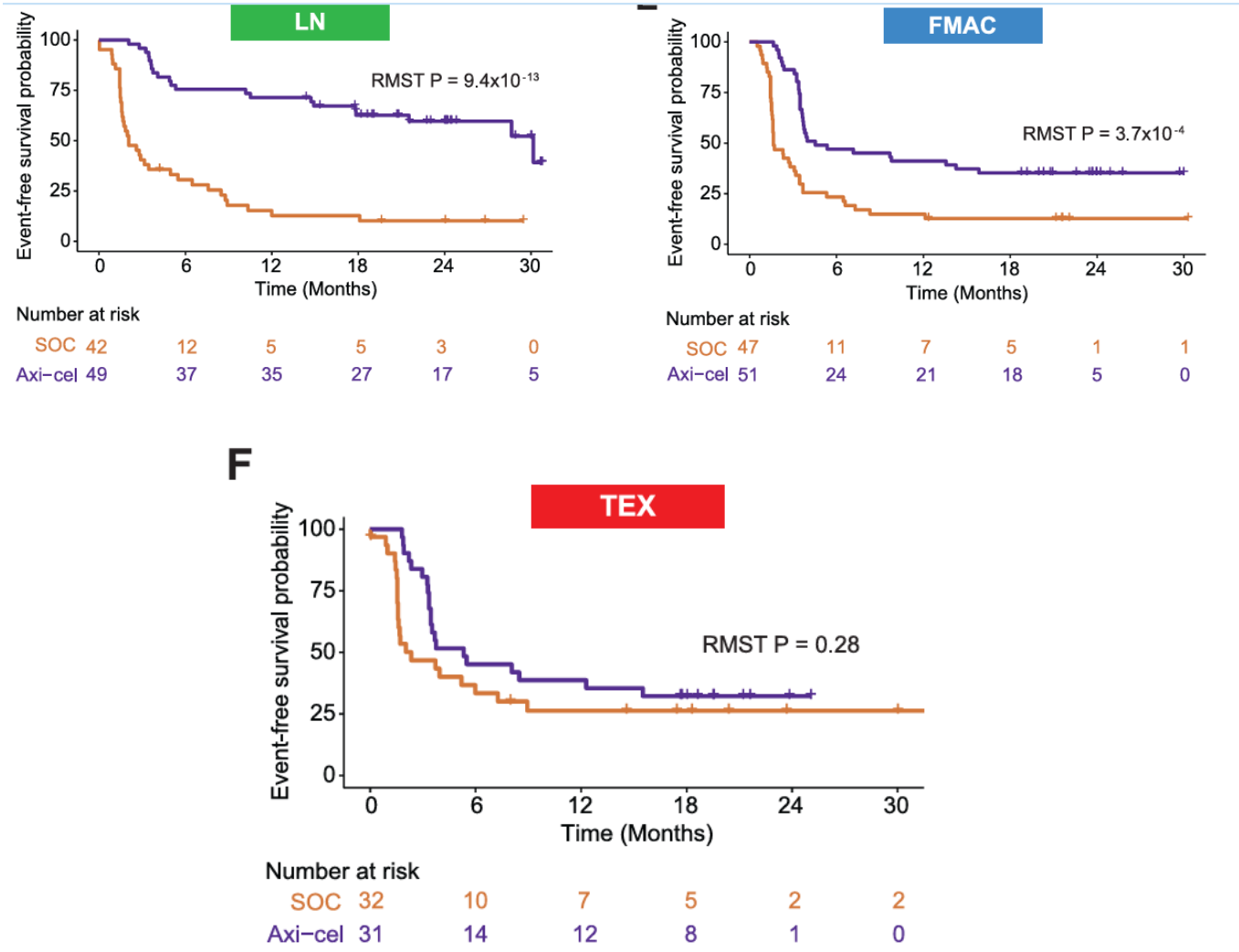
DR – durable response; NDR – no durable response

Nanostring RNA IO360 on fresh frozen

Jain et al. Blood 2021

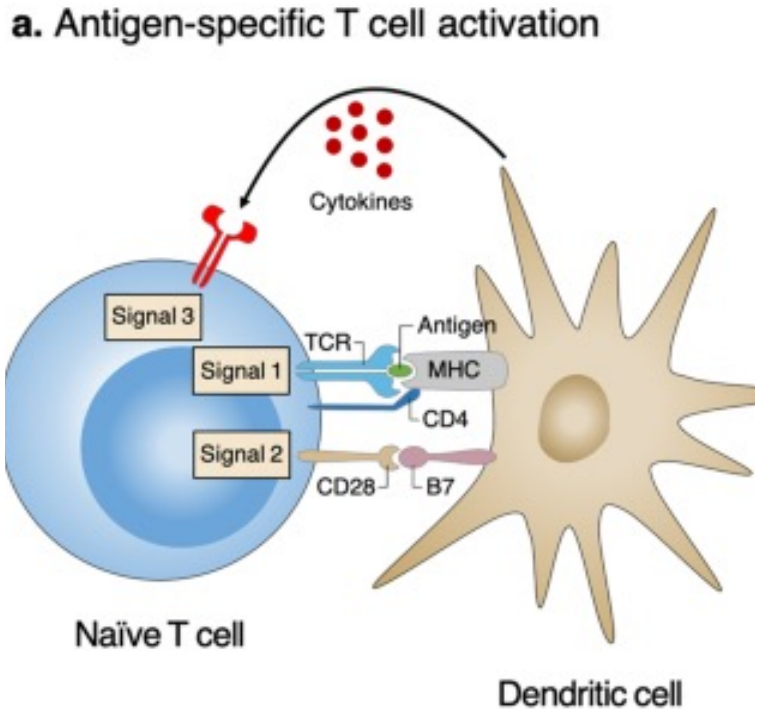
TME with macrophages super-activated by IFN have poor CAR T patient outcomes

