THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
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CAR T-cell Therapy for Diffuse Large B-Cell Lymphoma

Paolo Strati, MD
Department of Lymphoma and Myeloma
Department of Translational Molecular Pathology
The University of Texas MD Anderson Cancer Center

Texas Society of Clinical Oncology 2022

Disclosure of Conflicts of Interest

Paolo Strati, MD, has the following financial relationships to disclose:

- Consultant – ADC Therapeutics, Genentech
- Speaker – Astrazeneca, ALX Oncology, Sobi

Presentation Outline

- Definition and indication
- Screening
- Apheresis
- Manufacturing and bridging
- Lympho-depletion and infusion
- Toxicity monitoring
- Efficacy evaluation
- Management of relapse

FDA NEWS RELEASE

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

Axi-cel (2017)

DLBCL
HGBCL
PMBCL
tFL

Failed 2 lines of systemic therapy

For Immediate Release: Oct

The U.S. Food and Drug A arta (axicabtagene ciloleucel), a cell-based g ith certain types of large B-cell lymphoma who have sed after at least two other kinds of treatment. Yesca R) T cell therapy, is the second gene therapy appr rtain types of non-Hodgkin lymphoma (NHL).

"Today marks another mi le new scientific paradigm for the treatment of serio gene therapy has gone from being a promising concep d largely untreatable forms of cancer," said FDA Com s approval demonstrates the continued momentum of e and we're committed to supporting and helping e oducts. We will soon release a comprehensive policy to a development of cell-based regenerative medicine. Th ll apply our expedited programs to breakthroug other gene therapies. We remain committed to sup safe and effective treatments that leverage these new s

Tisa-cel (2018)

DLBCL
HGBCL
tFL

Liso-cel (2021)

DLBCL
HGBCL
PMBCL
tFL

FDA NEWS RELEASE

FDA approves CAR-T cell therapy to treat adults with certain types of large B-cell lymphoma

Axi-cel (2022)

DLBCL
HGBCL
PMBCL
tFL

Refractory or relapsed after 1 line

For Immediate Release: October 18, 2017

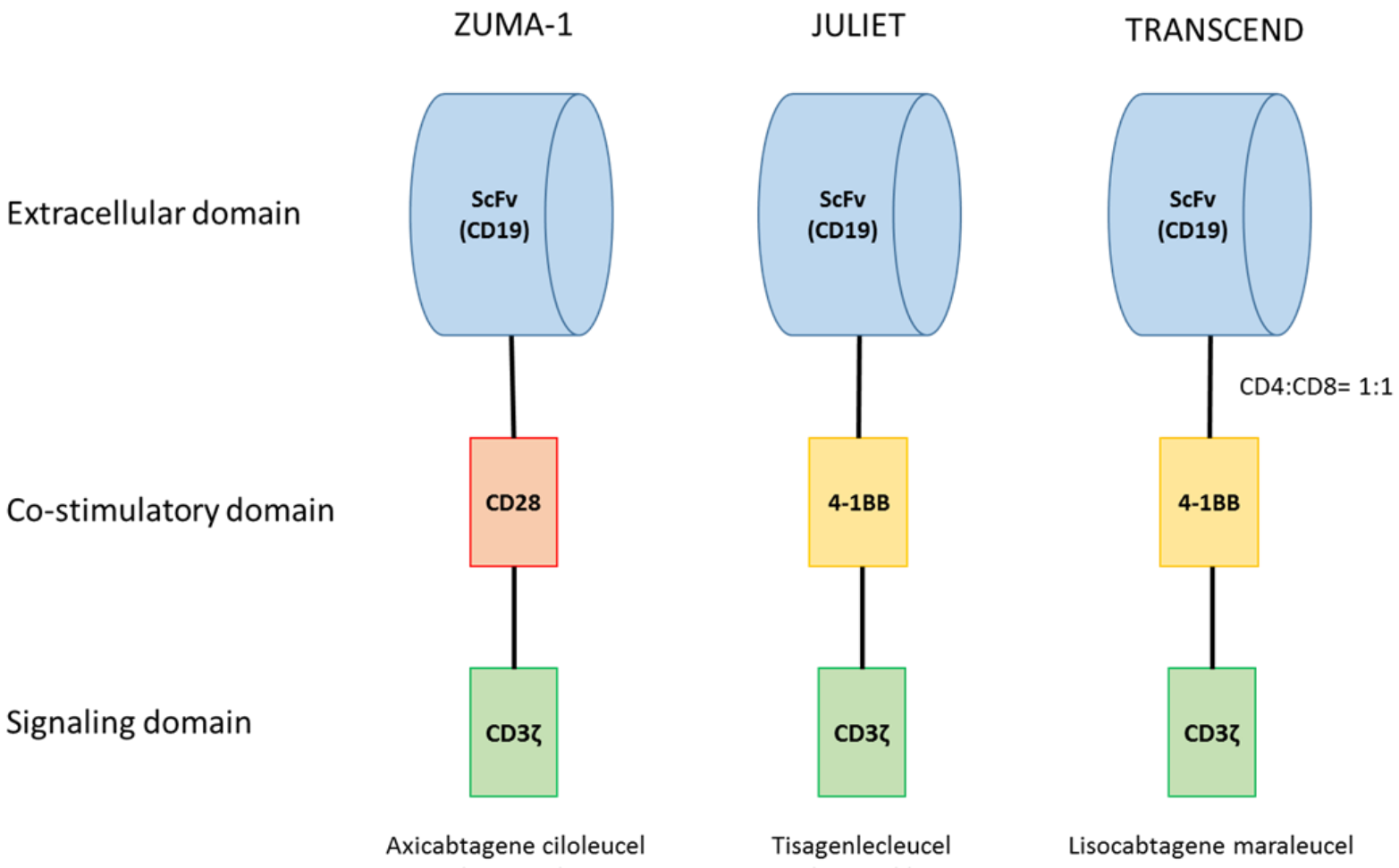
The U.S. Food and Drug Administration today approved Yescarta (axicabtagene ciloleucel), a cell-based gene therapy, to treat adult patients with certain types of large B-cell lymphoma who have not responded to or who have relapsed after at least two other kinds of treatment. Yescarta, a chimeric antigen receptor (CAR) T cell therapy, is the second gene therapy approved by the FDA and the first for certain types of non-Hodgkin lymphoma (NHL).

"Today marks another milestone in the development of a whole new scientific paradigm for the treatment of serious diseases. In just several decades, gene therapy has gone from being a promising concept to a practical solution to deadly and largely untreatable forms of cancer," said FDA Commissioner Scott Gottlieb, M.D. "This approval demonstrates the continued momentum of this promising new area of medicine and we're committed to supporting and helping expedite the development of these products. We will soon release a comprehensive policy to address how we plan to support the development of cell-based regenerative medicine. That policy will also clarify how we will apply our expedited programs to breakthrough products that use CAR-T cells and other gene therapies. We remain committed to supporting the efficient development of safe and effective treatments that leverage these new scientific platforms."

Liso-cel (2022)

DLBCL
HGBCL
PMBCL
tFL

Chimeric Antigen Receptor (CAR)



***Strati P** et al. Curr Oncol Rep 2019*

Toxicity remains a major ongoing challenge for CAR T-cell therapy

	ZUMA-1 (N=108)	JULIET (N=93)	TRANSCEND (N=73)
Histology	DLBCL, t-FL, PMBCL	DLBCL, t-FL	DLBCL, t-FL
Product	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Developed at	NCI	UPenn	SCH/FHCRC
Sponsor	Kite	Novartis	Juno
Conditioning	Flu-Cy	Flu-Cy or Benda	Flu-Cy
ORR	83%	52%	80%
CR rate	58%	40%	59%
Grade ≥3 CRS	13%	22%	1%
Grade ≥3 ICANS	31%	12%	13%
Grade ≥3 cytopenia	28%	32%	37%
FDA approval	2017 (Yescarta)	2018 (Kymriah)	2021 (Breyanzi)

Strati P et al. Curr Oncol Rep 2019

Screening (MDACC guidelines)

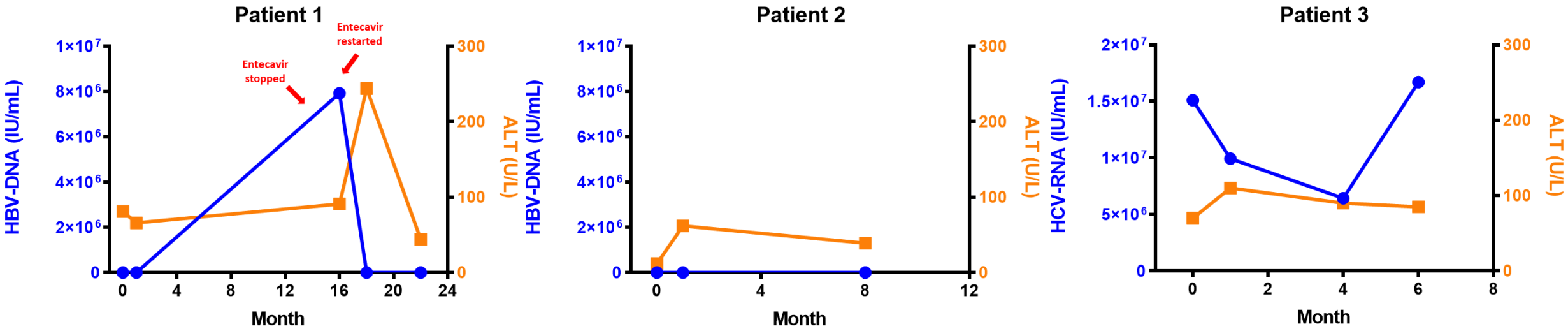
- ECOG 0-1
- LVEF >= 40% and/or no significant arrhythmia
- DLCO >= 55% of predicted value
- Platelet count >= 50 X 10^9/L (unless disease-related)
- ANC >= 1 X 10^9/L (unless disease-related)
- Creatinine clearance >= 30 mL/min
- No active secondary CNS lymphoma
- No significant psychiatric illness or cognitive impairment
- **How about HBV, HCV and HIV infection?**

Baseline characteristics

	Patient 1	Patient 2	Patient 3
HEPATITIS CHARACTERISTICS			
HBsAg	Negative	Positive	negative
HBcAb	Positive	Positive	Negative
HBV DNA (IU/mL)	<20	<10	--
HBV NAT	Negative	--	--
Anti-HCV	Negative	Negative	Positive
HCV RNA (IU/mL)	--	--	15.1 millions
ALT (U/L)	162	12	70
Bilirubin total (mg/dL)	0.7	0.5	0.8
CT evidence of cirrhosis	No	No	No
Previous hepatitis	No	Yes	Yes
Antiviral therapy	Entecavir	Tenofovir	--

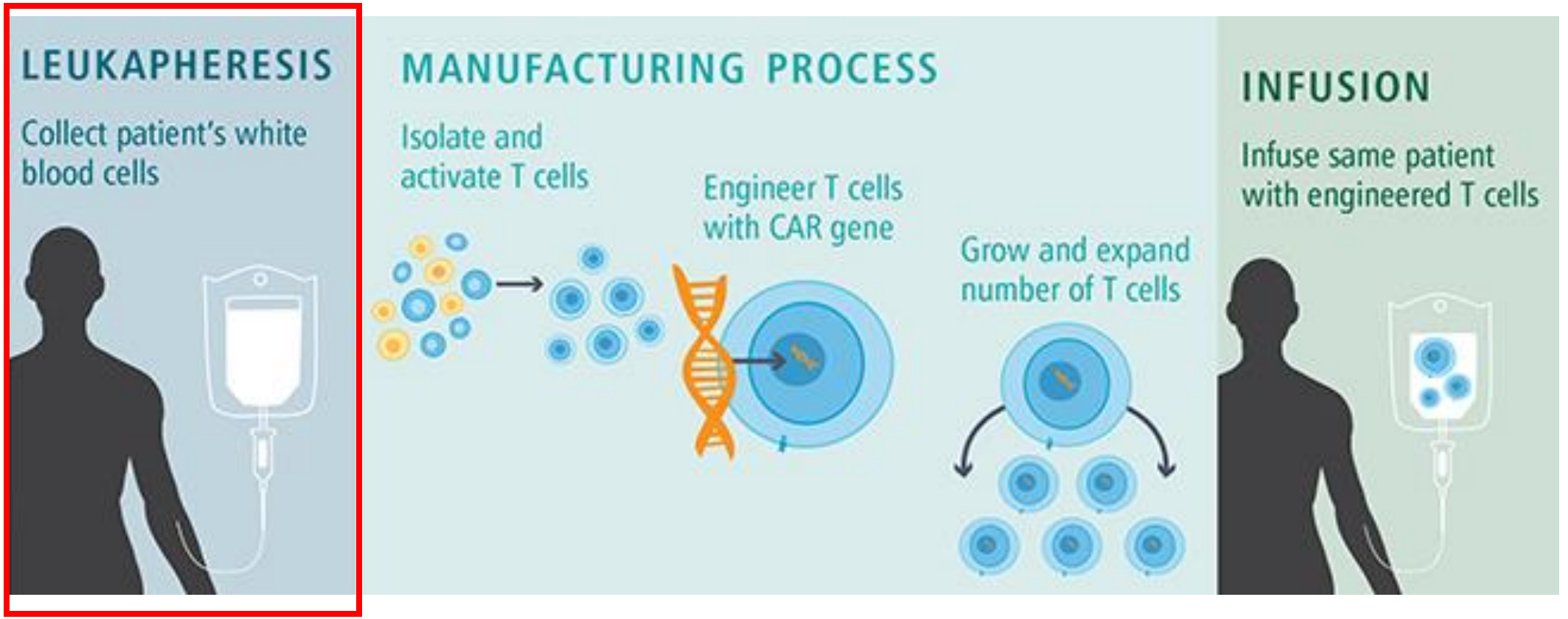
Strati P et al. Blood 2019

Prolonged antiviral prophylaxis is needed



Strati P et al. Blood 2019

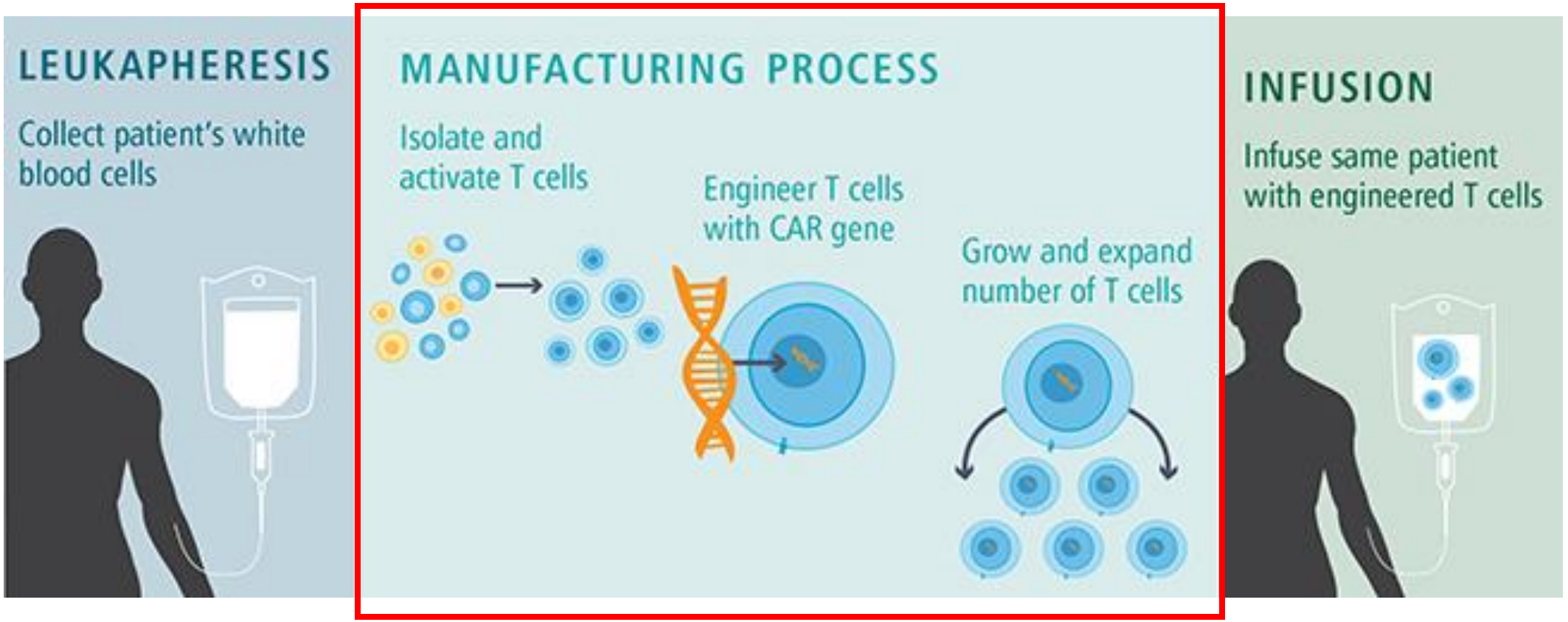
Apheresis



No corticosteroids for 7 days prior
No systemic therapy for 14 days prior

Manufacturing: how to bridge?