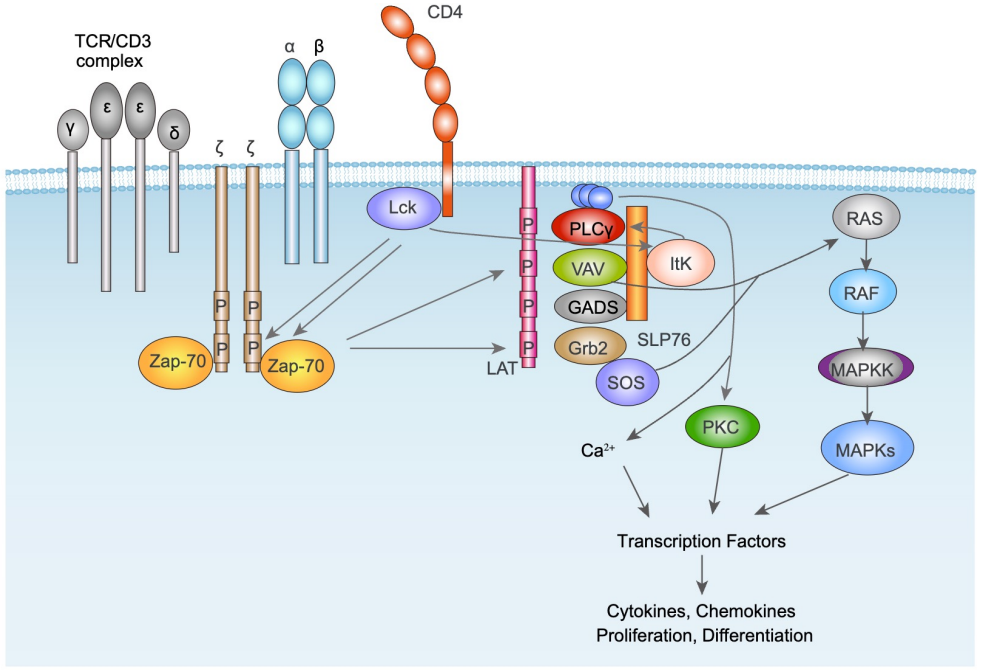




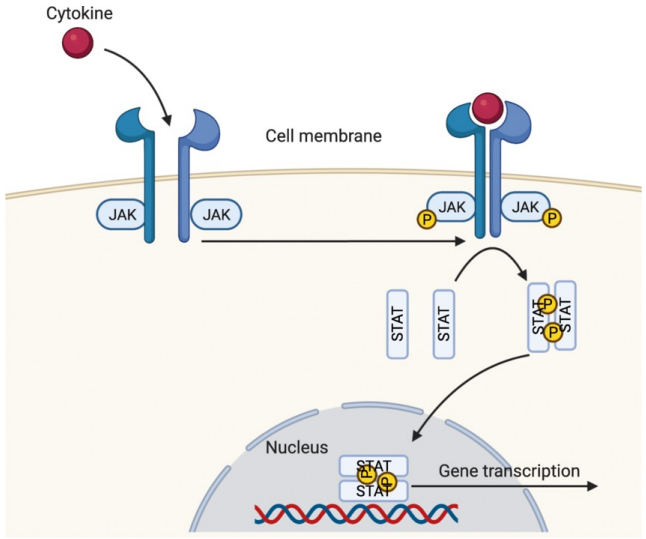
Li et al. Cancer Cell 2025

JAK/STAT inhibition to “uncouple” CRS and efficacy





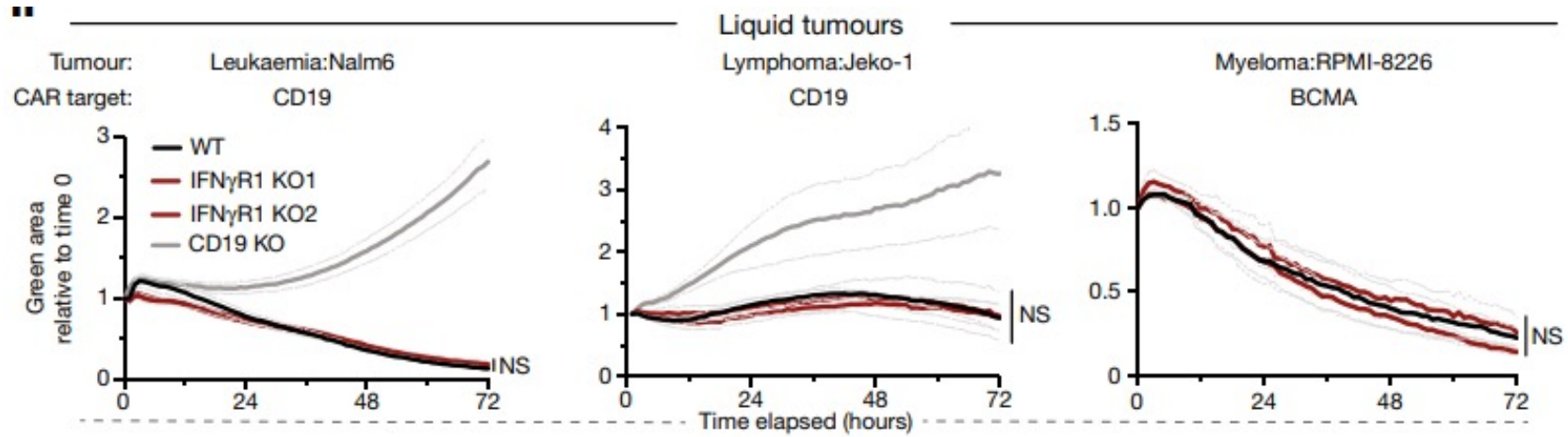
TCR signaling



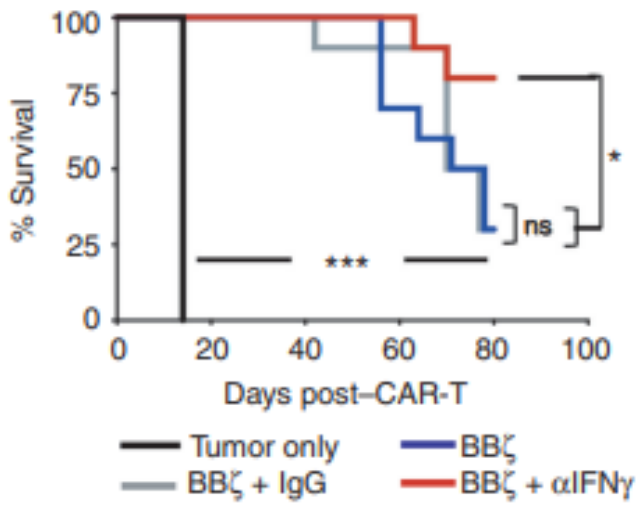
Cytokine (i.e. IFN) signaling

Akkoc and Khan 2021

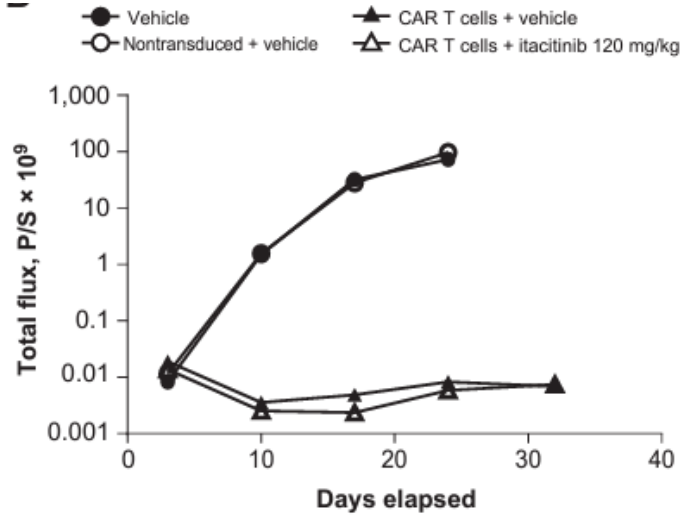
CAR T cells function without JAK-STAT-IFN in heme malignancies



IFN R KO: Larson et al. Nature 2022



Anti-IFN gamma: Bailey et al. Blood Cancer Discovery 2022



JAK1 inhibition: Huarte et al. Clin. Cancer Res. 2020

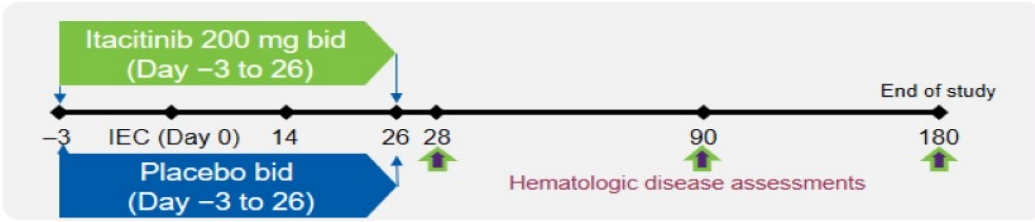
Itacitinib, a JAK1 inhibitor, and CAR T to decrease CRS

PART 2

Main eligibility criteria

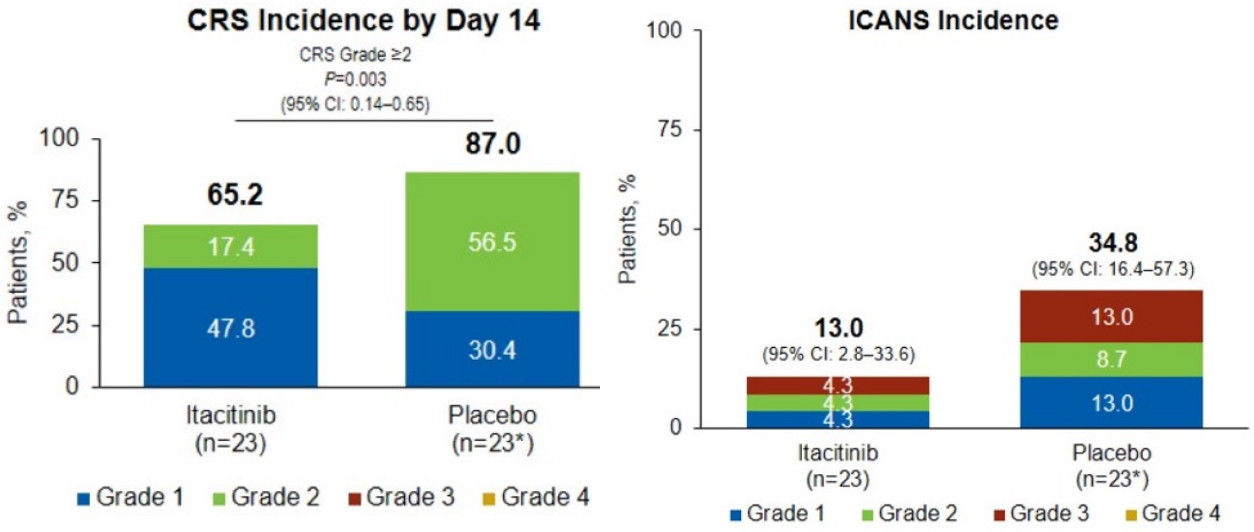
- Age ≥18
- Eligible for treatment with axicabtagene ciloleucel
- ECOG 0 or 1

N=46 patients (23 patients/arm)



Tocilizumab could be given for CRS grade 1 if no improvement was observed within 72 hours

- **Primary endpoint**: Incidence of CRS grade ≥2 by Day 14 per ASTCT consensus grading
- **Secondary endpoints**: ICANS incidence by Day 28 per ASTCT consensus grading, CRS and ICANS duration, safety, PK, biomarkers, ORR to IEC

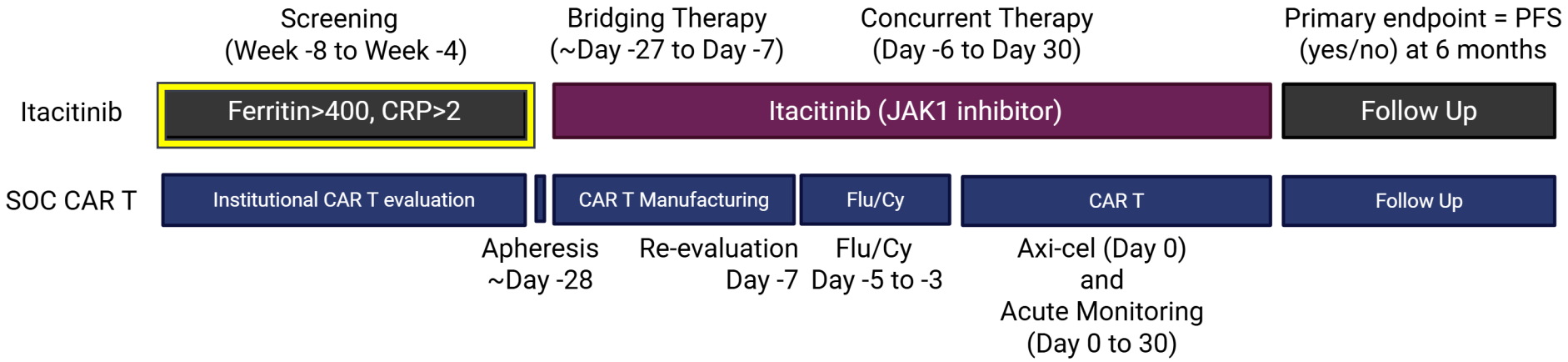


	Itacitinib 200 mg bid (N=23)	Placebo 200 mg bid (N=23)*
Best ORR, n (%) [95% CI]	**18 (78.3)** [56.3, 92.5]	**17 (73.9)** [51.6, 89.8]
ORR at 6 months,† n (%) [95% CI]	**9 (39.1)** [19.7, 61.5]	**6 (26.1)** [10.2, 48.4]
CR	9 (39.1)	5 (21.7)
PR	0	1 (4.3)

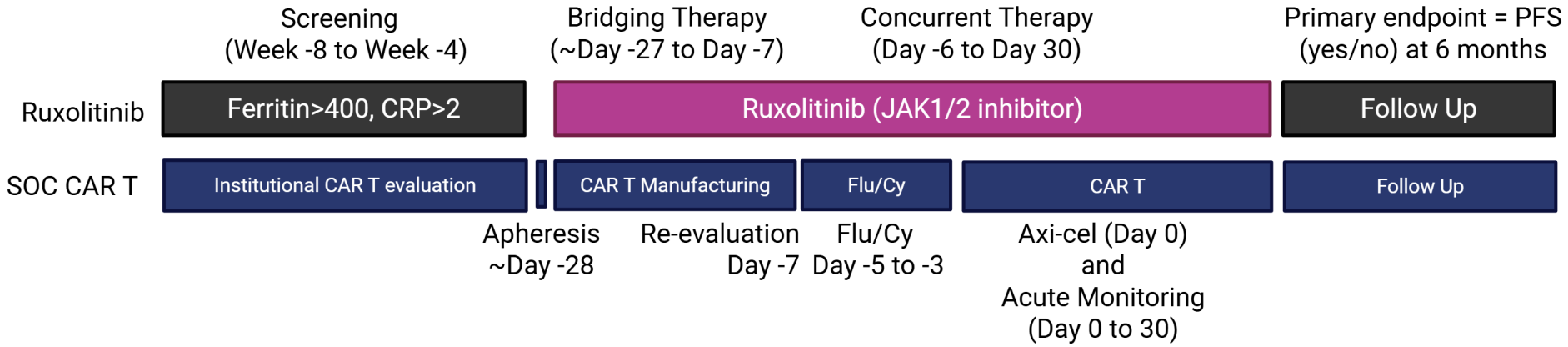
Frigault et al. ASH 2023

Can we improve outcomes for inflamed patients?