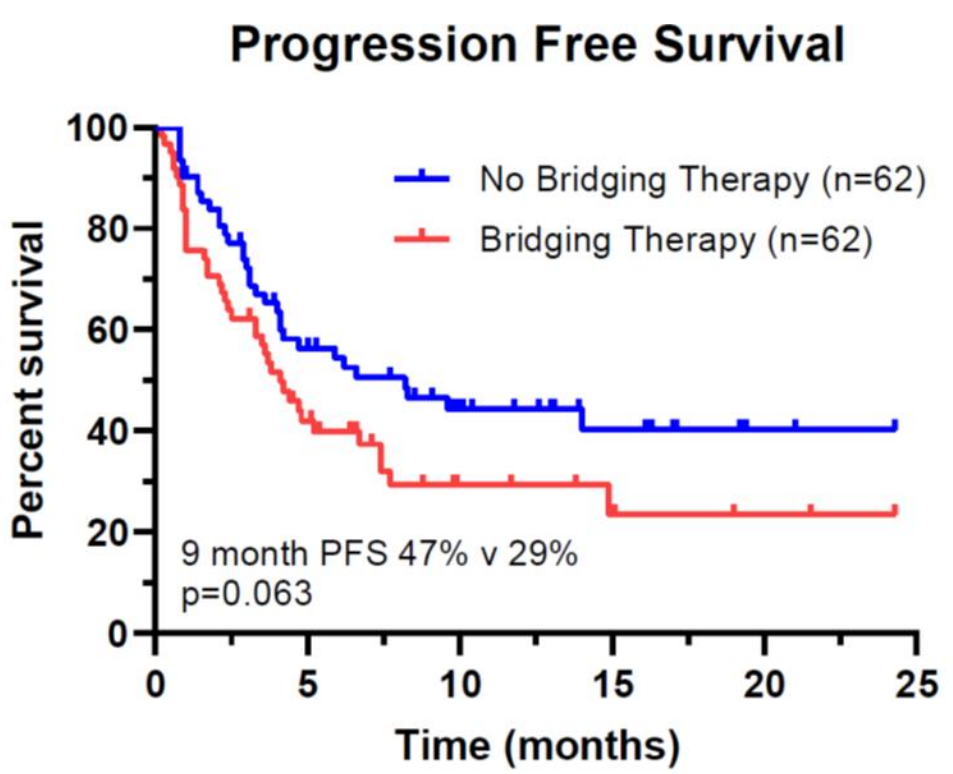
Median of 17-28 days



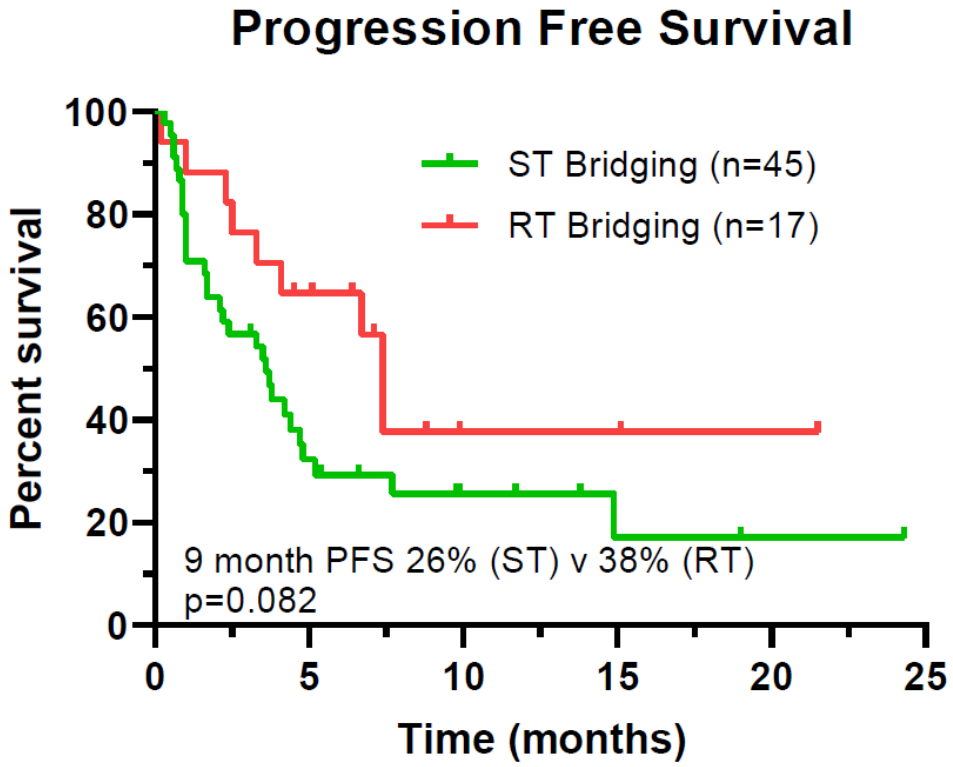
No bridging
Chemo-immunotherapy

Biological therapy
Radiation therapy

Bridging with radiation therapy



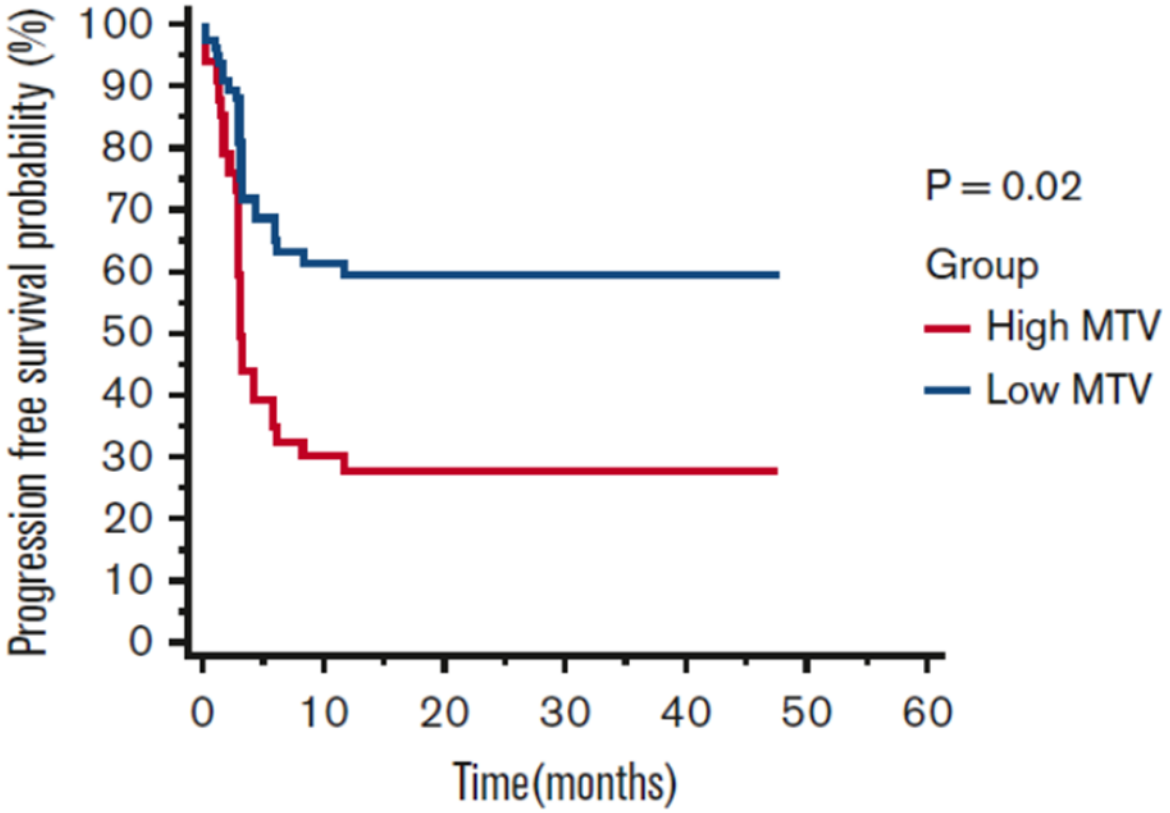
No Bridging	62	31	19	11	4
Bridging	62	22	9	5	3

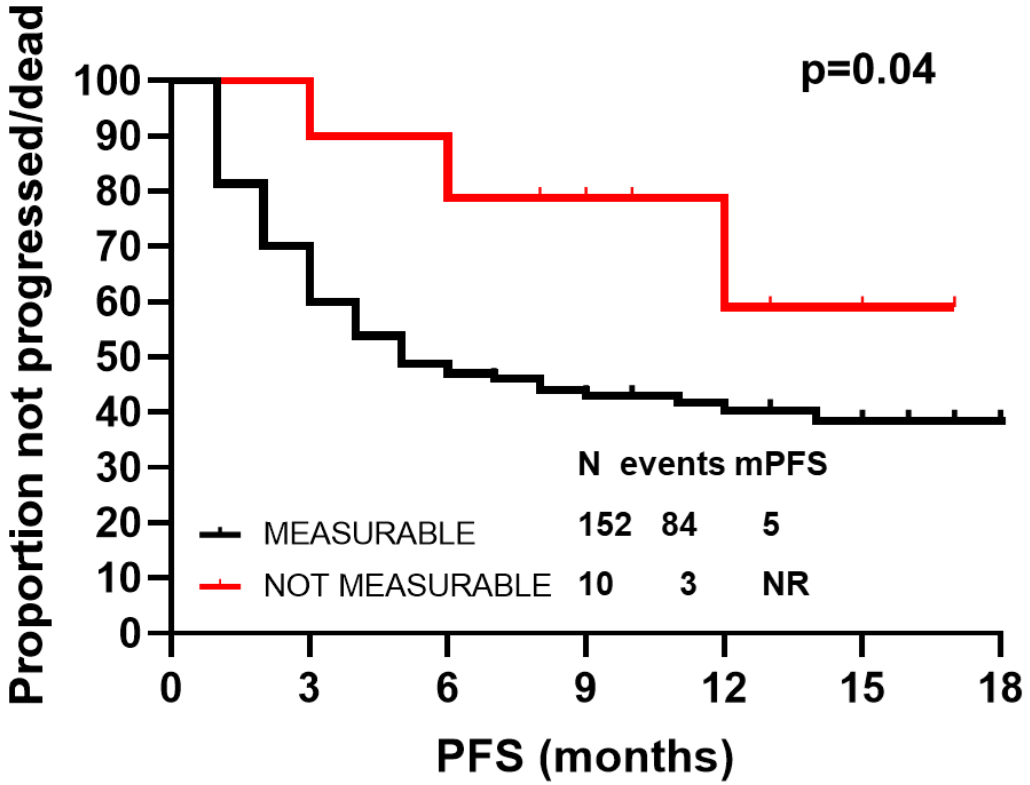


ST Bridging	45	12	6	3	2
RT Bridging	17	11	3	3	2

***Pinnix CC** et al. Blood Adv 2020*

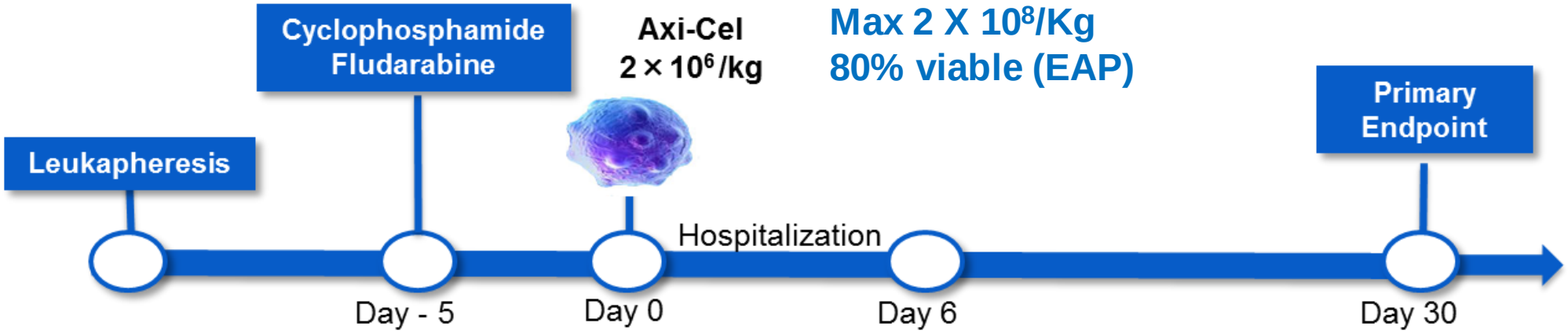
Low tumor burden before axi-cel infusion associates with longer PFS





***Dean EA et al**, Blood Adv 2020; **Gouni S** et al. ASH 2021*

Lympho-depletion and infusion

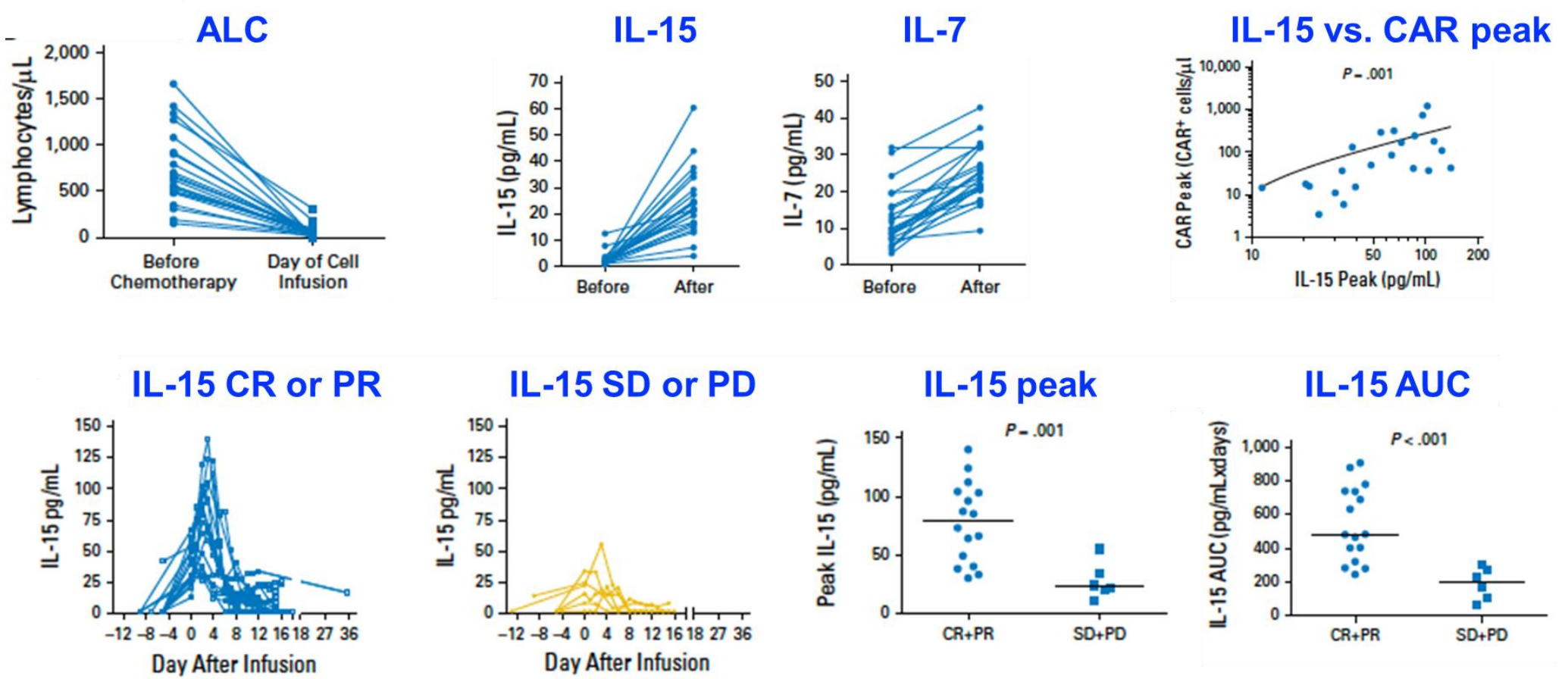


On days -5, -4, and -3

Cyclophosphamide (500 mg/m²/day)

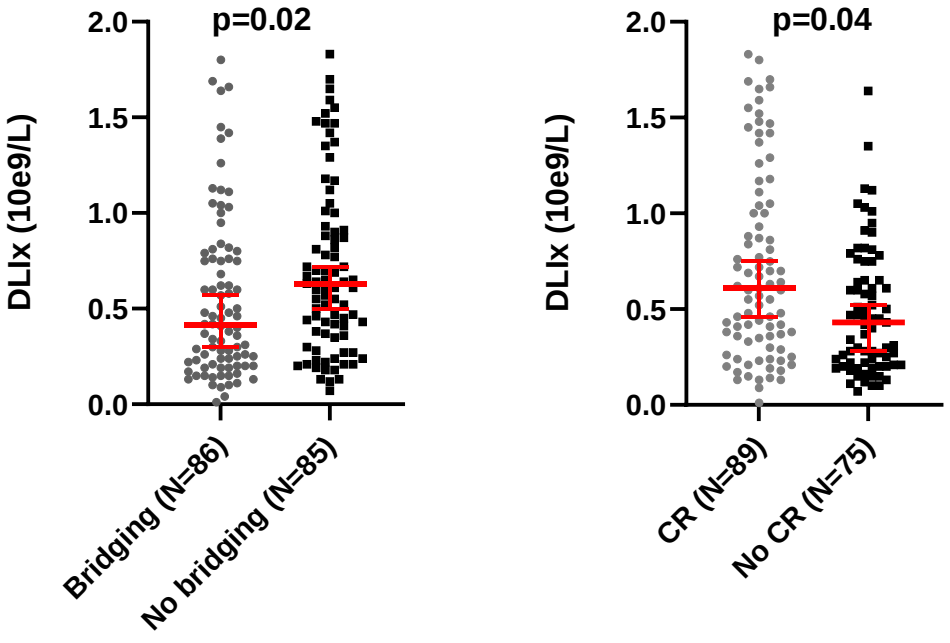
Fludarabine (30 mg/m²/day)

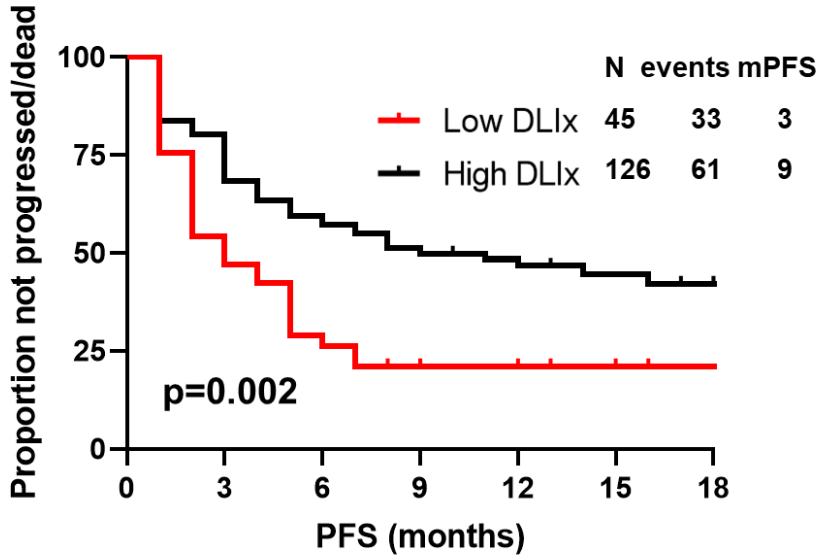
Conditioning chemotherapy affects the cytokine milieu