Stage 1 n=15: Itacitinib 200 mg PO x 2 months (days -27 to day +30)



Stage 2 n=12: Ruxolitinib 10 mg PO x 2 months (days -27 to day +30)



NCT05757219; MCC21892

Itacitinib (JAK1i) Pre-Modulation Trial Stage 1 Results

- N=16 enrolled, 1 patient did not get CAR T cell infusion due to disease progression, replaced
- N=15 evaluable

Toxicity	N = 15
CRS grade 0-2	15 (100%; three grade 2)
CRS grade 3+	0
ICANS grade 0-2	12 (80%)
ICANS grade 3+	3 (20%)

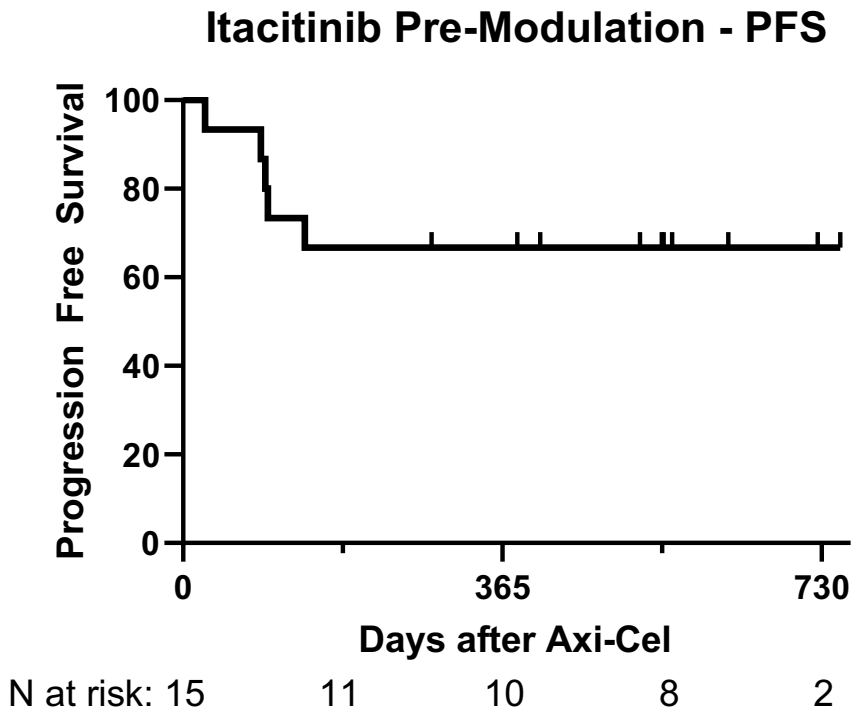
Decreased toxicity compared to expected for this population of high ferritin/CRP

NCT05757219; MCC21892

Itacitinib (JAK1i) Pre-Modulation Trial Stage 1 Results

- N=16 enrolled, 1 patient did not get CAR T cell infusion due to disease progression, replaced
- N=15 evaluable

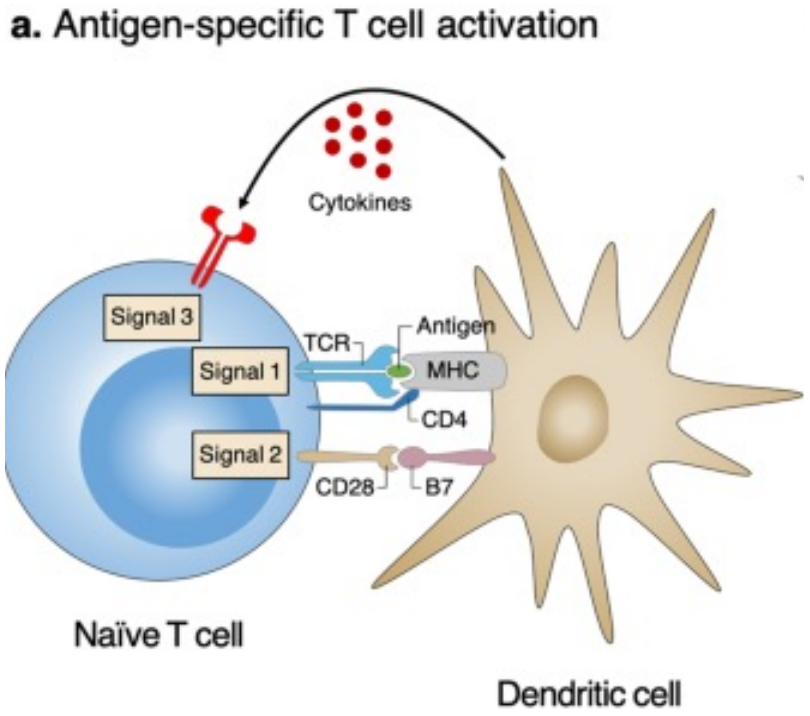
Efficacy	N = 15
6 month PFS	10 (67%)
6 month OS	13 (93%)

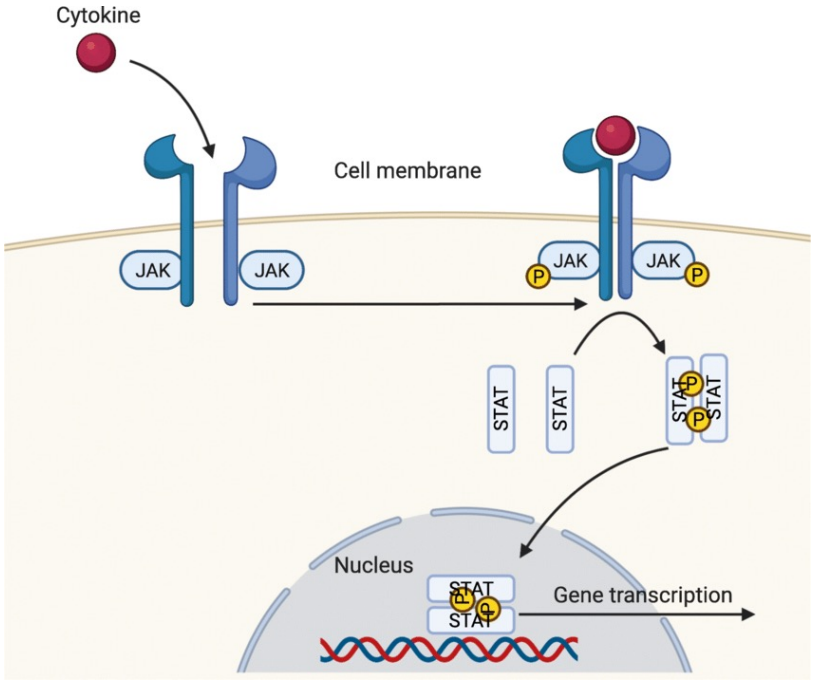


Increased efficacy compared to expected for this population of high ferritin/CRP

NCT05757219; MCC21892

Can you uncouple CRS from CAR T efficacy?

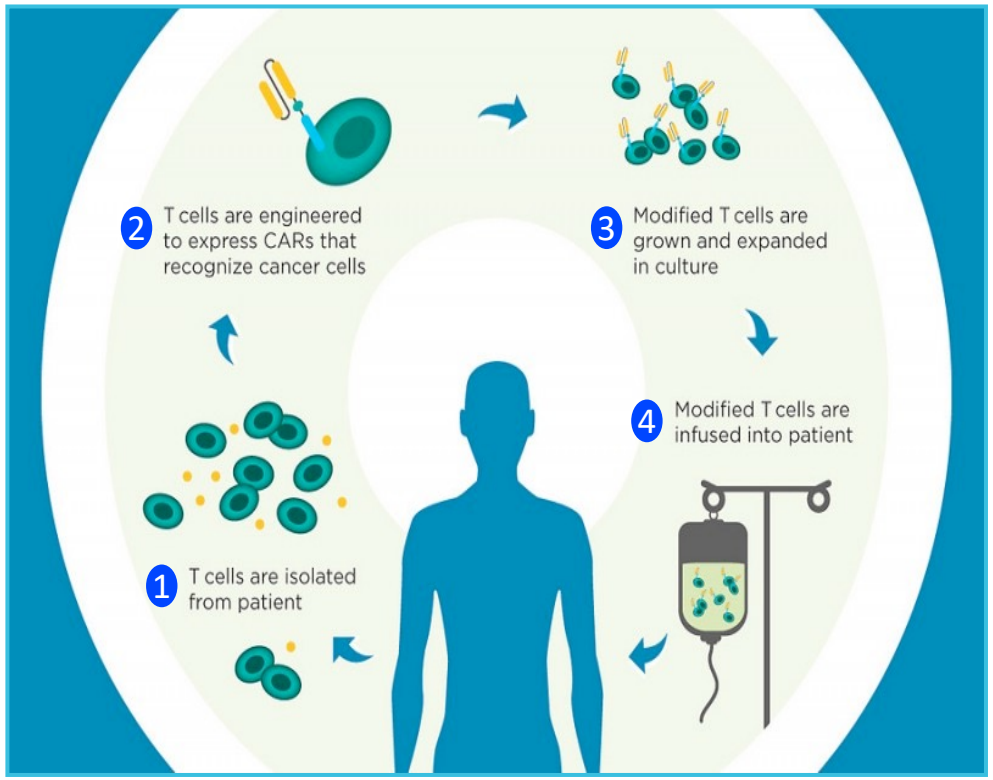


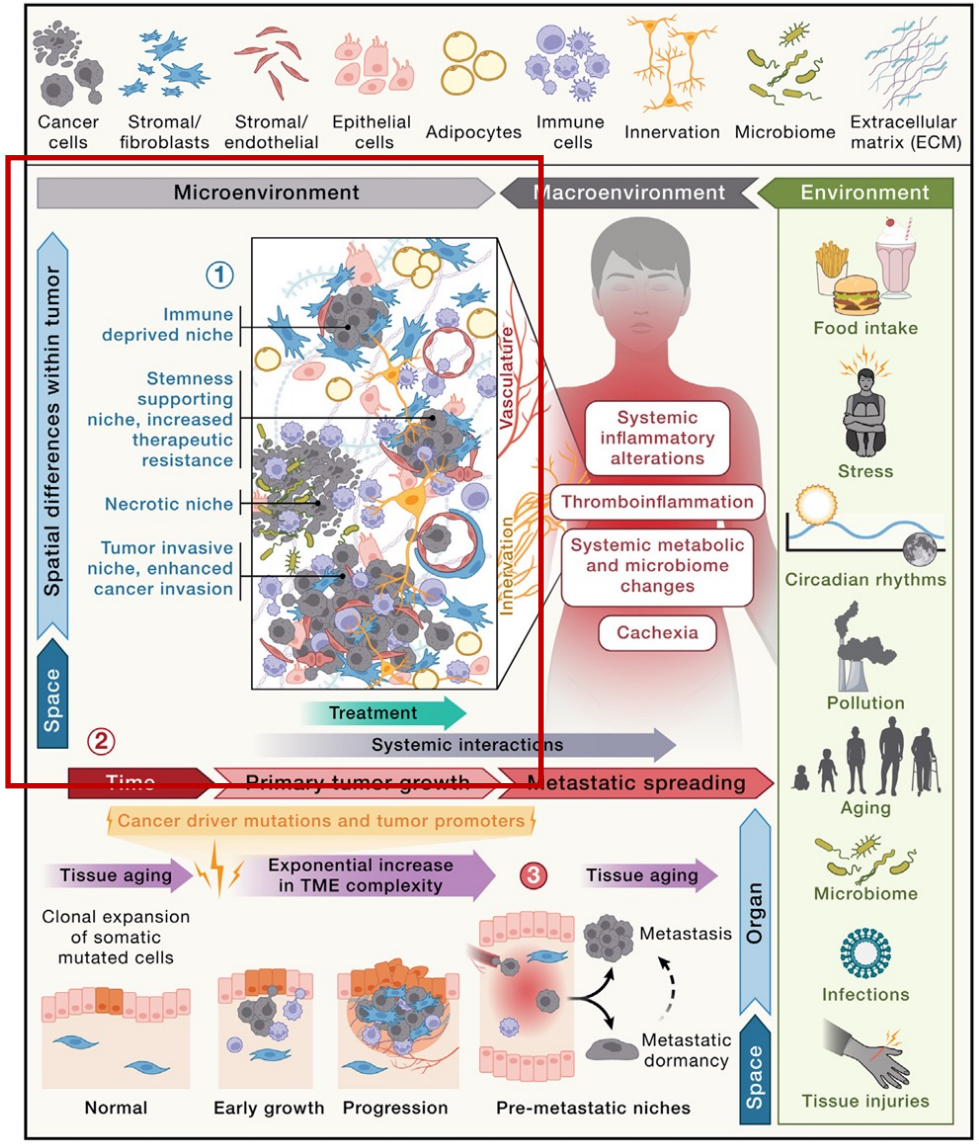


Outline

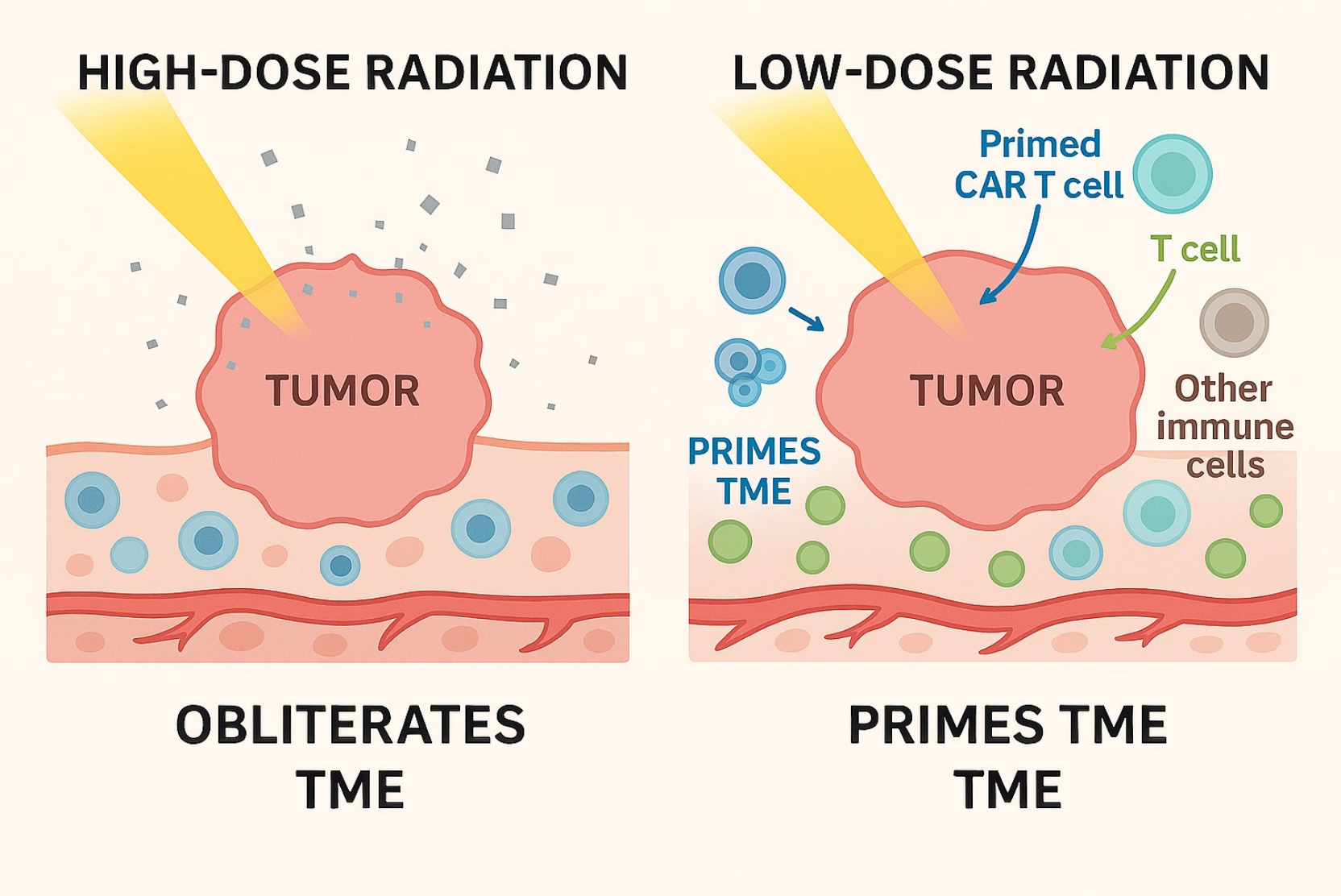
1. Intermediary Therapies: Holding and Bridging
2. Systemic inflammation
3. Radiation bridging therapy
4. Lymphodepletion

Autologous CAR T cells





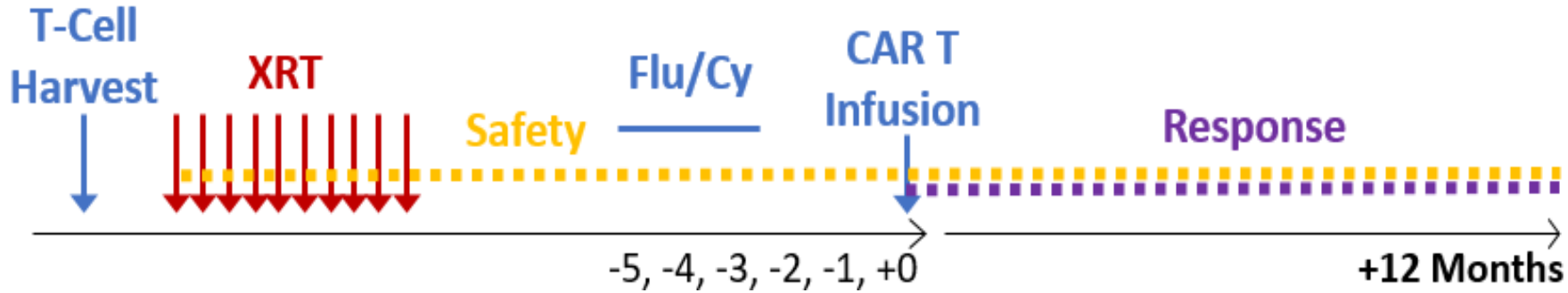
Radiation dose and the TME



Comprehensive bridging irradiation trial: Moffitt

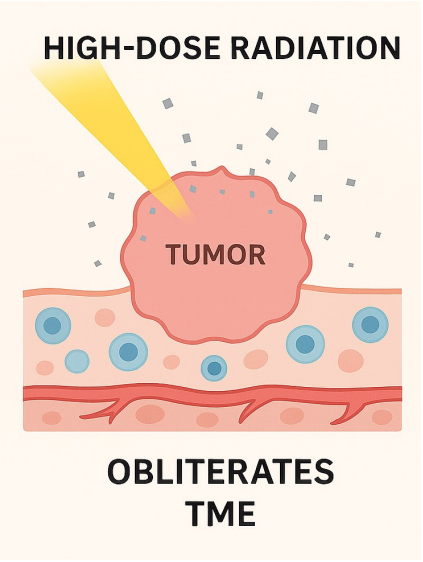
"Irradiate into CR"