***Kochenderfer et al**, J Clin Oncol 2017*

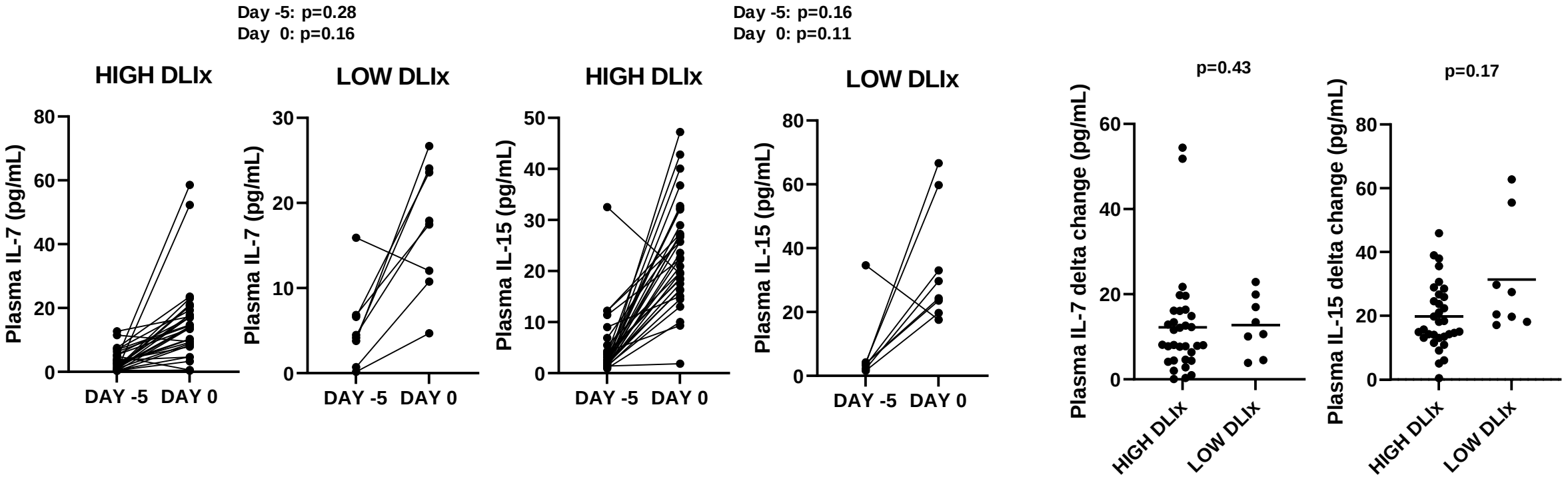
Low variation in ALC (DLIx) associates with use of BT and worse outcome





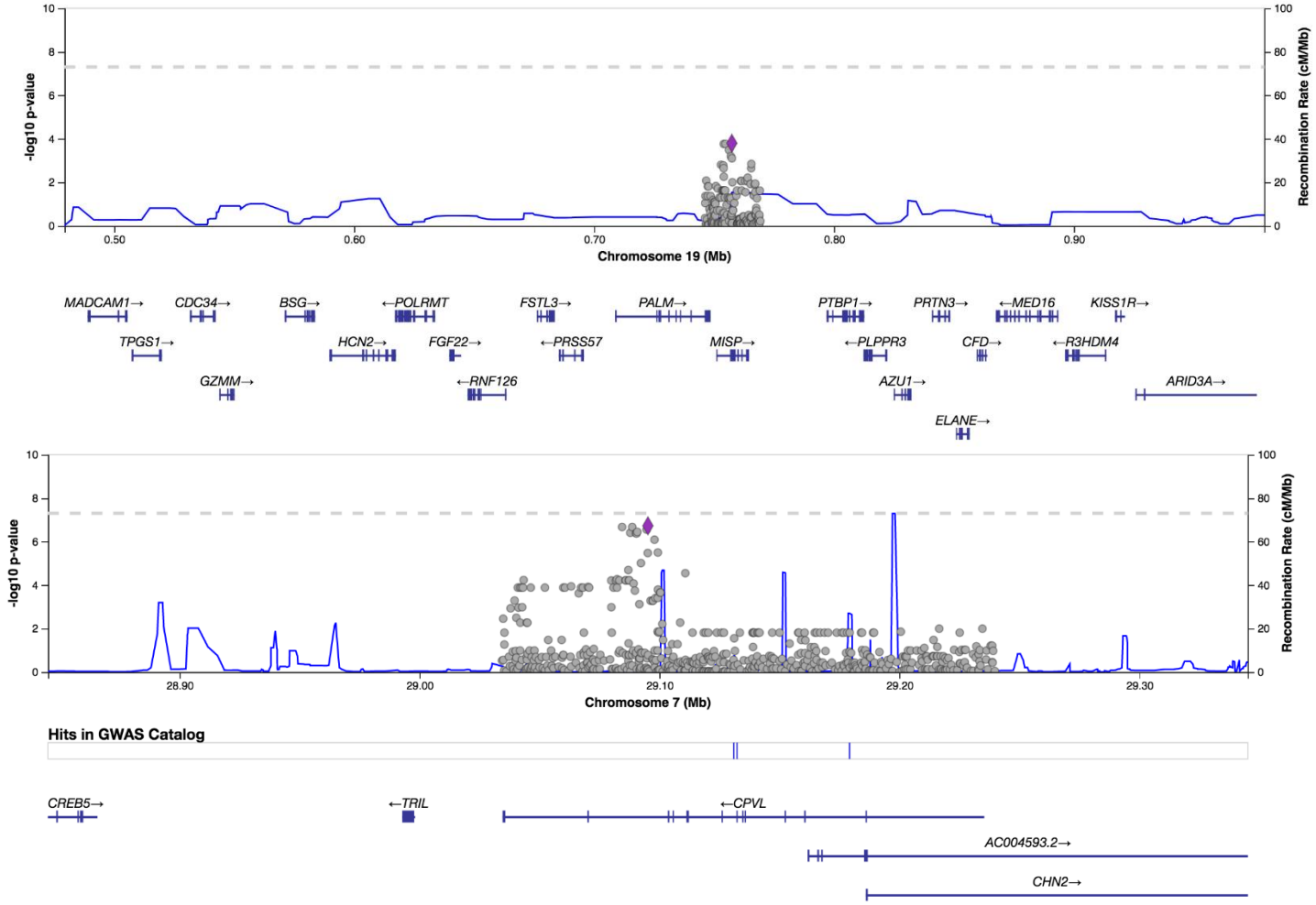
***Strati P et al**, ASH 2020*

Variation in ALC (DLIx) is not driven by IL-7 nor IL-15



***Strati P et al**, ASH 2020*

Polymorphisms in macrophage-related genes are associated with variation in ALC (DLIx)



***Strati P et al**, ASH 2020*

Post-infusion monitoring

- **7 days** on inpatient service
- **3 days** at infusion center until day 10
- **Twice a week** in fast track until day 30
- First restaging in clinic at **day 30**
- If PR/CR, return for restaging at **day 90**

Cytokine release syndrome (CRS) management

Grade	Parameter	Intervention
1	Fever Normal BP/sO2	**Acetaminophen** up to 3 days (then tocilizumab)
2	No vasopressors Low flow oxygen	**Tocilizumab** (8 mg/Kg IV Q8H, max X 4)
3	1 vasopressor High flow oxygen	Tocilizumab **Dexamethasone 10-20 mg** IV Q6H
4	> 1 vasopressor Positive pressure	Tocilizumab **Methylprednisolone 1 g IV daily**

Neelapu SS *et al. Nat Rev Clin Oncol 2018 (ASTCT guidelines)*

Immune effector cell associated neurotoxicity (ICANS) grading: a moving target

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Lee DW et al. Biol Blood Marrow Transplant 2019 (**ASTCT grading system**)

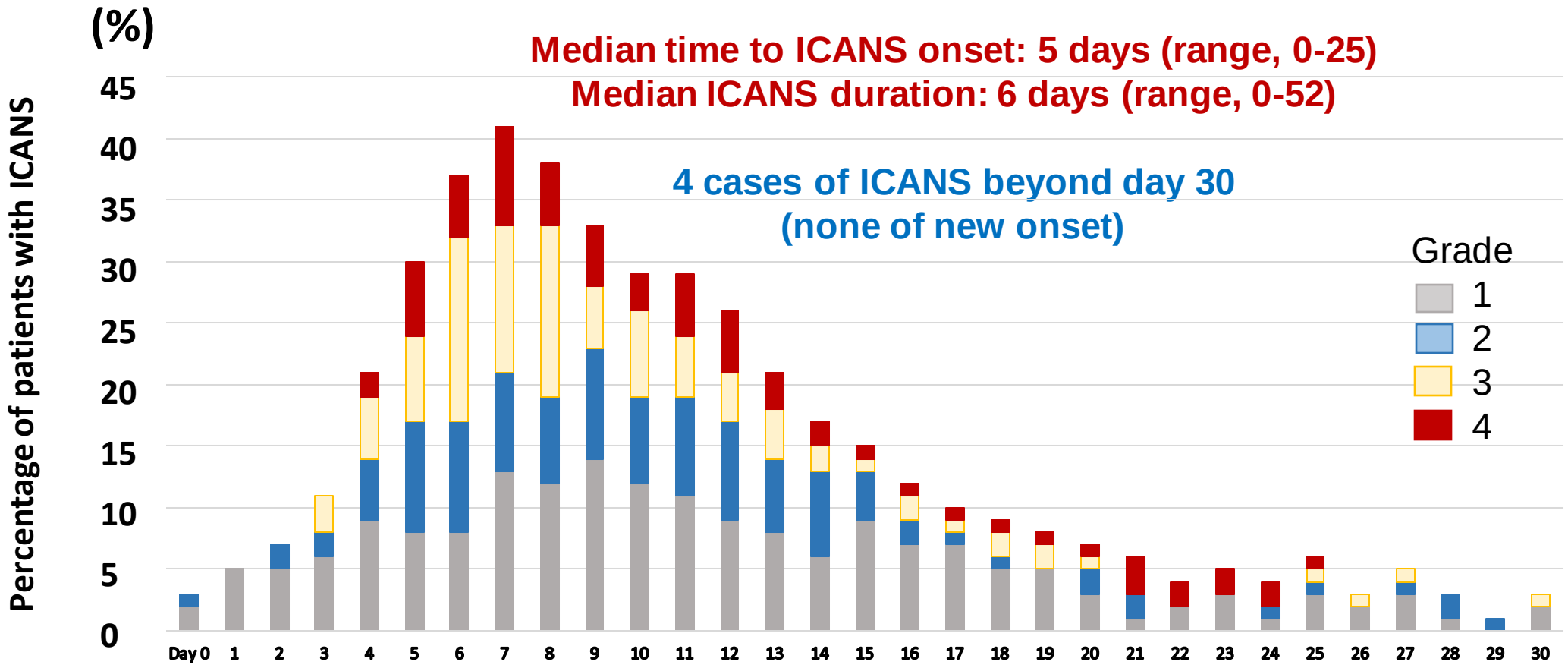
ICANS management

Levetiracetam 500 mg PO BID (prophylaxis for 30 days)

Grade	Parameter	Intervention
1	ICE score 7-9	Fundoscopic exam, MRI, EEG
2	ICE score 3-6	**Dexamethasone 10-20 mg** X 1
3	ICE score 0-2 Seizure < 5 minutes Focal edema on CT/MRI	**Dexamethasone 10-20 mg** IV Q6H
4	ICE score 0 Seizure > 5 minutes Diffuse edema on CT/MRI Focal motor weakness	**Methylprednisolone 1 g IV daily**

***Neelapu SS** et al. Nat Rev Clin Oncol 2018 (ASTCT guidelines)*

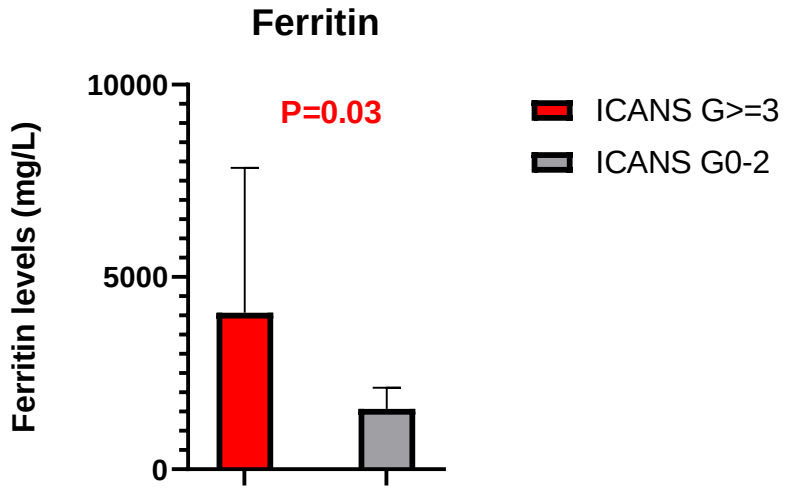
ICANS characteristics and trends (30 days)

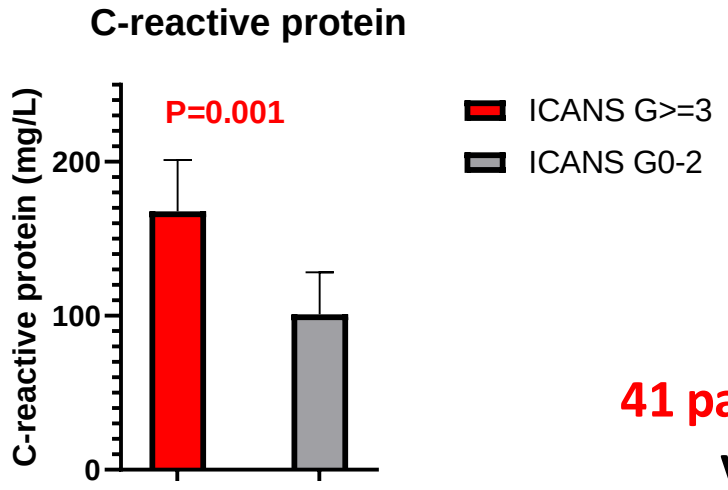


1 IRREVERSIBLE CASE (status epilepticus, day 51)

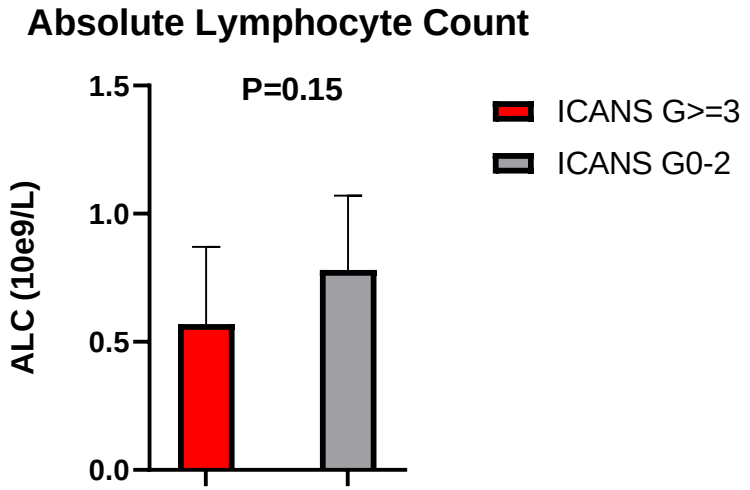
***Strati P et al**, Blood Adv 2021*

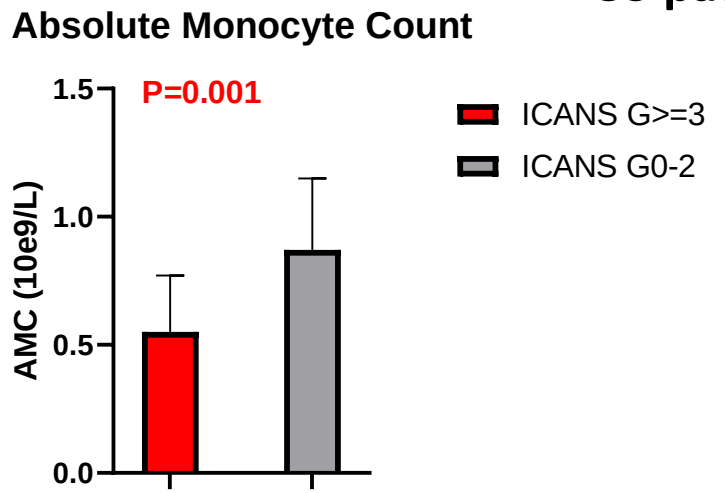
High ferritin and CRP and low AMC 30-day peaks associate with grade ≥3 ICANS





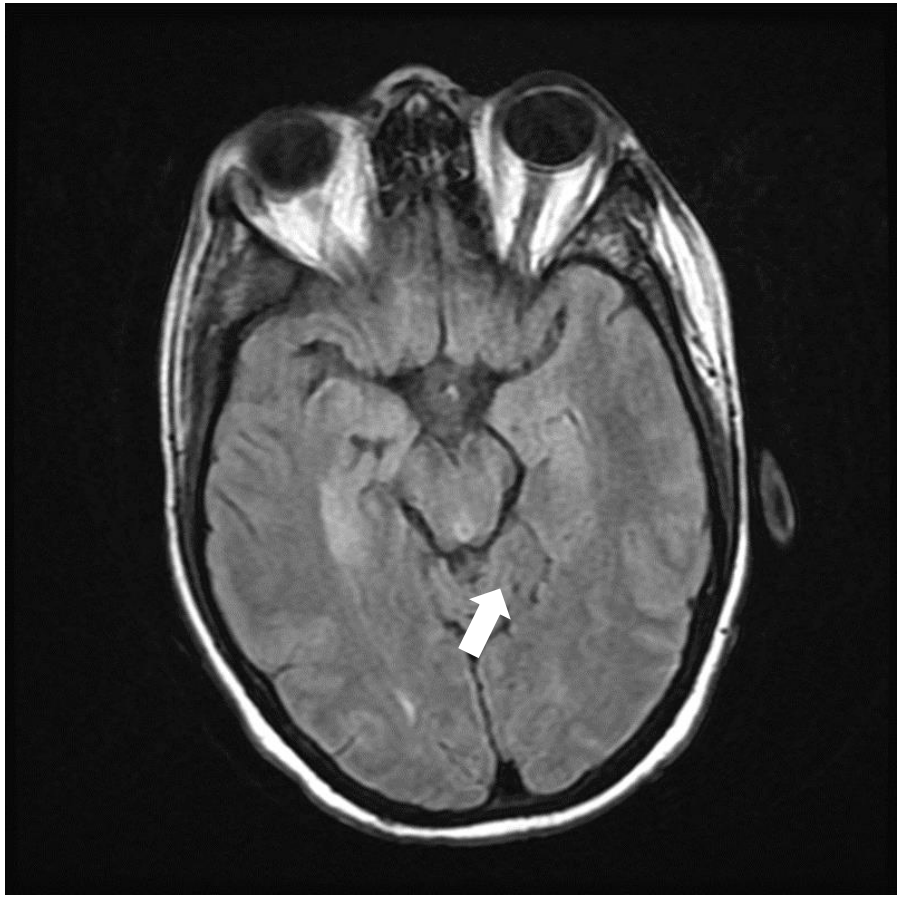
41 patients
vs
59 patients





***Strati P et al**, Blood Adv 2021*

Four MRI patterns of ICANS were observed

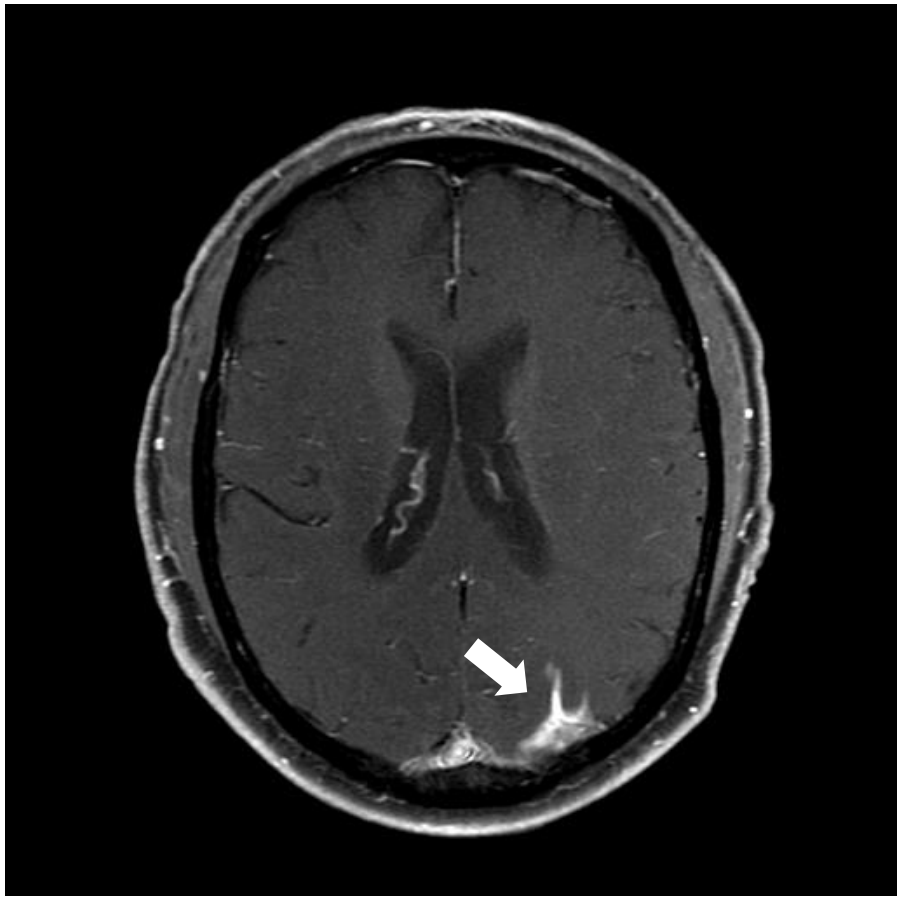


Encephalitis-like (N=7)
(all with AMS)

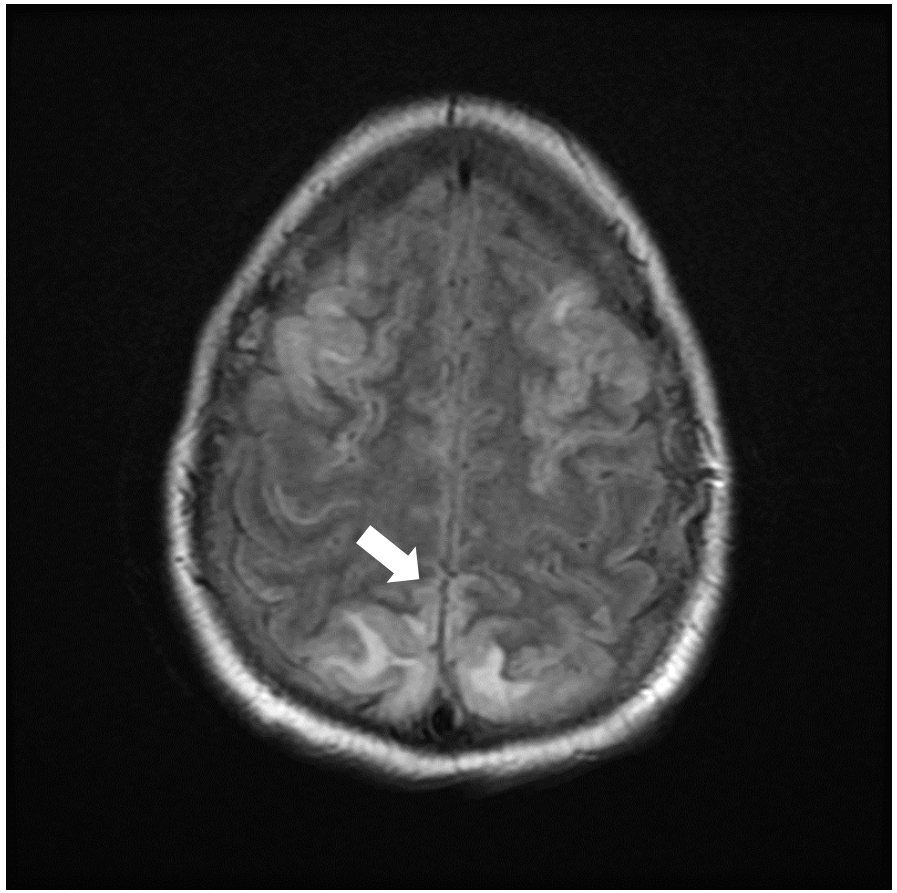
Stroke-like (N=3)
(all with AMS)

***Strati P et al**, Blood Adv 2021*

Four MRI patterns of ICANS were observed



Leptomeningeal disease-like (N=2)
(both with AMS)

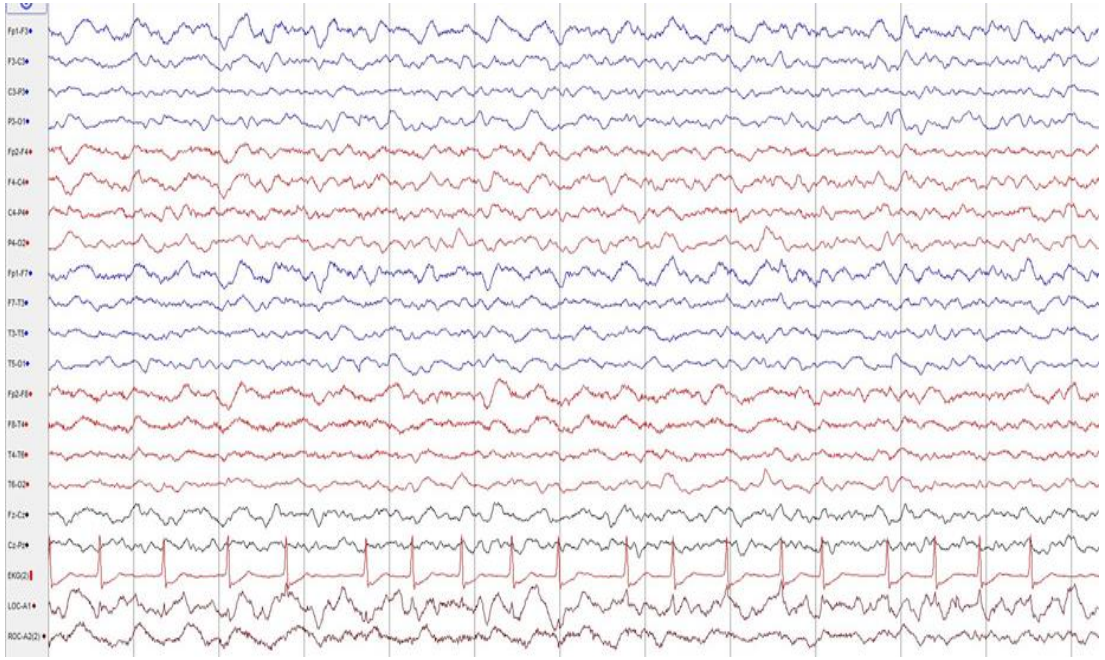


PRES-like (N=2)
(both with AMS)

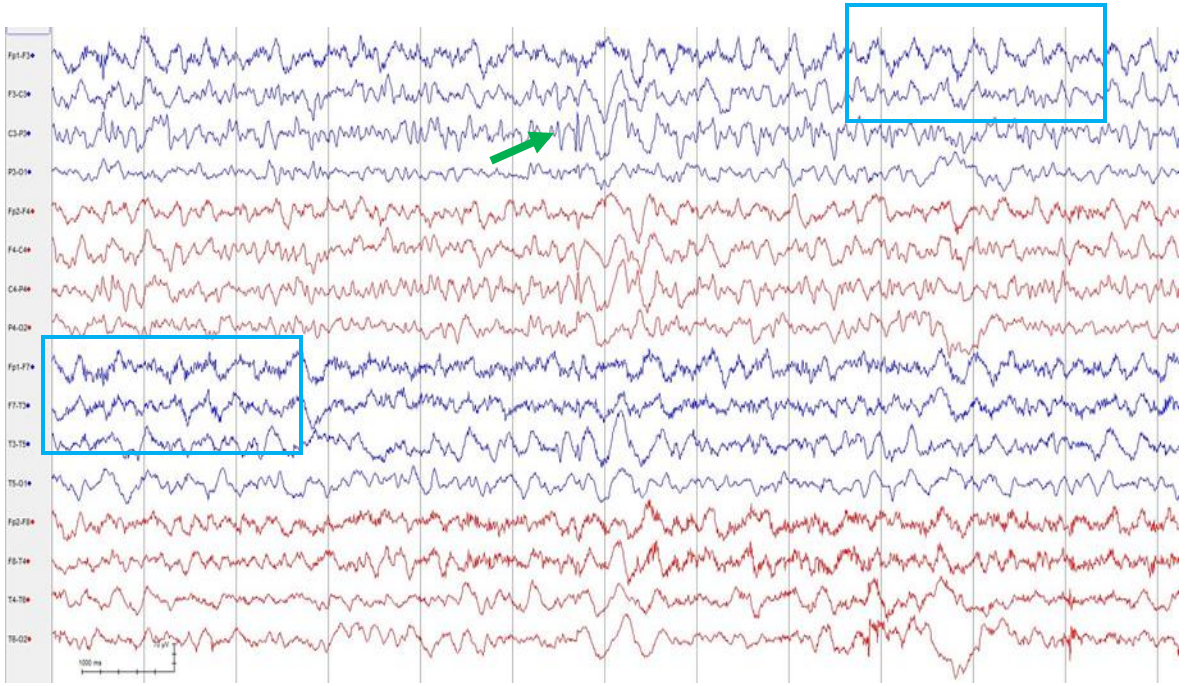
***Strati P et al**, Blood Adv 2021*

Four EEG patterns of ICANS were observed

EEG performed in 55 patients with ICANS, multiple per patient, abnormal in 50



Diffuse slowing (N=49)

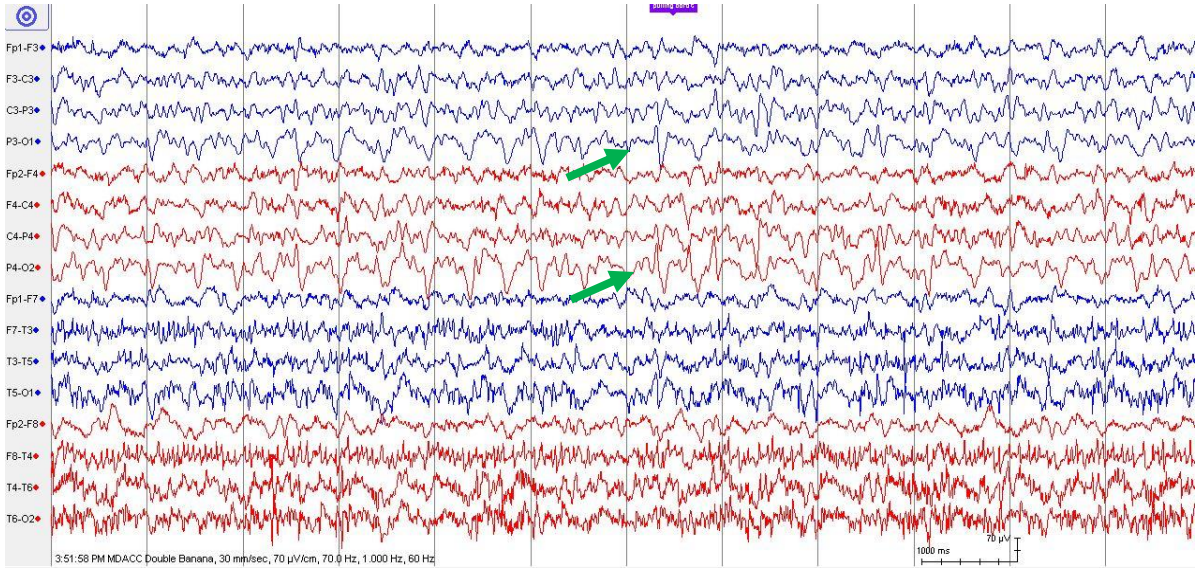


Focal slowing (N=3)

***Strati P et al**, Blood Adv 2021*

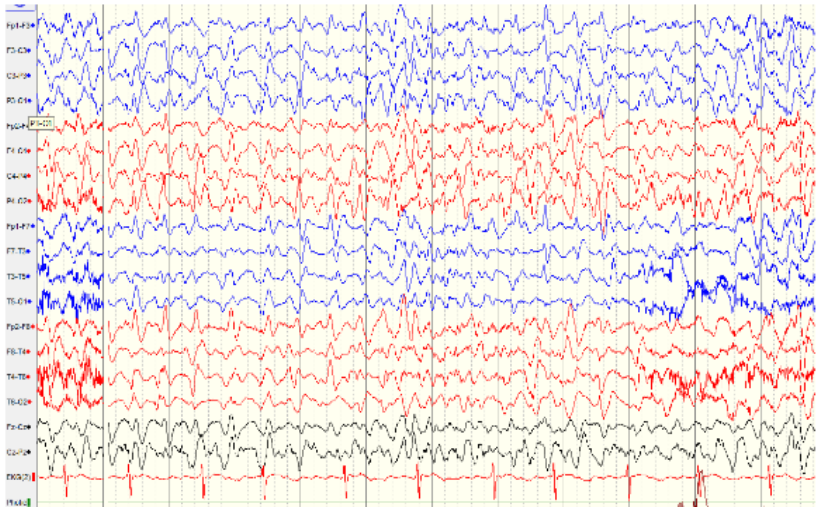
Four EEG patterns of ICANS were observed

Epileptiform discharges/NCSE were more common in patients progressing from G1-2 to G≥3 ICANS in < 24 hours (41% vs 17%, p=0.17)

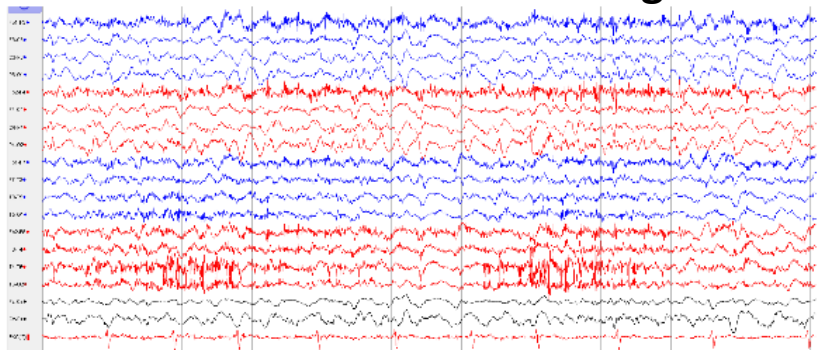


Epileptiform discharges (N=6)

Prior to lorazepam



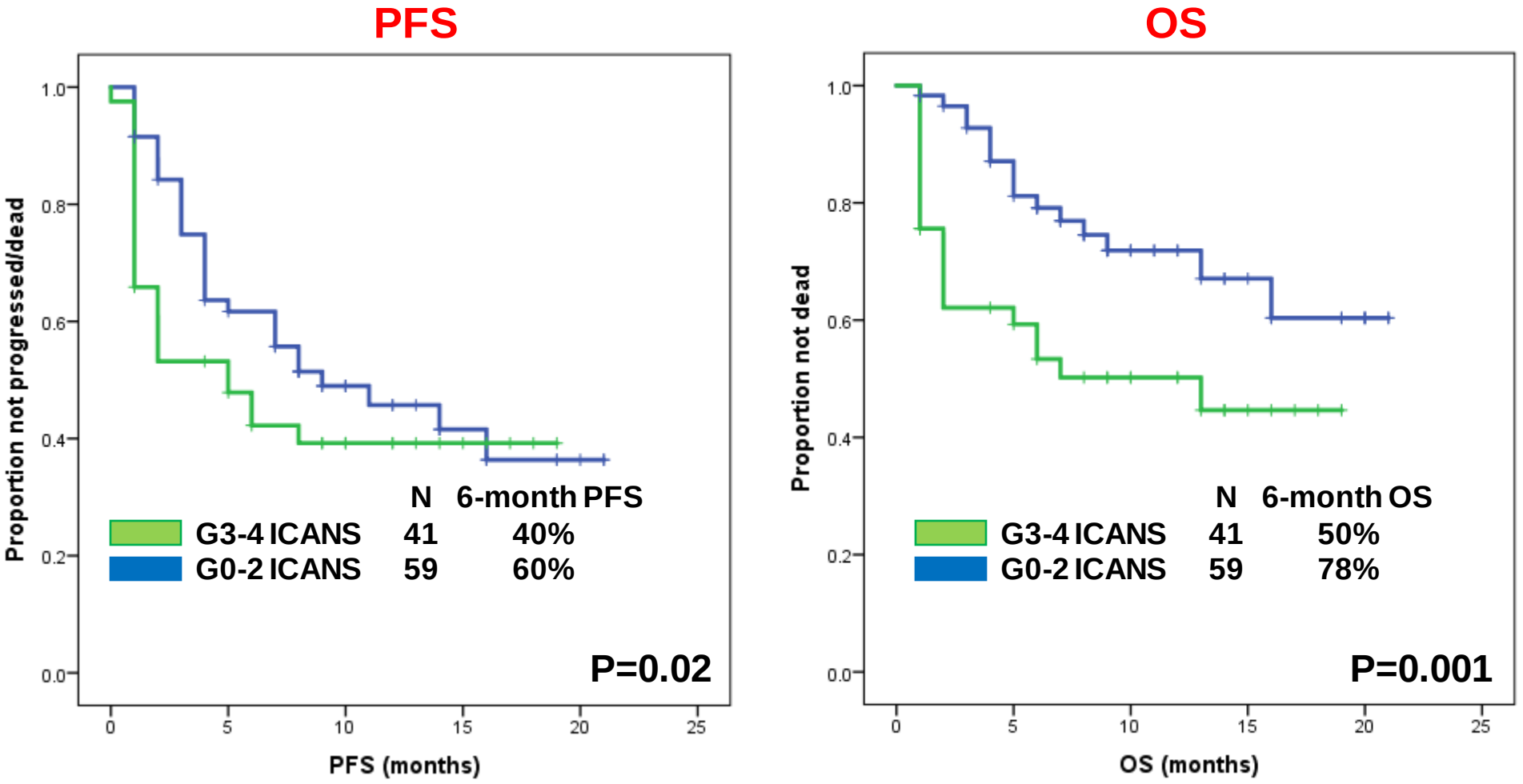
After 1 mg of lorazepam



Non-convulsive status epilepticus (N=8)