37.5Gy in 15 fractions. Hypothesis: Improve 12-month PFS from 30% -> 55%



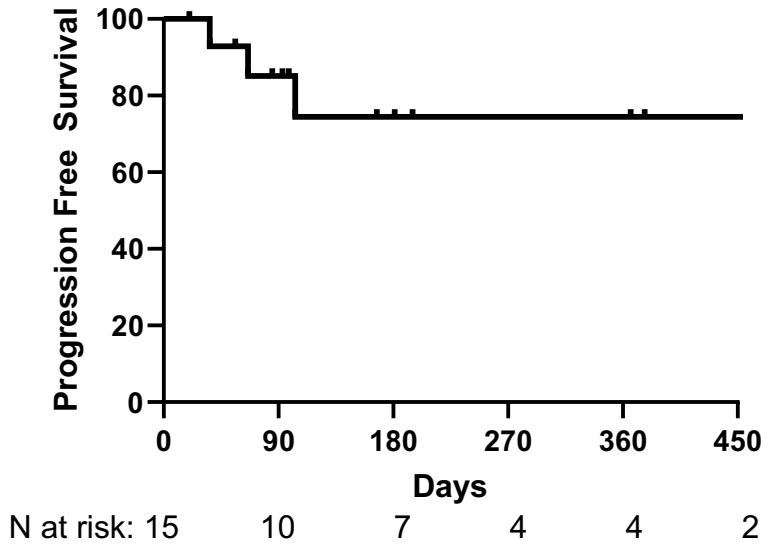
Nick Figura

Planned enrollment N=24.
Axi-cel for R/R DLBCL



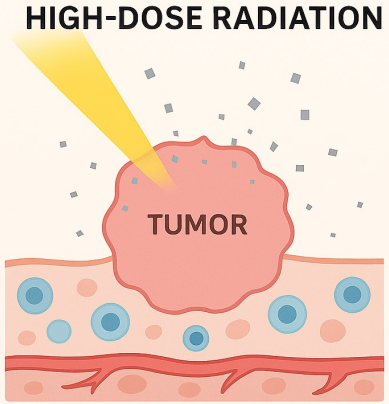
Comprehensive bridging irradiation trial: Moffitt

PET Response to Bridging XRT	% n=15
CR	27%
PR	27%
SD	20%
PD	27%



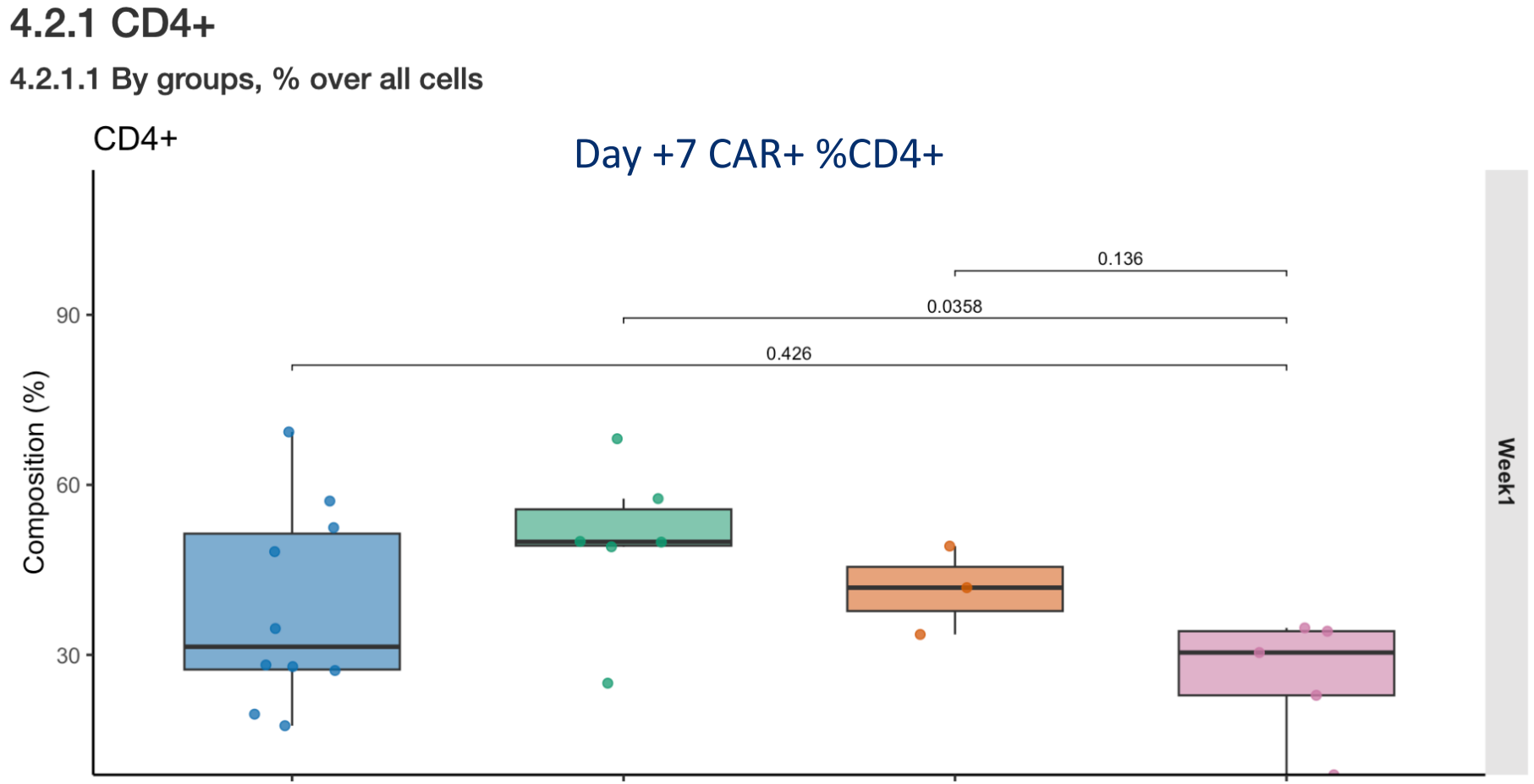
CAR T Toxicity	% n=15
Any CRS	100%
Grade 3+ CRS	13%
Any ICANS	80%
Grade 3+ ICANS	47%

Planned enrollment N=24
Axi-cel for R/R DLBCL



NCT06104592

The CD4:CD8 ratio of expanding CAR T cells is affected by previous bridging radiation



10x-scCITEseq

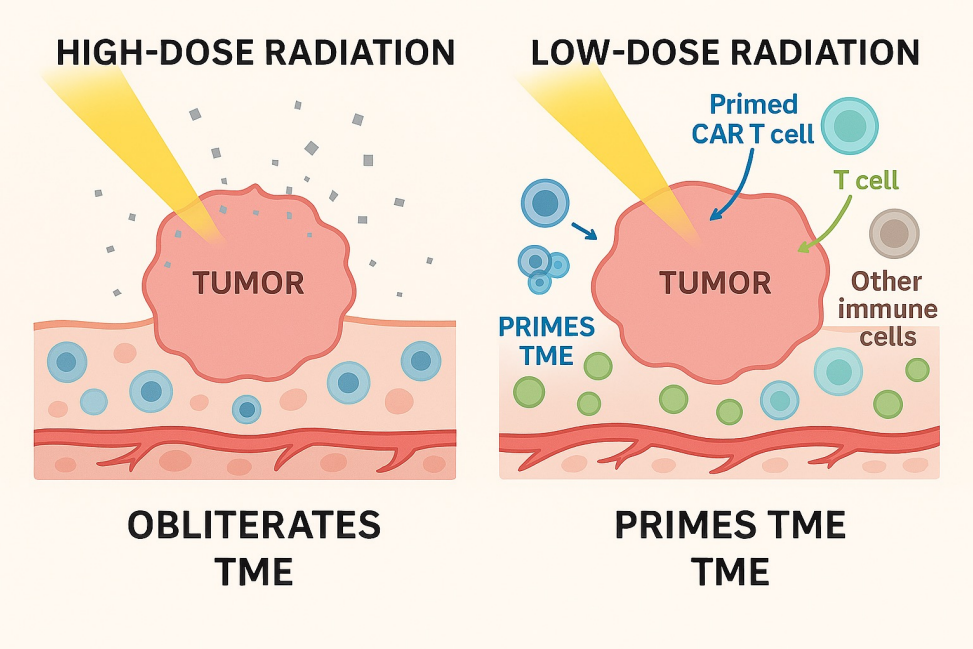
Bridging	JAK1i	Radiation (high dose)	Any Bridging	Any Bridging
Lymphodepletion	Flu/Cy	Flu/Cy	Clad/Cy	Flu/Cy
During/post axi-cel	JAK1i	-	-	-

Xiaoqing Yu

Other radiation bridging trials in progress

- Nebraska “boom-boom” 2 Gy x 2 plus liso-cel (low dose)
- MSKCC “split-dose” 30 Gy/10# to significant lesions, 3 Gy x 1 to all other areas
- City of Hope ”radiation to all PET-avid sites” (unsure of dose)
- UK REMIT – similar split dose of 20-30 Gy to significant lesions, 4 Gy to other areas
- Some smaller pilot/feasibility approaches
- Some studies in China

Summary of Radiation



- Possible effects on TME, lymphodepletion, and CAR T cells
- When all the different radiation trials are complete we will need to do patient-level and lesion-level analyses to understand optimal dosing