***Strati P et al**, Blood Adv 2021*

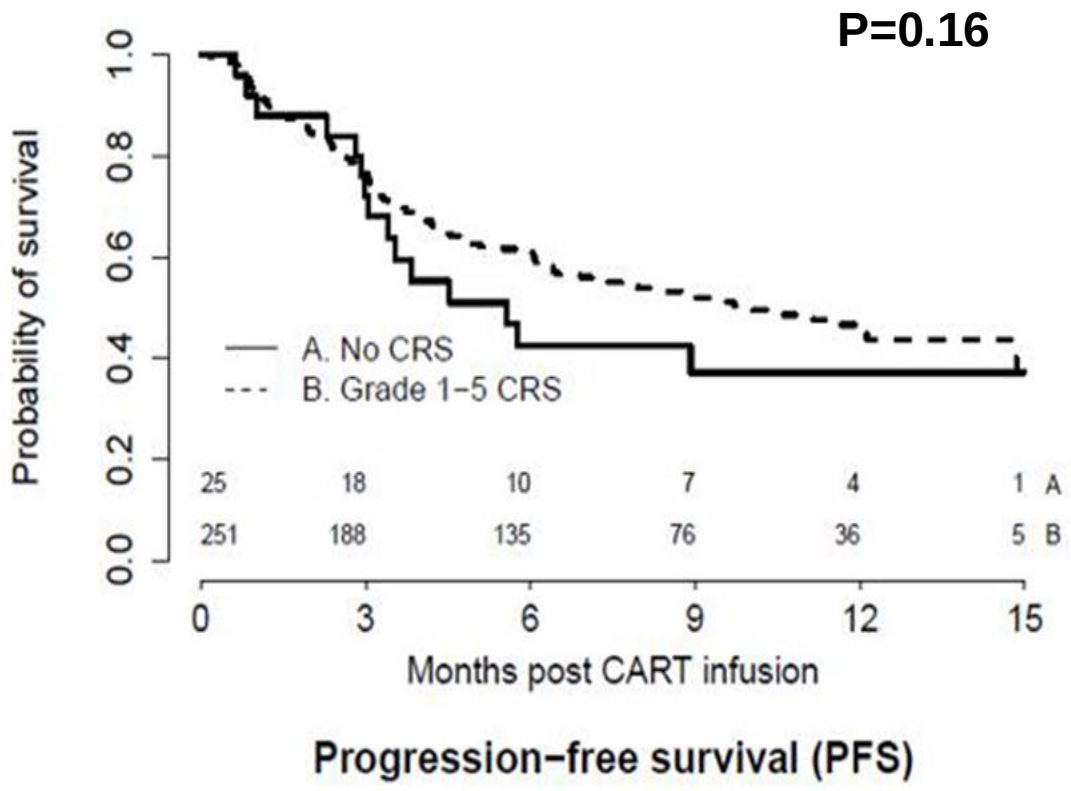
Grade ≥3 ICANS was associated with shorter PFS and OS



Median follow-up of 10 months (95% CI, 8-15 months)

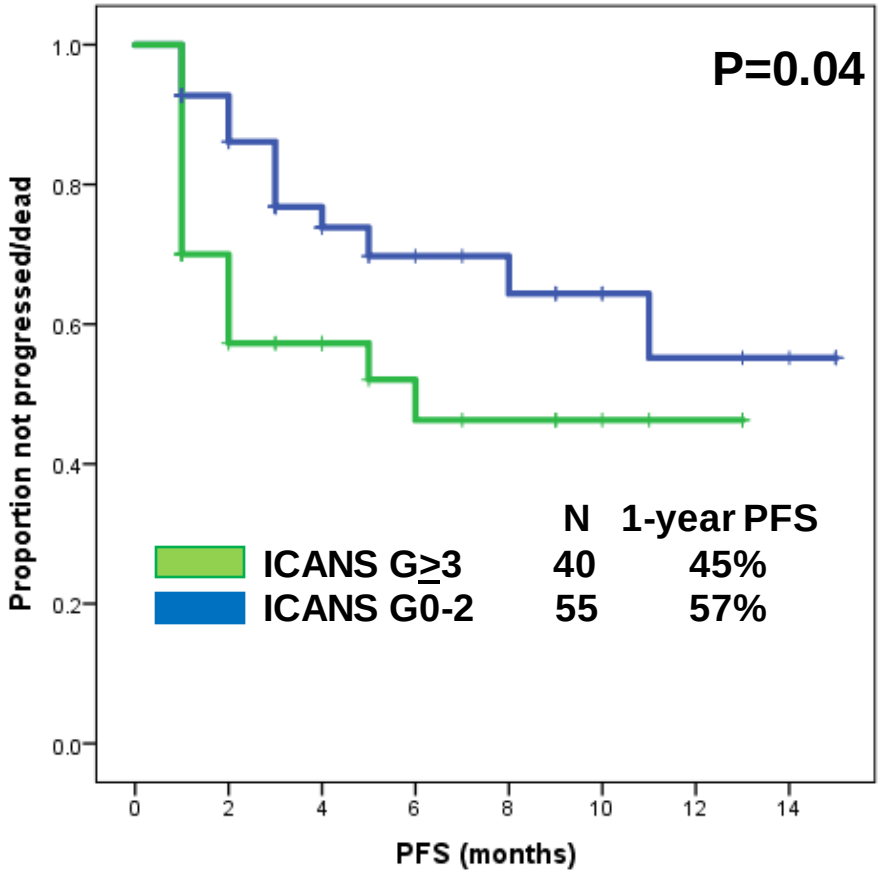
G3-4 CRS does not associate with worse outcome

CRS
(mostly treated with tocilizumab)



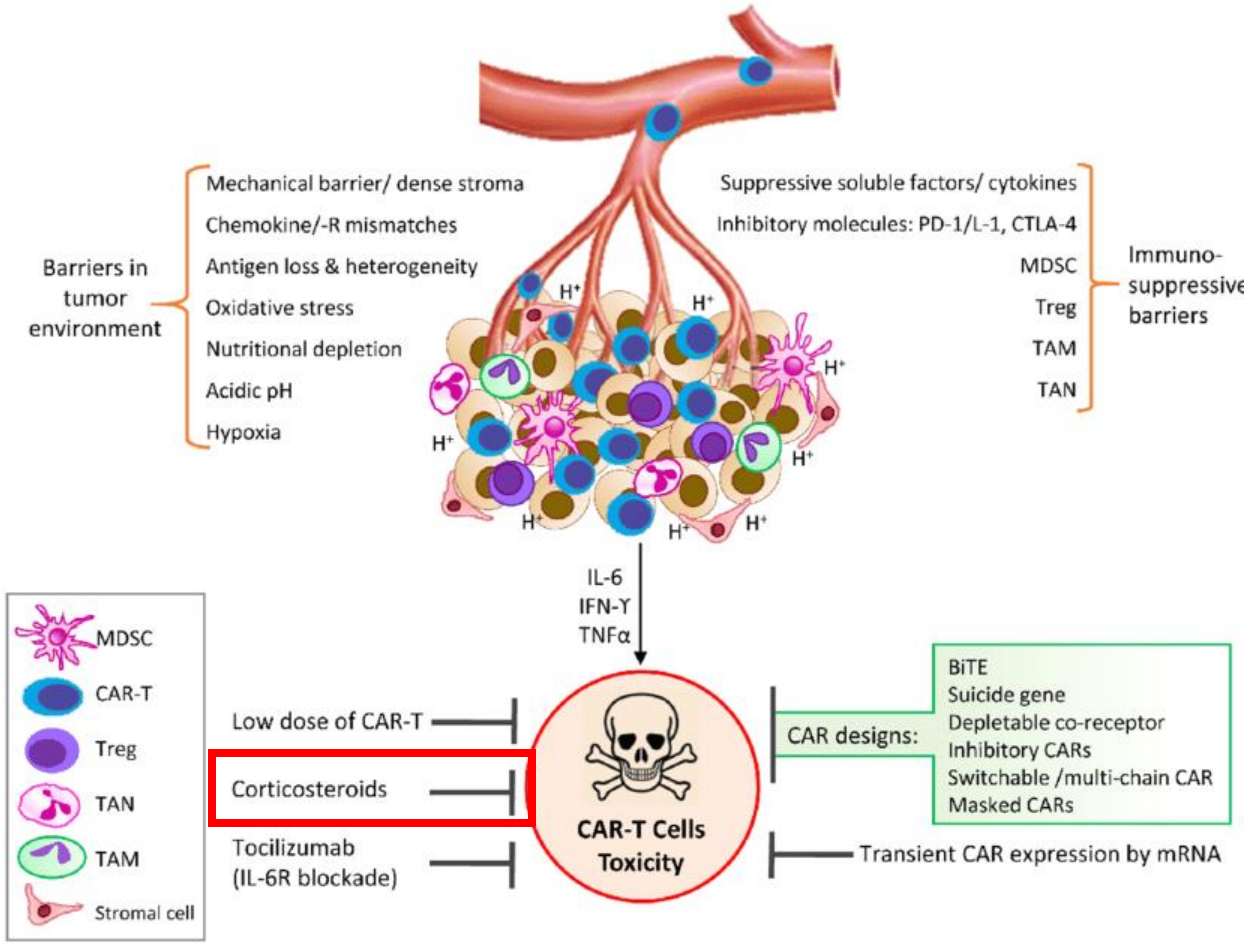
Progression-free survival (PFS)

ICANS
(mostly treated with corticosteroids)



Strati P et al, Blood Adv 2020; ***Jacobs MT et al***, ASH 2019

Corticosteroids are frequently used to mitigate CAR T-cell-associated toxicity

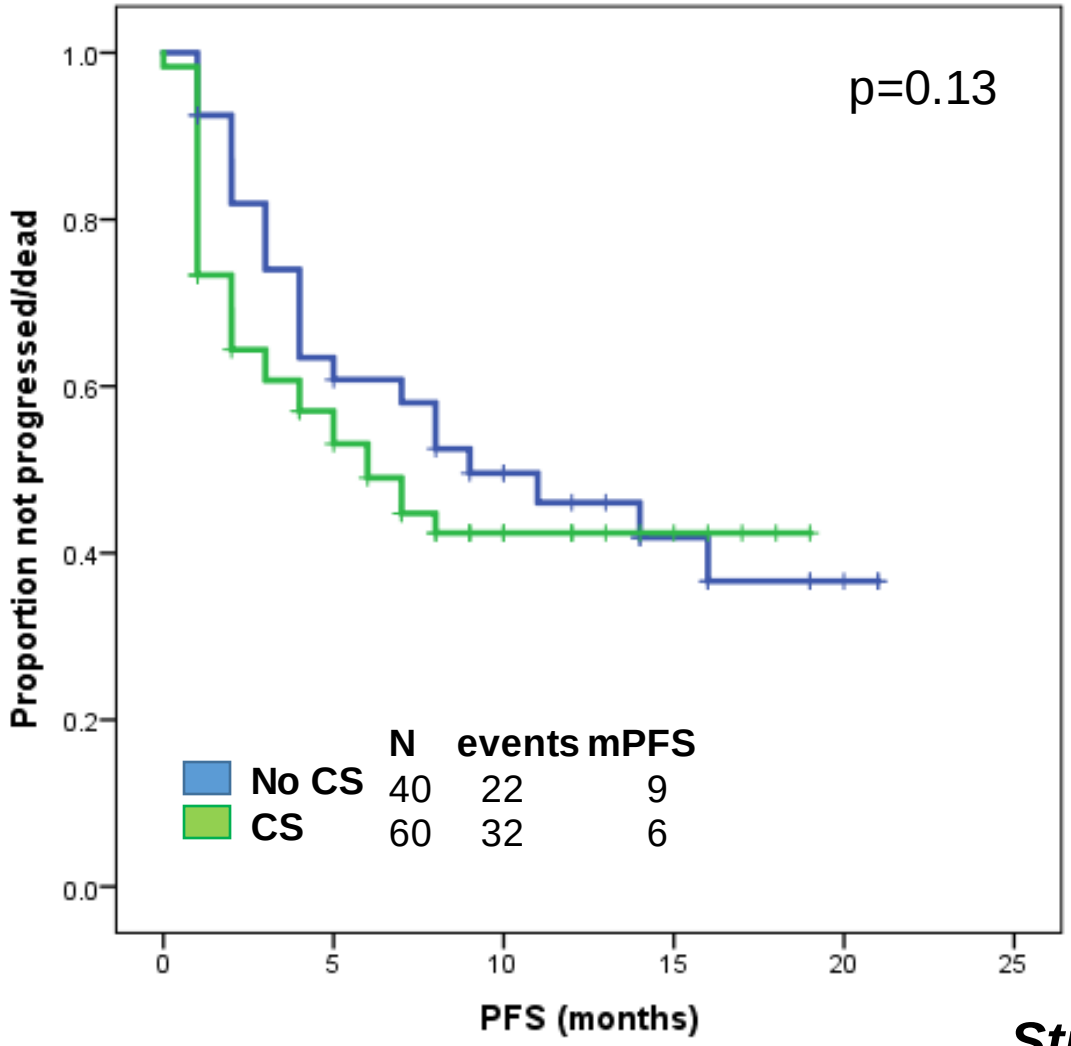


Study	Percentage of patients requiring corticosteroids
ZUMA-1	27%
JULIET	10%
TRANSCEND	21%
Real world	55%

Use of corticosteroids associated with shorter OS in real world, but not in ZUMA-1

Nastoupil LJ et al, JCO 2020; ***Strati P et al***, Front in Oncol 2020

Use of corticosteroids did not significantly associate with shorter PFS after CAR T-cell therapy



CR rate 55/96 (57%).

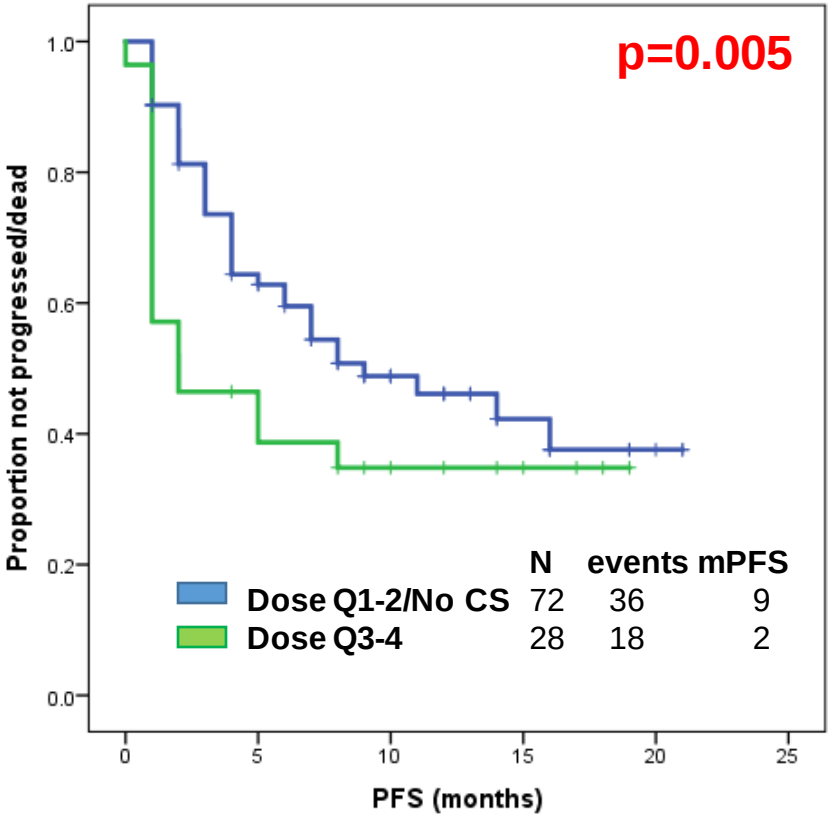
Median follow-up:10 months (95% CI 8-12 months)

Median PFS: 8 months (95% CI 3-13 months, 54 events)

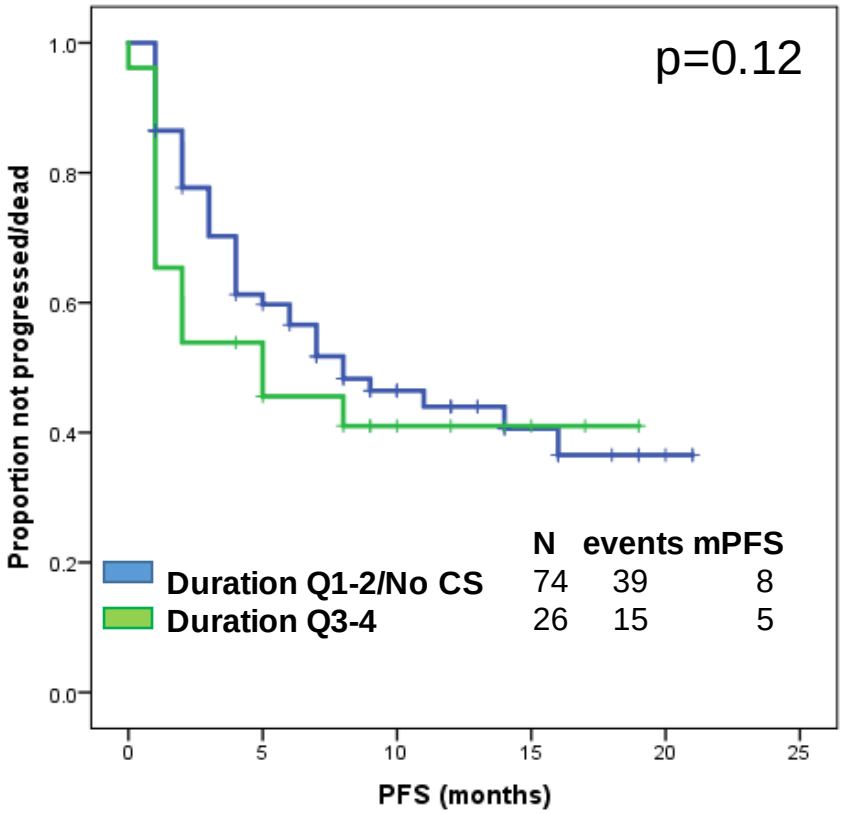
***Strati P et al**, Blood 2021*

Use of high dose corticosteroids associated with shorter PFS after CAR T-cell therapy

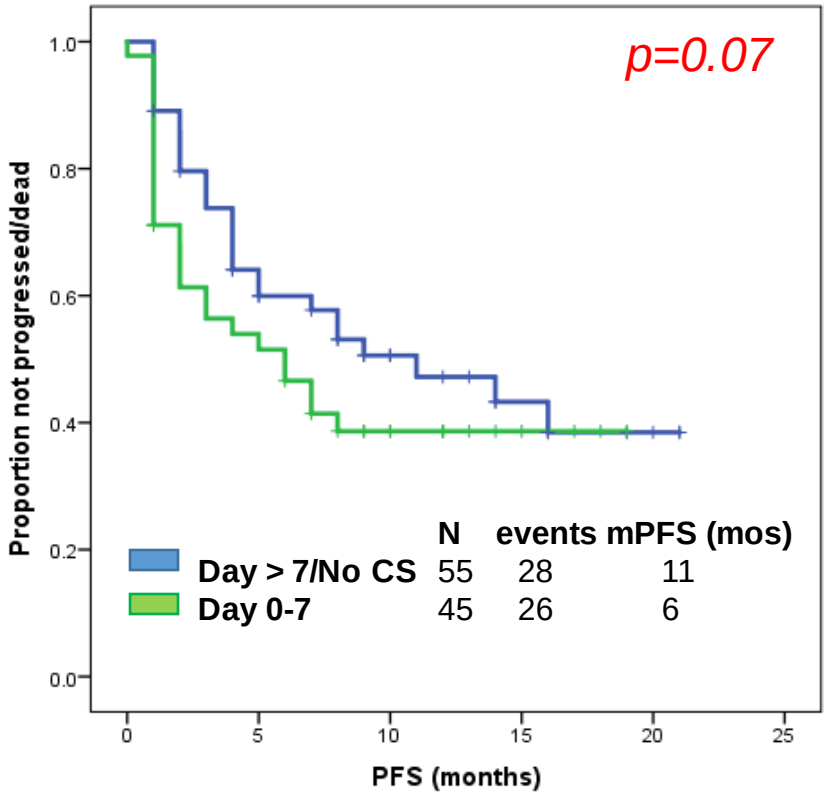
Effect of corticosteroid dose



Effect of corticosteroid duration

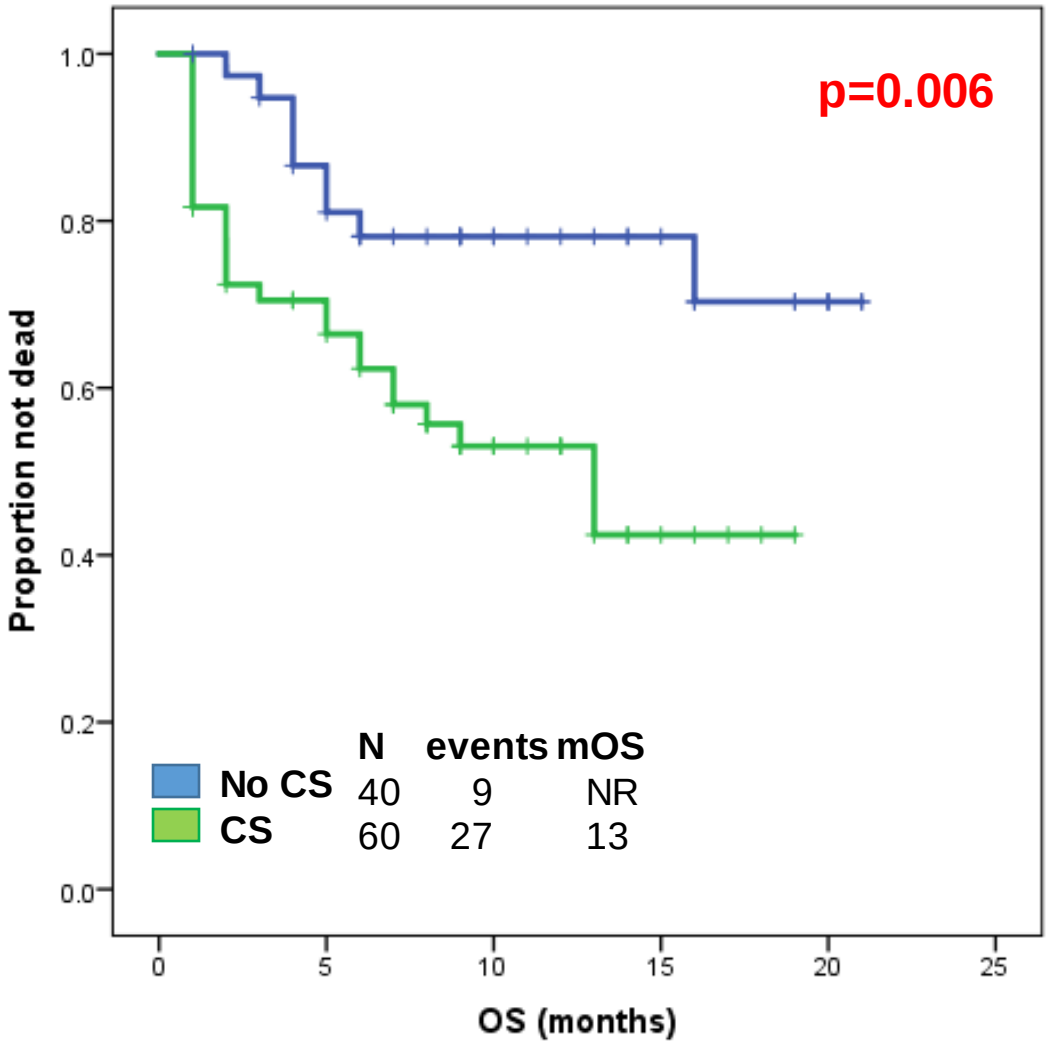


Effect of corticosteroid timing



***Strati P et al**, Blood 2021*

Use of corticosteroids associated with shorter OS after CAR T-cell therapy



Median follow-up:10 months (95% CI 8-12 months)

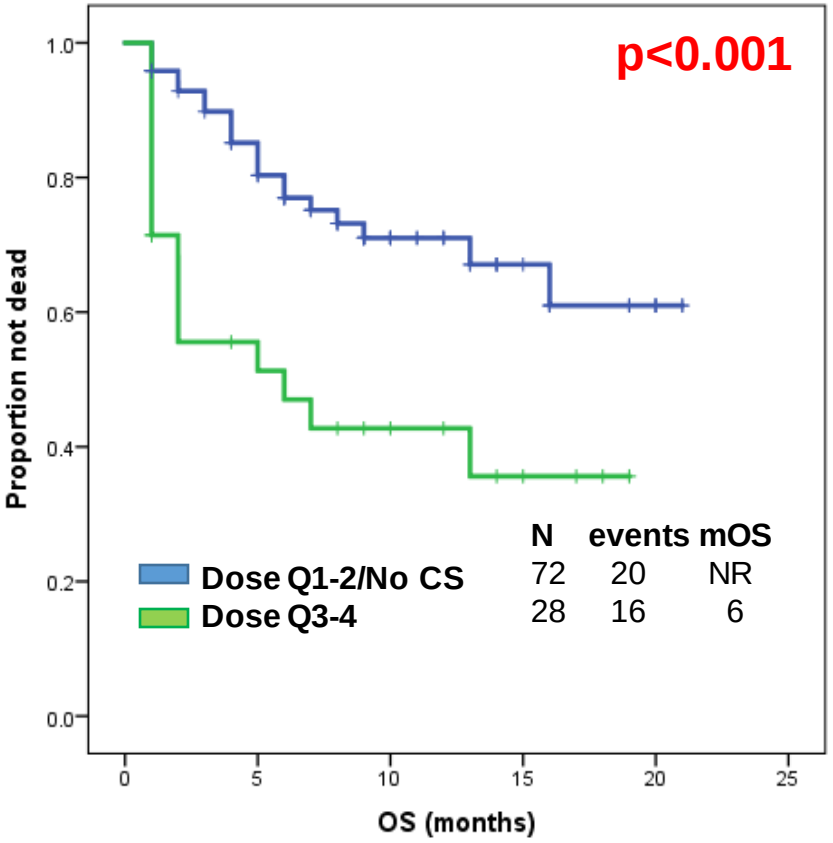
36 patients died
28 of progressive lymphoma

Median OS: not reached (36 deaths, 28 PD-related)

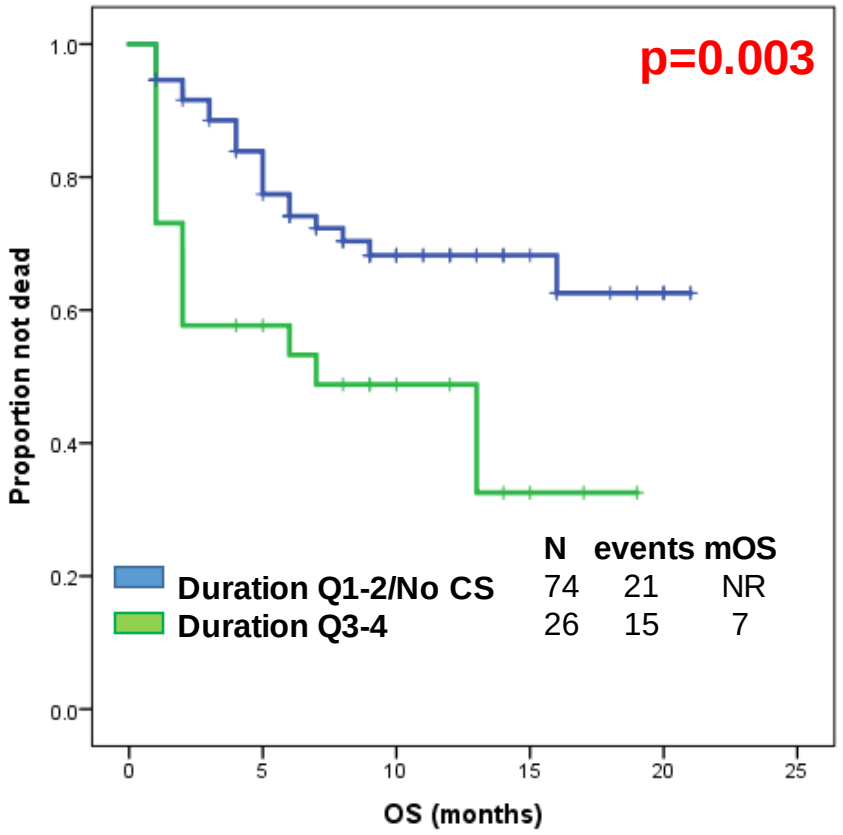
***Strati P et al**, Blood 2021*

Use of early and prolonged high dose corticosteroids associated with shorter OS after CAR T-cell therapy

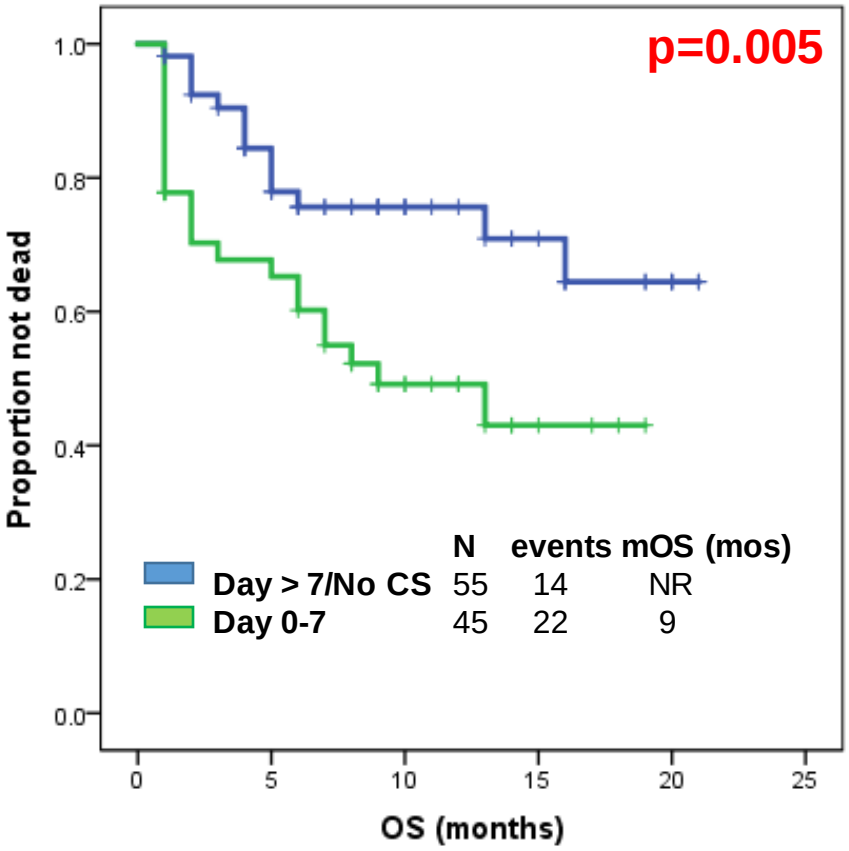
Effect of corticosteroid dose



Effect of corticosteroid duration

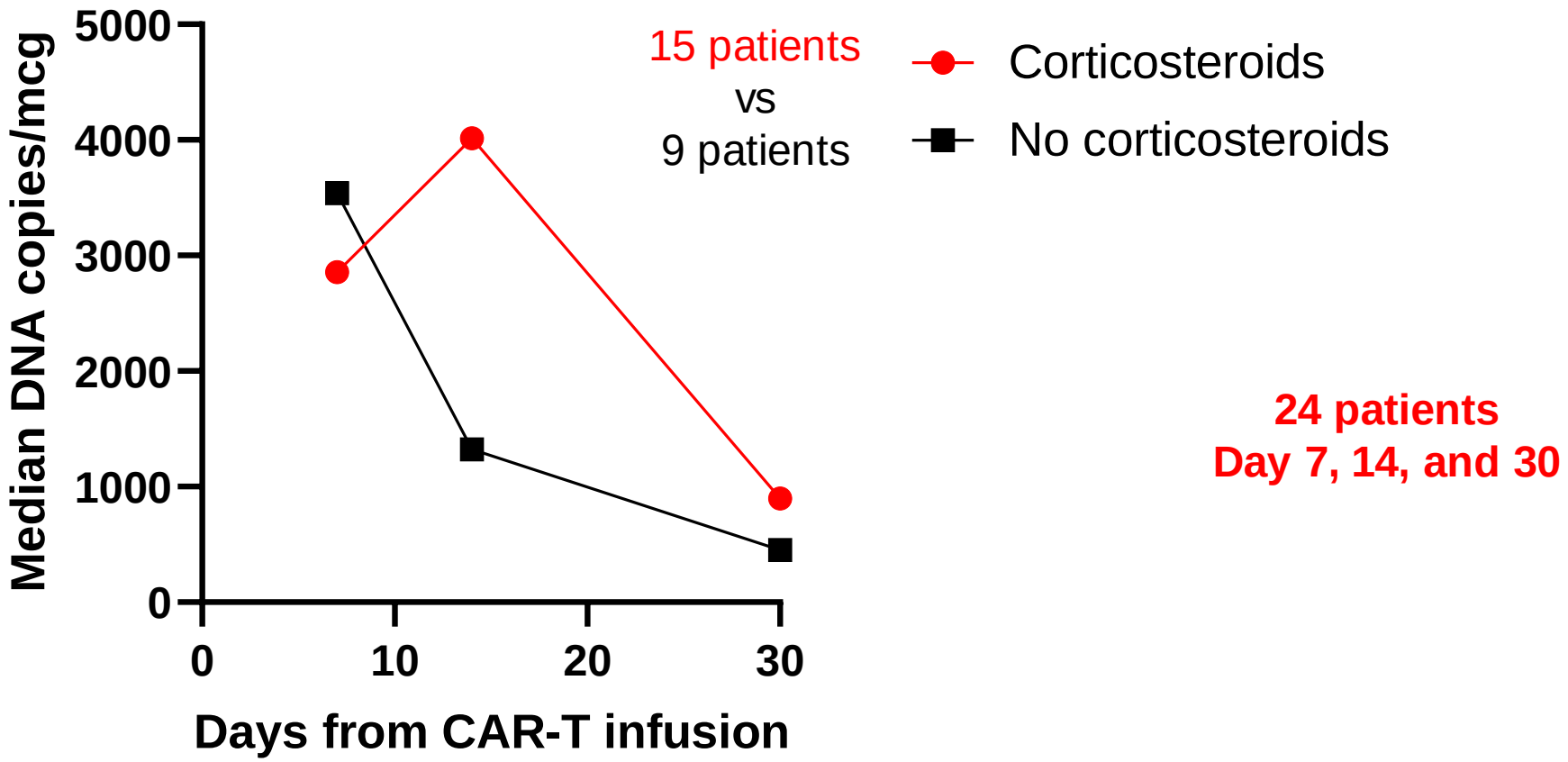


Effect of corticosteroid timing



***Strati P et al**, Blood 2021*

Use of corticosteroids associated with increased CAR T-cells amplification

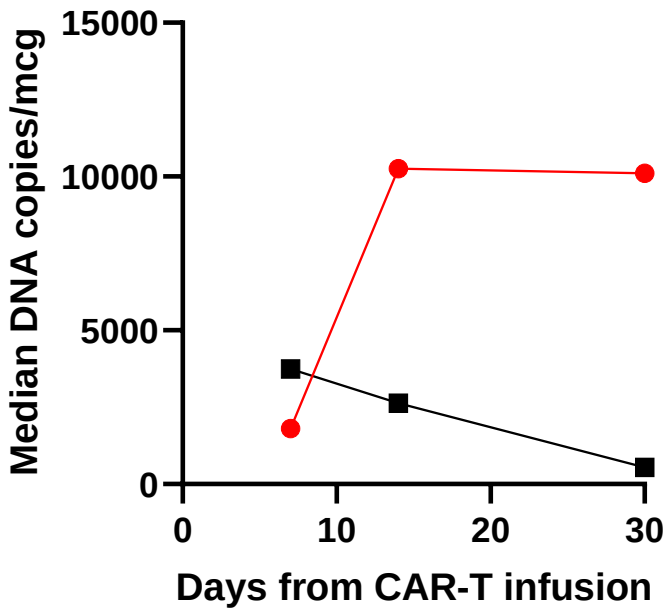


24 patients
Day 7, 14, and 30

***Strati P et al**, Blood 2021*

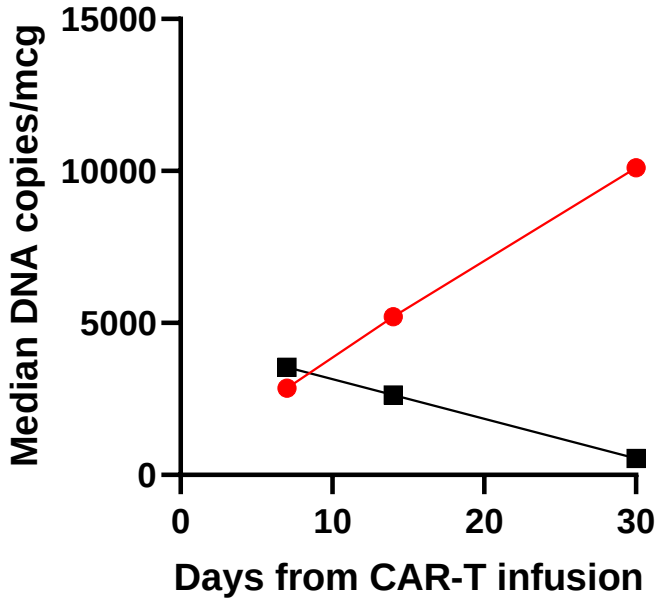
Use of early and prolonged high dose corticosteroids associated increased CAR T-cells amplification