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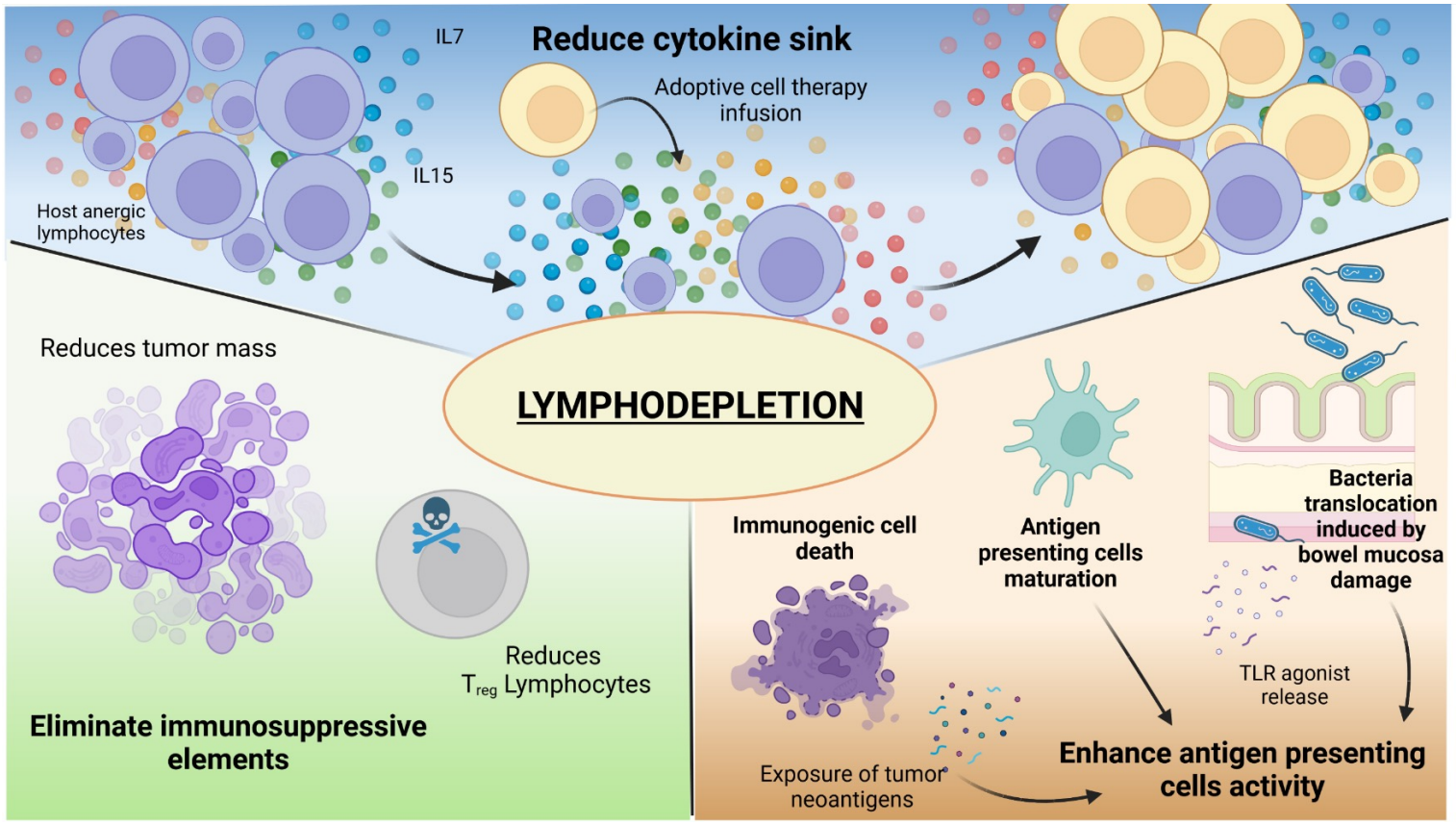
Lymphodepletion and CAR T-cell expansion



G. Ghilardi

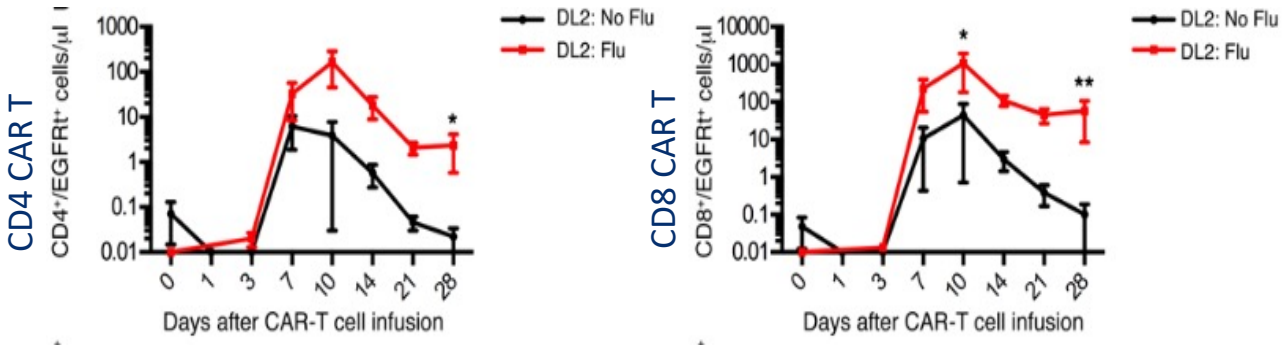
Homeostatic Expansion

- Depth of T cell depletion
- IL-7, IL-15 promote adoptive T cell expansion
- MDSCs and Tregs suppress
- T cell quality

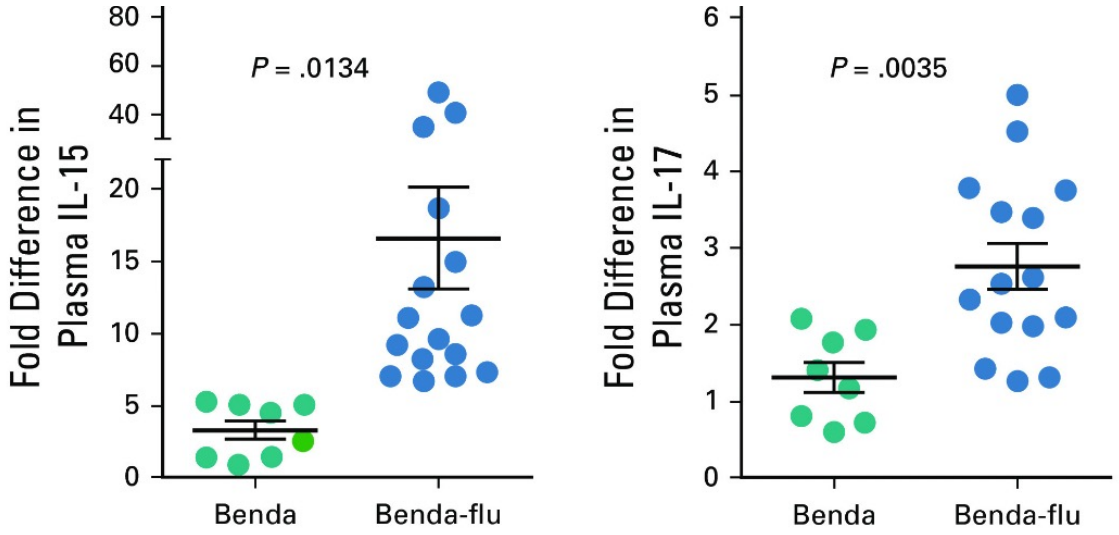
Antigen-driven Expansion

- CAR target abundance
- CAR design (proliferation vs. exhaustion)

Increasing the intensity of LD affects expansion



Adding Flu to Cy increases expansion in patients (Turtle et al. JCI 2016)



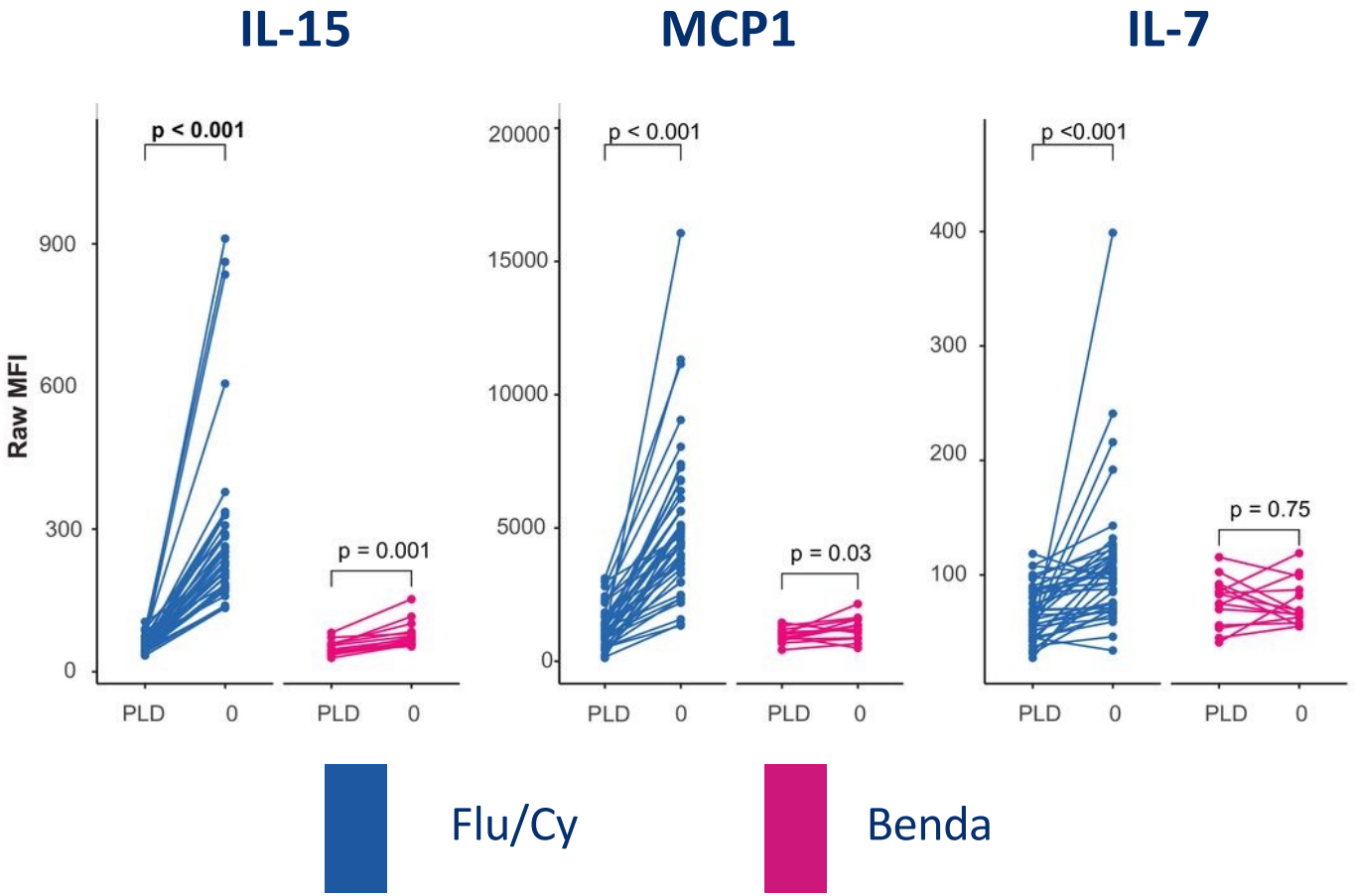
Adding Flu to Benda improves IL-15 and IL-7 conditioning (CD30 CAR T in Hodgkin Lymphoma; Ramos et al., *J Clin Oncol*. 2020).

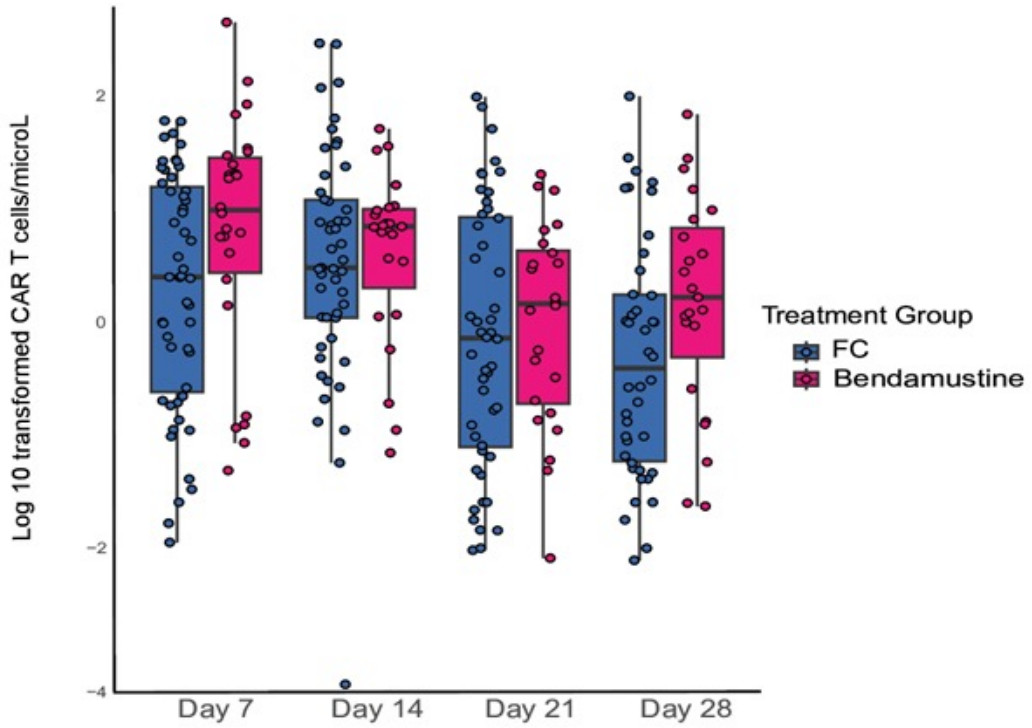
What is the best regimen for lymphodepletion?

	Axi-cel	Brexu-cel	Tisa-cel	Liso-cel	Ide-cel	Cilta-cel
Flu dose (mg/m^2)	30	30	25	30	30	30
Cy dose (mg/m^2)	500	500	250	300	300	300

Reference	CAR Product	Regimen	N	Grade 3+ CRS	Grade 3+ ICANS	Grade 3+ Cytopenia (Day 30)	Grade 3+ Infection	Efficacy Comment
U Penn [a]	Tisa-cel	Bendamustine	90	3.3%	7.8%		7.8%	Similar PFS at 2 years
		Flu/Cy	42	4.8%	21.4%	ND-1	42.9%	
Stanford [b]	Axi-cel	Bendamustine	27	11.1%	18.5%			9 month PFS 70.4%
		Flu/Cy	57	0.0%	12.2%	NR	NR	9 month PFS 63.4%
City of Hope [h]	Axi-cel	Bendamustine	27	3.7%	19.0%		19.0%	6 month PFS 43.8%
		Flu/Cy	42	4.8%	31.0%	ND-2	24.0%	6 month PFS 55.6%
Moffitt [c]	Axi-cel	Clad/Cy	23	0.0%	26.0%	39.0%	13.0%	Similar PFS at 3 months
		Flu/Cy	60	10.0%	32.0%	48.0%	15.0%	

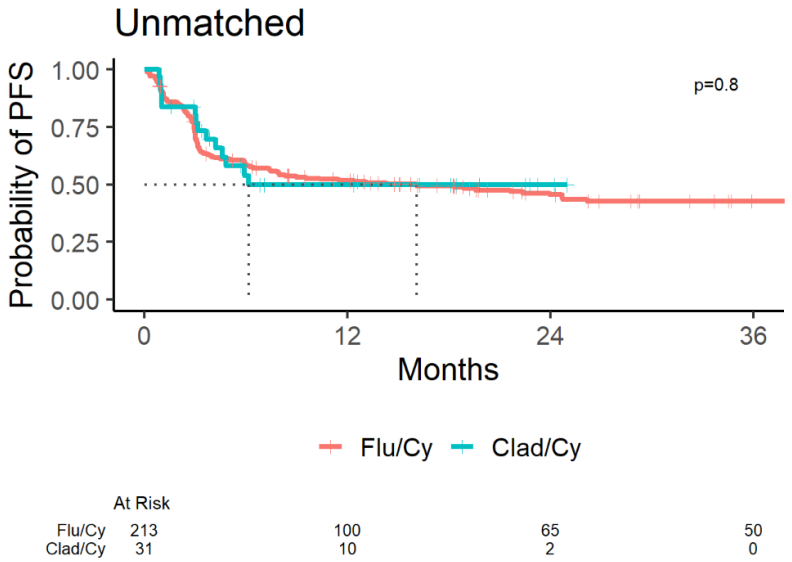
Expansion without conditioning IL-7 or IL-15





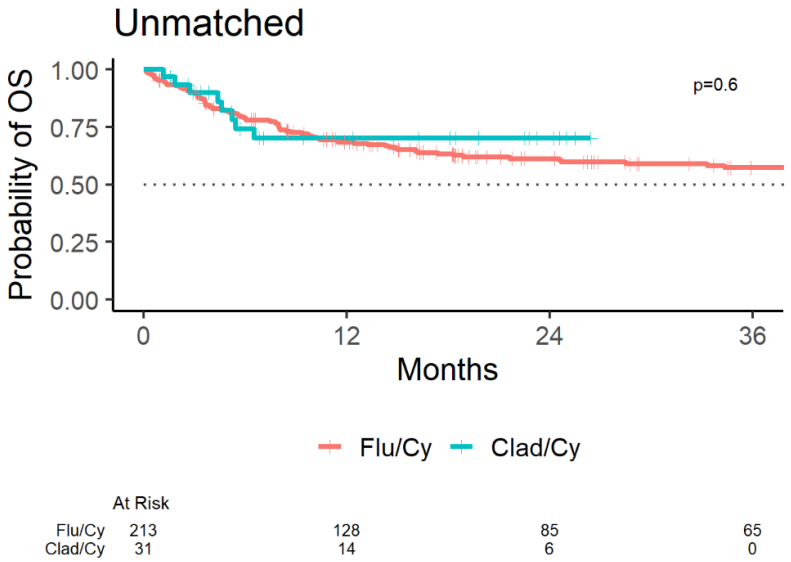
Bharadwaj et al. JITC 2024

Flu/Cy vs. Cladribine/Cy (Axi-Cel)