Effect of corticosteroid dose



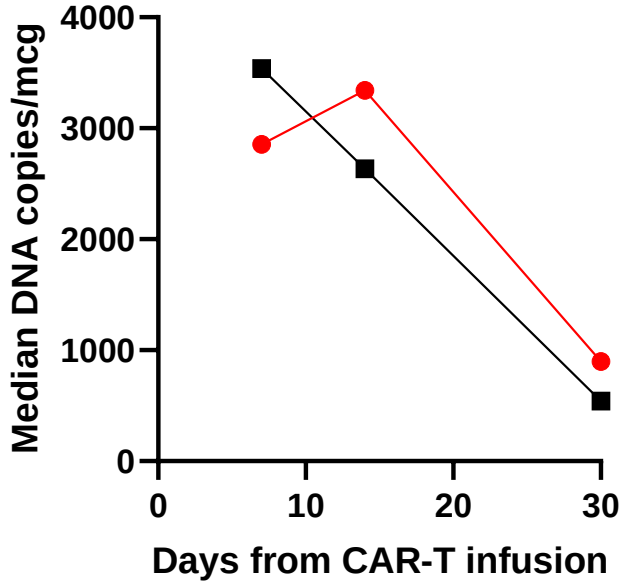
7 patients
vs
17 patients

Effect of corticosteroid duration



6 patients
vs
18 patients

Effect of corticosteroid timing

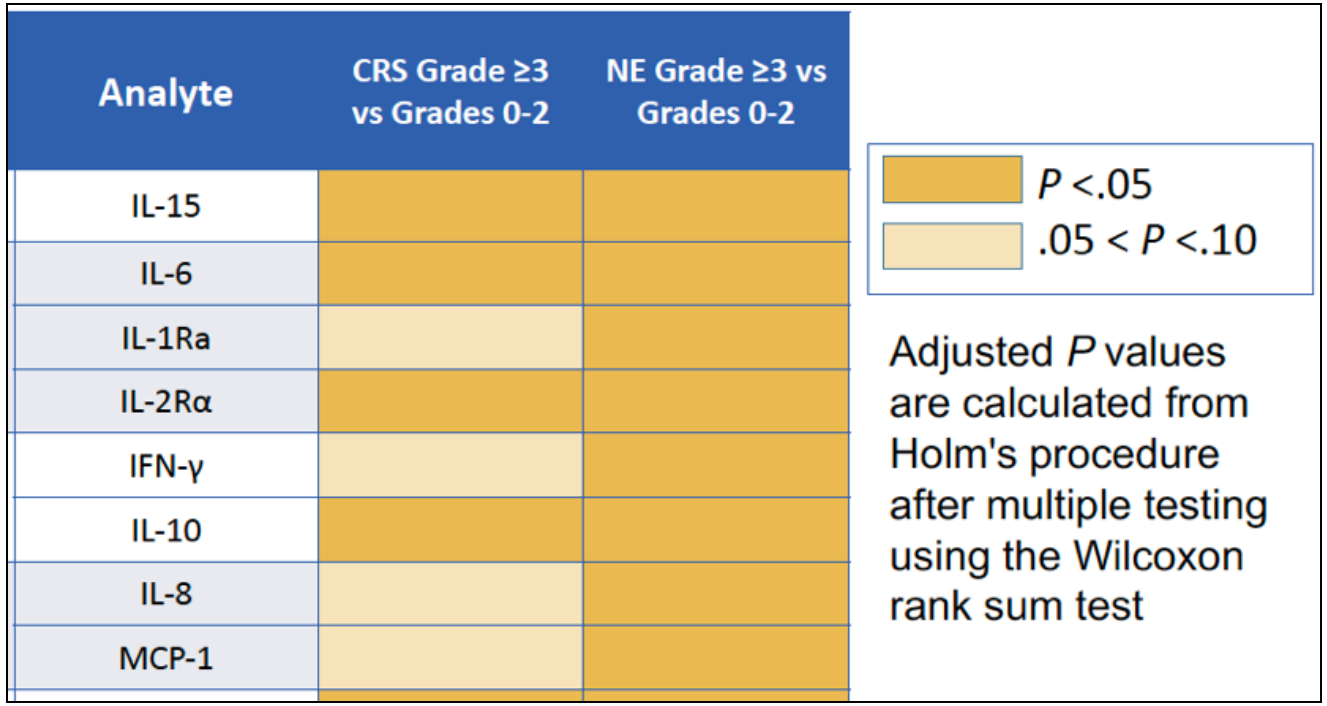


11 patients
vs
13 patients

***Strati P et al**, Blood 2021*

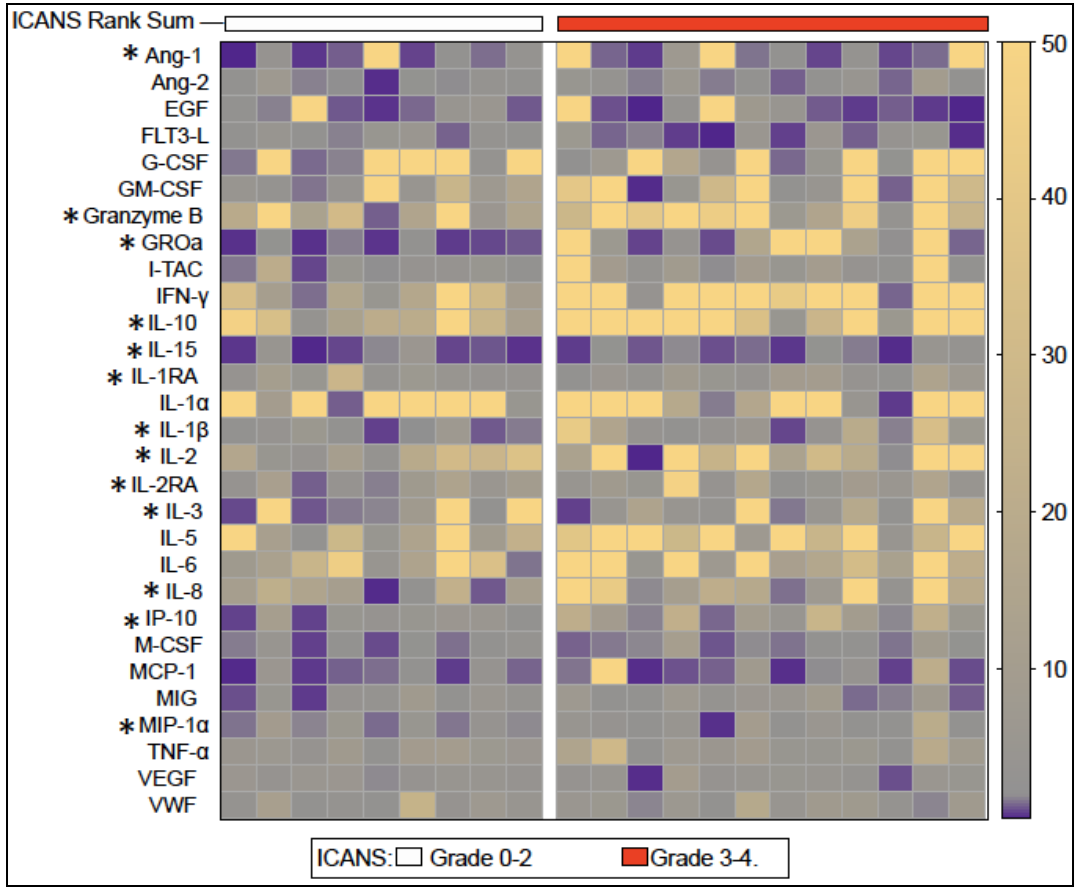
IL-1 peak levels associate with severe ICANS in clinical trials (ZUMA-1)

IL1-RA used as surrogate marker of IL-1



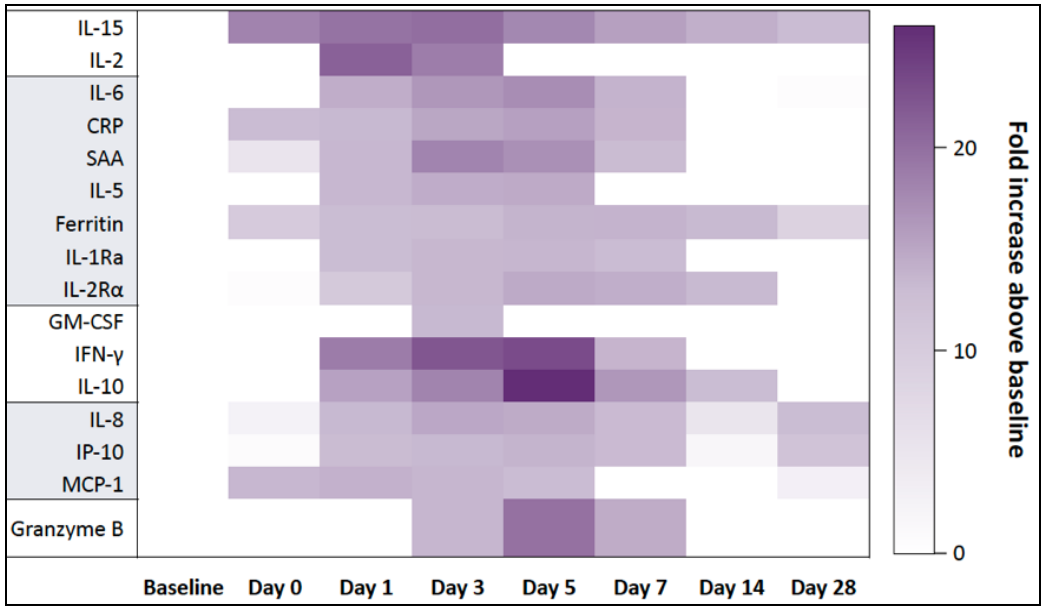
Courtesy of Dr. Sattva S Neelapu

IL-1 peak levels associate with severe ICANS in real world experience

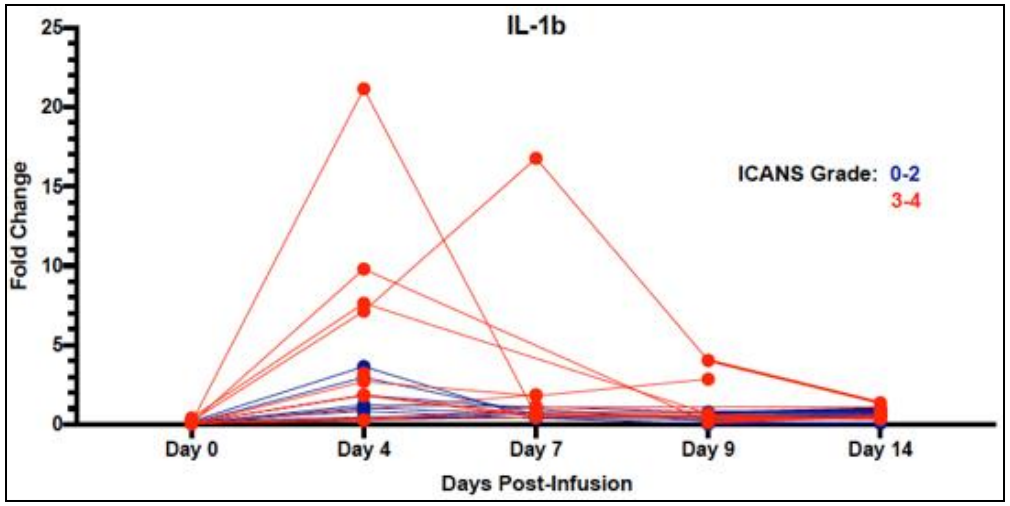


Courtesy of Dr. Sattva S Neelapu

IL-1 peaks the first 7 days after axi-cel infusion in relapsed DLBCL



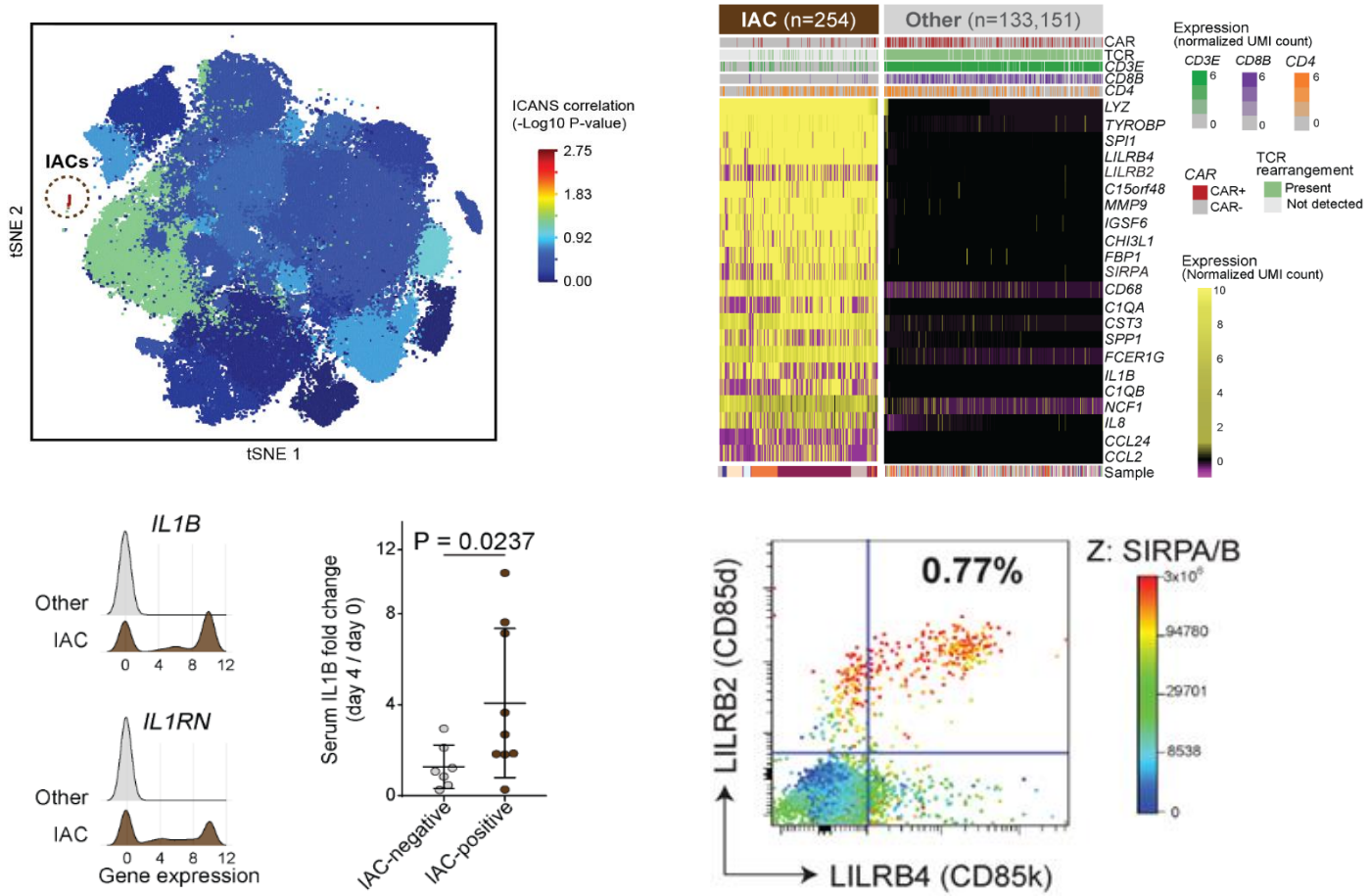
ZUMA-1



Real world experience

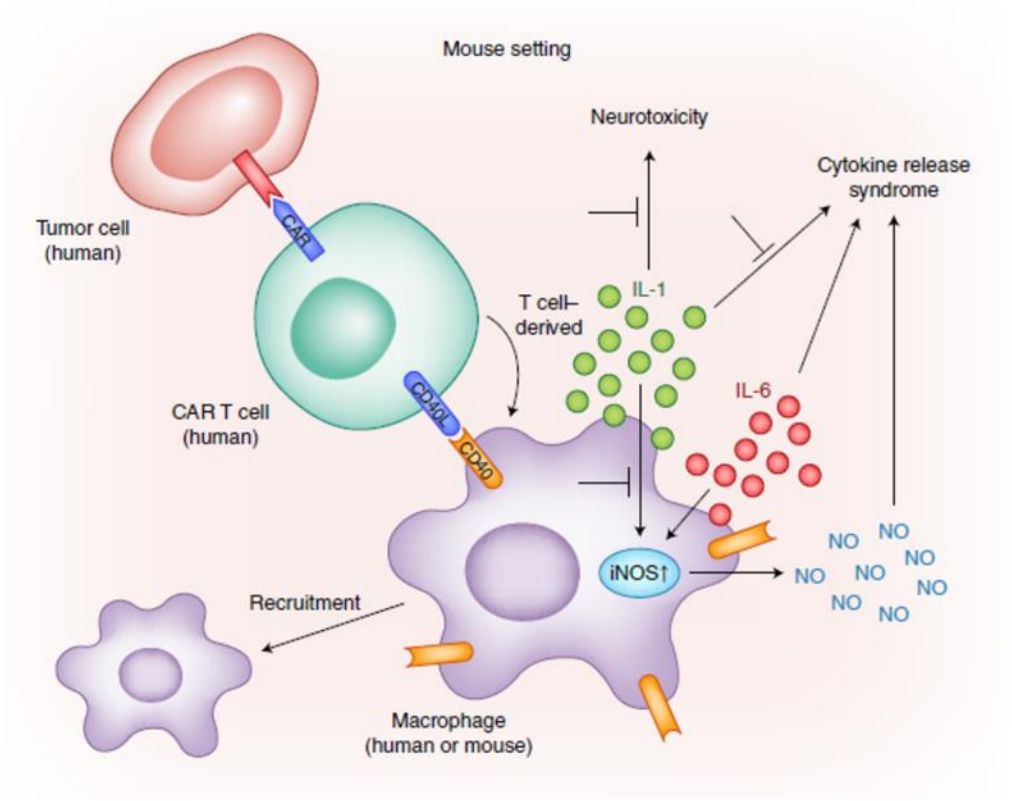
Courtesy of Dr. Sattva S Neelapu

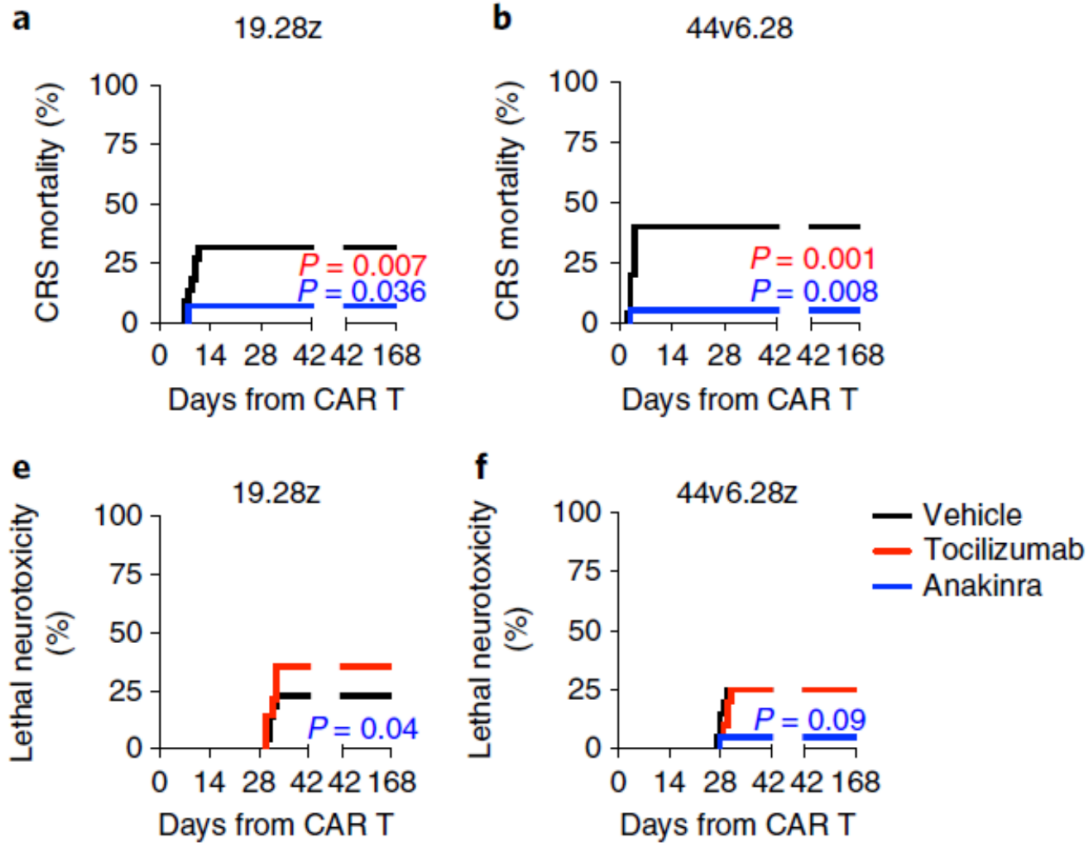
IL-1 expressing monocytes in the infusion product are associated with ICANS