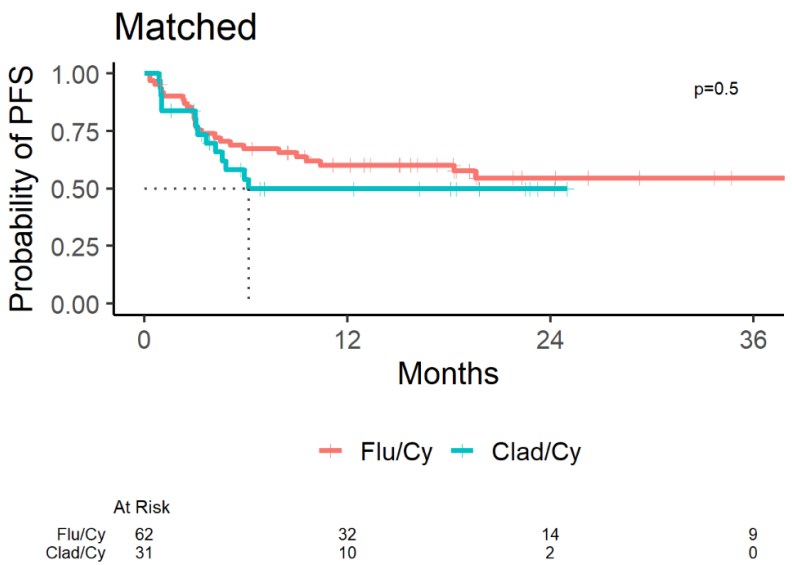
At Risk

Flu/Cy	213	100	65	50
Clad/Cy	31	10	2	0



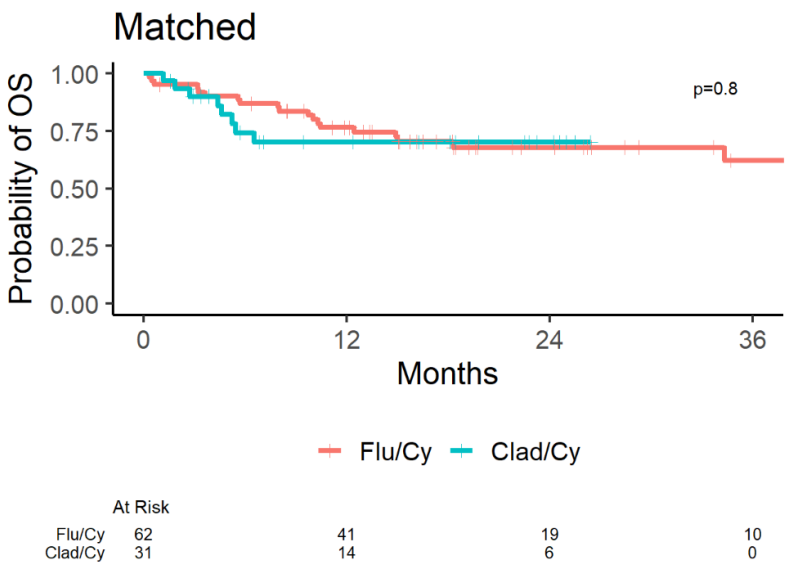
At Risk

Flu/Cy	213	128	85	65
Clad/Cy	31	14	6	0



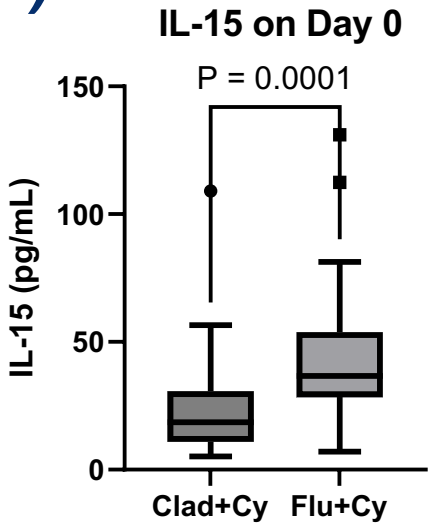
At Risk

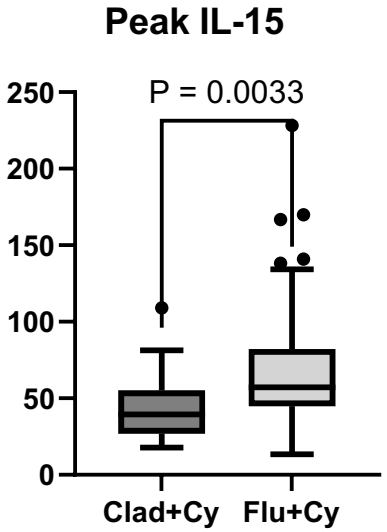
Flu/Cy	62	32	14	9
Clad/Cy	31	10	2	0



At Risk

Flu/Cy	62	41	19	10
Clad/Cy	31	14	6	0



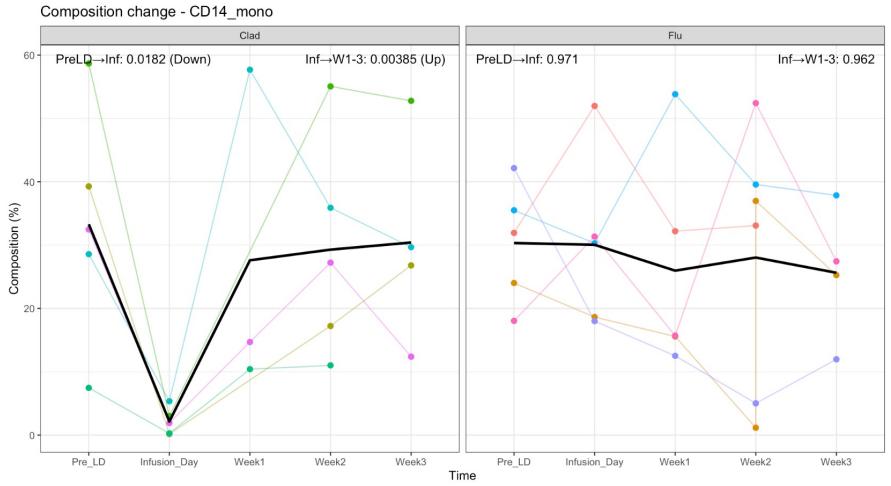


Filip Ionescu

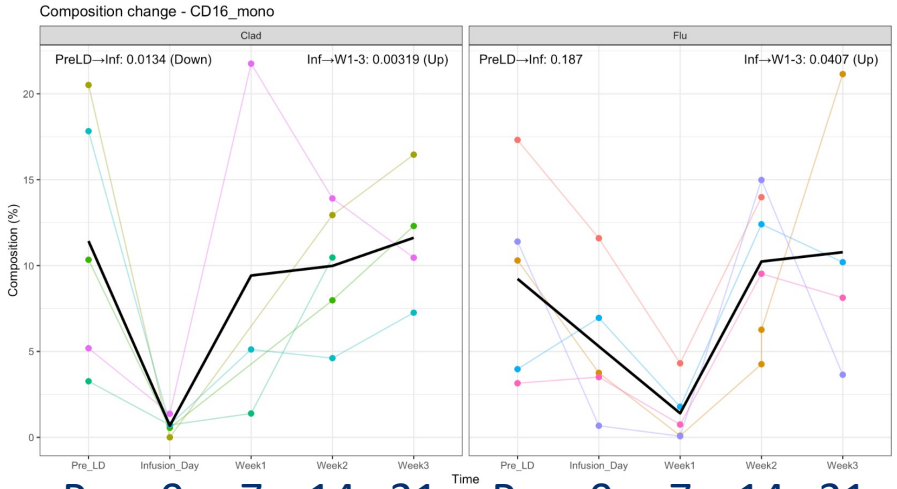
Differential effects on NK cells and myeloid cells

Clad/Cy Flu/Cy

CD14+ classical monocytes



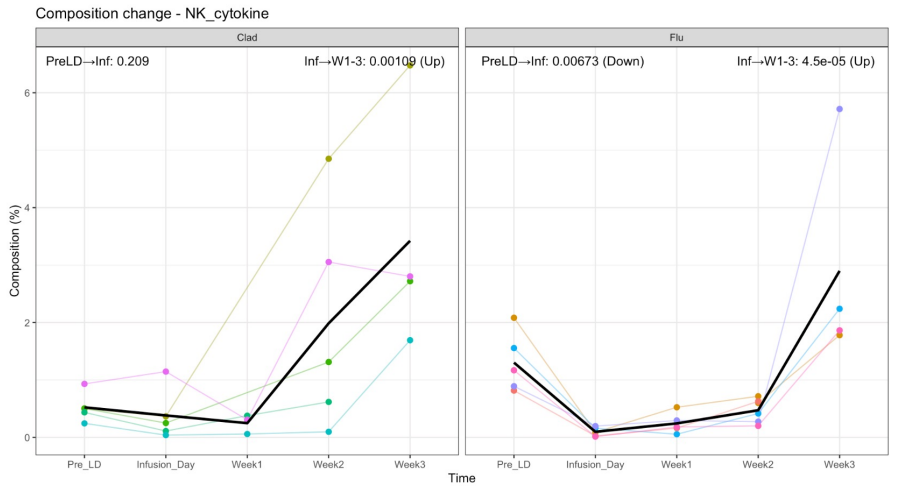
CD16+ non-classical monocytes



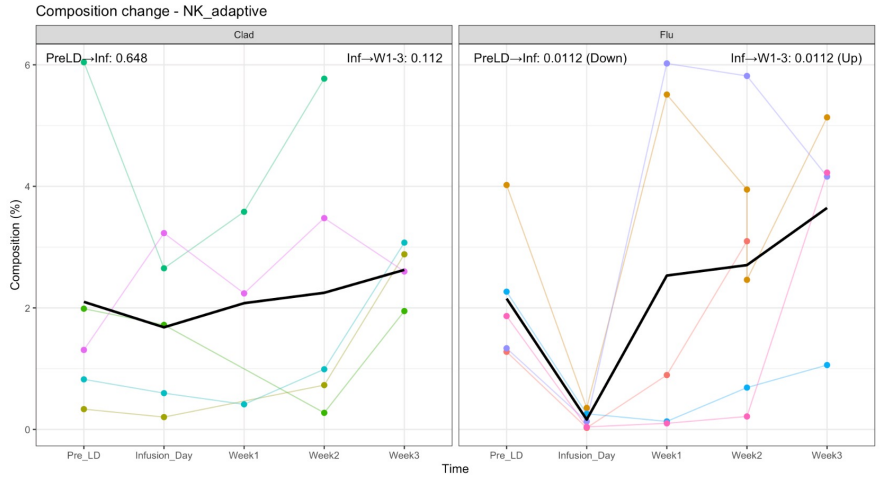
Day: Pre 0 7 14 21 Pre 0 7 14 21

Clad/Cy Flu/Cy

NK "cytokine"



NK "adaptive"



Day: Pre 0 7 14 21 Pre 0 7 14 21

Many Open Questions with Lymphodepletion

- What is the optimal regimen and dose for lymphodepletion? Is it the same for every patient?
- To what extent does CAR T cell efficacy depend on homeostatic expansion versus antigen-dependent expansion?
- What are the critical factors for lymphodepletion? Is it:
  - T cell depletion
  - IL-15 and IL-7 conditioning
  - Elimination of suppressive cells and/or immunity?
  - Stimulation of anti-tumor immunity?

- Could chemotherapy be replaced with something safer?

All the therapy around CAR T affects the outcome

1. Intermediary Therapies: Holding and Bridging
2. Systemic inflammation
3. Radiation bridging therapy
4. Lymphodepletion

Systemic Inflammation
Fred Locke and lab
Rawan Faramand
Marco Davila, Roswell Park

JAKi Pre-Modulation in DLBCL
Xuefeng Wang, statistician
Kelsey Lee, clinical trial coordinator

Radiation bridging
Nick Figura
Tim Robinson, Yale
Ruthie Chae, clinical trial coordinator
Matt Lunning, Chris D'Angelo, Nebraska

Lymphodepletion
Filip Ionescu
Jongphil Kim
Denise Kalos
Xiaoqing Yu
Guido Ghilardi, UPenn