Green MG, Strati P et al. Nature Med 2020

IL-1 inhibition abrogates ICANS in mouse models





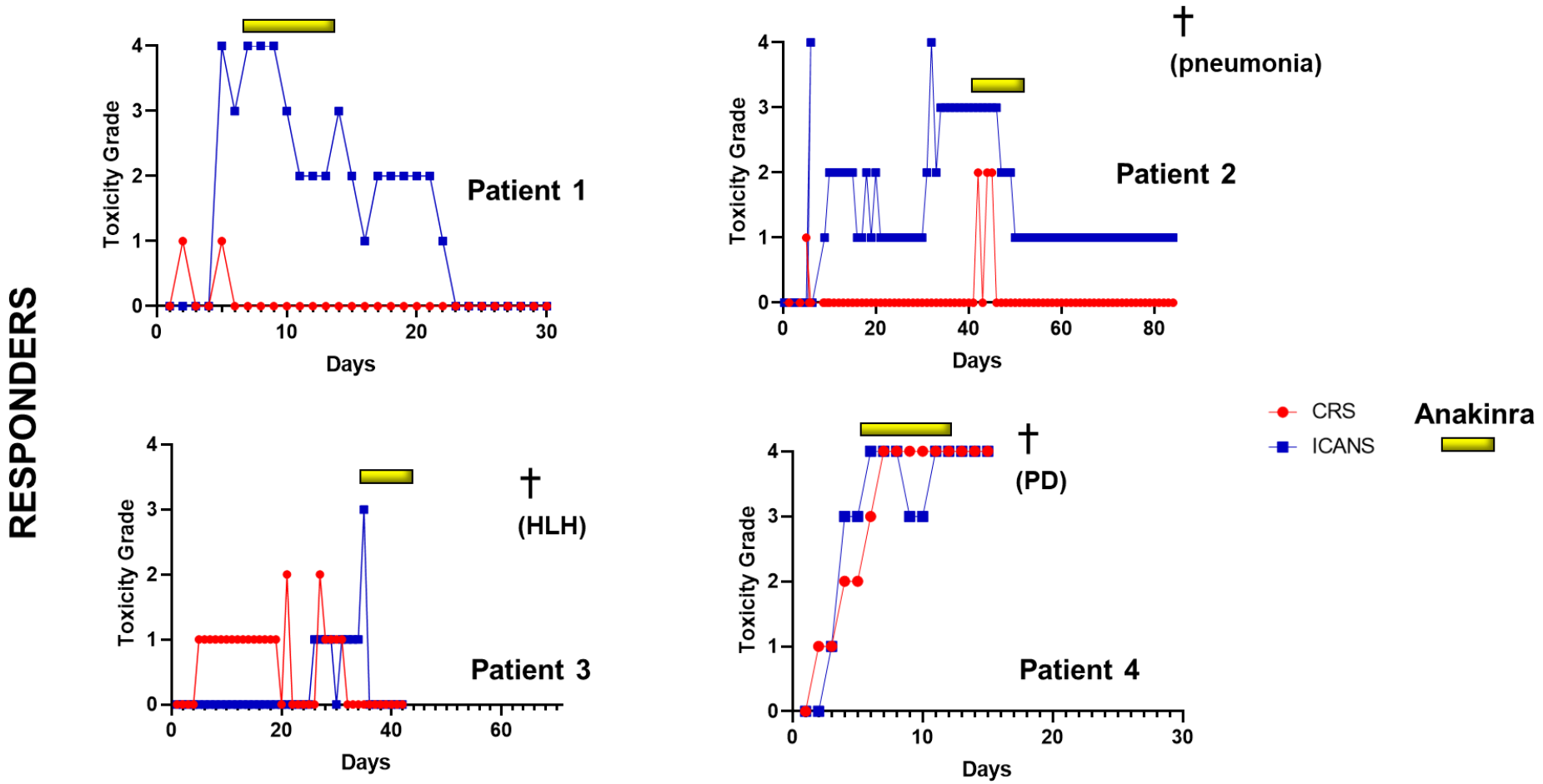
Norelli M et al. Nature 2018; ***Giavridis T et al***. Nature 2018

Response to anakinra

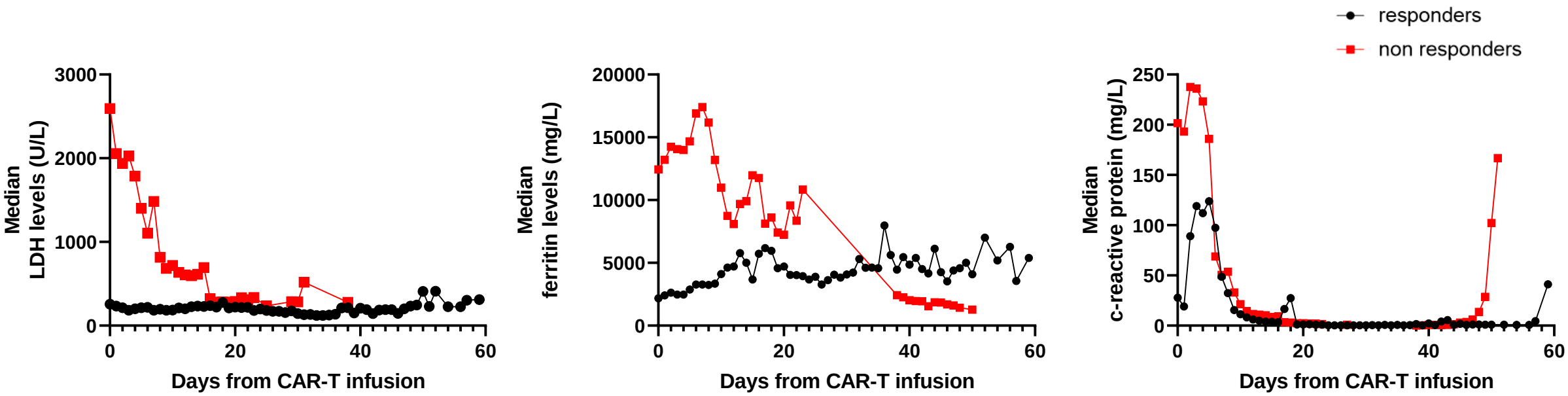
NON RESPONDERS

Total (N=8)	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
TOXICITY MANAGEMENT								
Treated toxicity	ICANS G4	ICANS G3	ICANS G4	ICANS G4	ICANS G4	ICANS G4	HLH	HLH
Tocilizumab start	day 4	day 5	--	day 4	day 4	--	day 3	day 11
Tocilizumab dose	8 mg/Kg IV X 2	8 mg/Kg IV X 2	0	8 mg/Kg IV X 2	8 mg/Kg IV X 2	0	8 mg/Kg IV X 1	8 mg/Kg IV X 2
Corticosteroid start	day 4	day 5	day 34	day 5	day 6	day 7	day 3	day 7
Dexamethasone dose	8-186 mg X 24 days	1-186 mg X 57 days	10 mg X 1 day	40-186 mg X 13 days	40-80 mg X 19 days	4-186 mg X 35 days	12-186 mg X 14 days	40-80 mg X 9 days
Anakinra start	day 6	day 41	day 31	day 7	day 10	day 31	day 7	day 14
Anakinra dose	100 mg SC daily X 7	100 mg SC daily X 7	100 mg SC daily X 7	100 mg SC daily X 7	100 mg SC QOD X 5	100 mg SC daily X 7	100 mg SC daily X 7	200 mg SC daily X 1
RESPONSE TO ANAKINRA								
Toxicity response	Yes (G0)	Yes (G1)	Yes (G0)	Yes (G2)	No	No	No	No
Toxicity recurrence	No	No	No	Yes	Yes	Yes	Yes	Yes
Death day and cause	--	Day 80 (PNA)	Day 71 (HLH)	Day 18 (PD)	Day 31 (ICH)	Day 51 (ICANS)	Day 17 (PD)	Day 15 (HLH)

IL-1 inhibition abrogates ICANS in patients treated with axi-cel

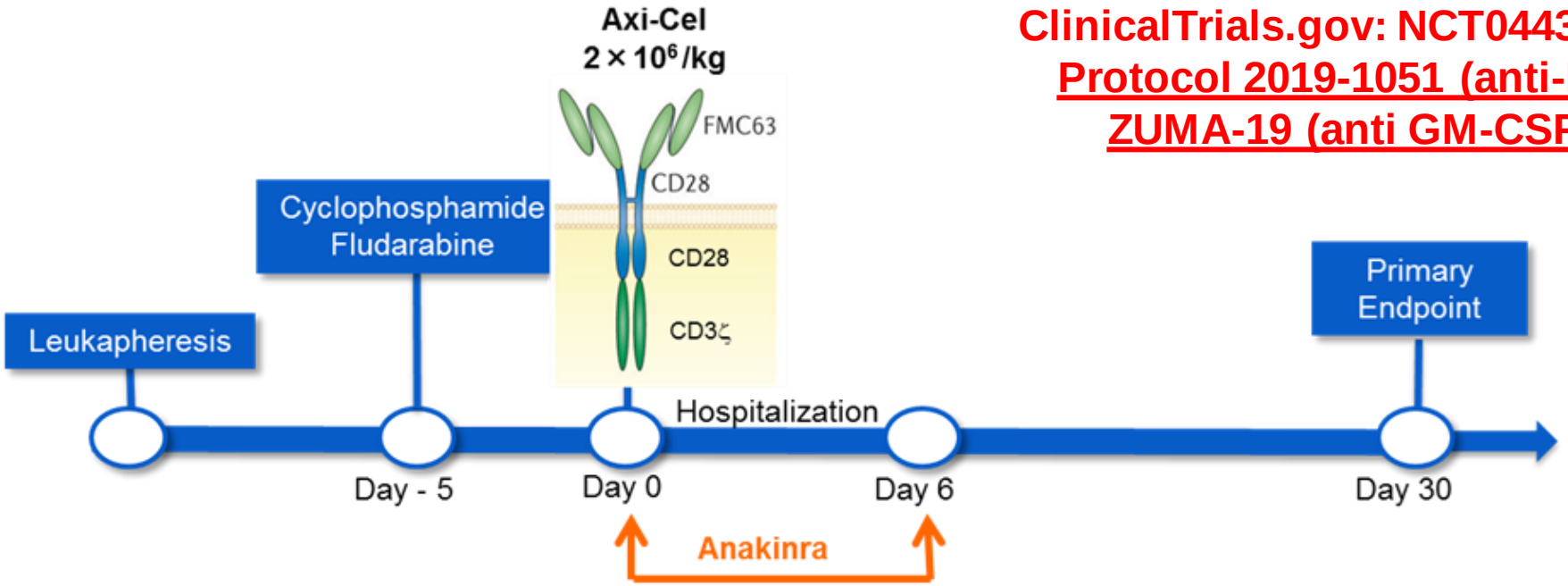


Anakinra is more active in patients with low tumor/inflammatory burden



None of the 4 patients who responded to anakinra had LDH > 500 U/L, ferritin > 10,000 mg/L or c-reactive protein > 300 mg/L

A Phase I/II study of anakinra to mitigate CAR T-cell therapy-associated toxicity



ClinicalTrials.gov: NCT04432506
Protocol 2019-1051 (anti-IL1)
ZUMA-19 (anti GM-CSF)

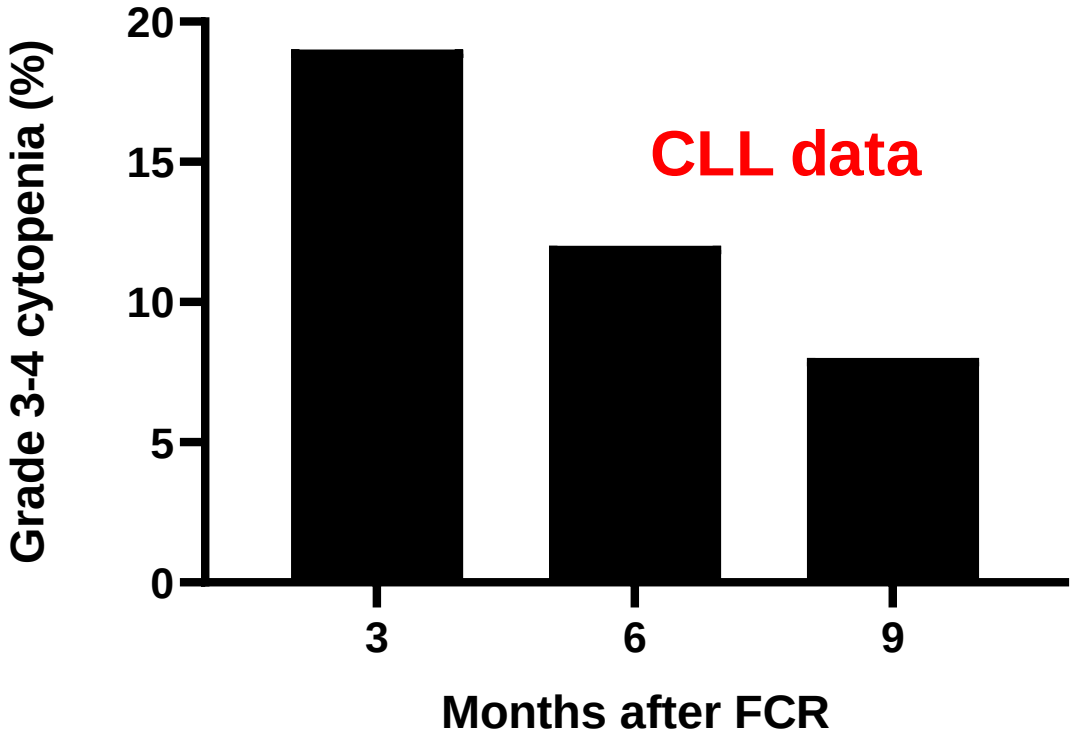
Severe cytopenia is frequent after CAR T-cell therapy

	ZUMA-1 (N=108)	JULIET (N=93)	TRANSCEND (N=73)
Histology	DLBCL, t-FL, PMBCL	DLBCL, t-FL	DLBCL, t-FL
Product	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Developed at	NCI	UPenn	SCH/FHCRC
Sponsor	Kite	Novartis	Juno
Conditioning	Flu-Cy	Flu-Cy or Benda	Flu-Cy
ORR	83%	52%	80%
CR rate	58%	40%	59%
Grade ≥3 CRS	13%	22%	1%
Grade ≥3 ICANS	31%	12%	13%
Grade ≥3 cytopenia	**28%**	**32%**	**37%**
FDA approval	2017 (Yescarta)	2018 (Kymriah)	pending

Strati P et al. Curr Oncol Rep 2019

Lymphodepleting chemotherapy can cause prolonged severe cytopenia

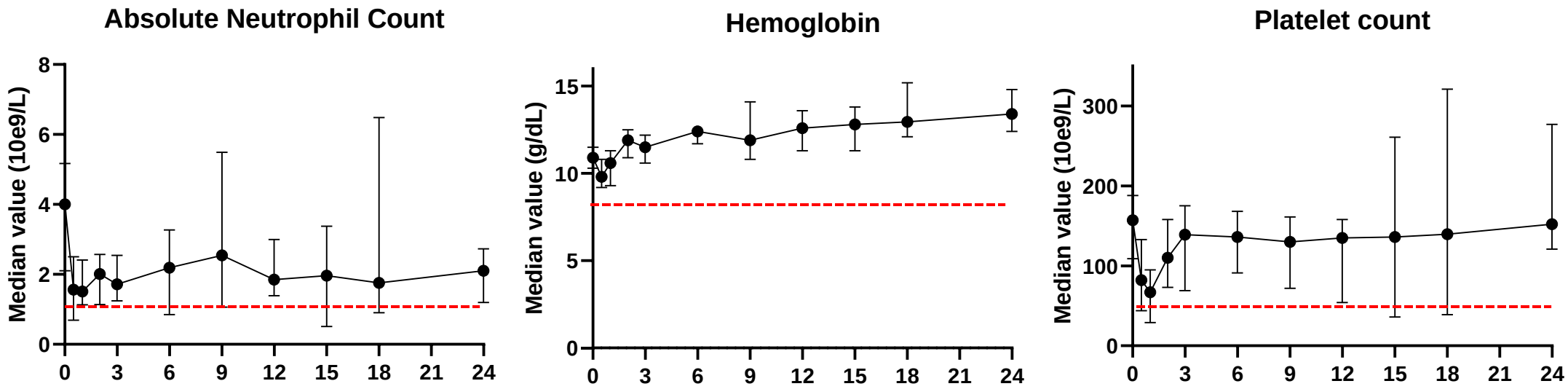
	FCR for CLL	LDC for CART
FLU	25 mg/m2 IV for 3 days (6 cycles)	30 mg/m2 IV for 3 days (1 cycle)
CTX	250 mg/m2 IV for 3 days (6 cycles)	500 mg/m2 IV for 3 days (1 cycle)



Strati P et al. Cancer 2013

Hematopoietic recovery

4 cases of MDS, after a median of 13.5 months (range, 4-26 months)

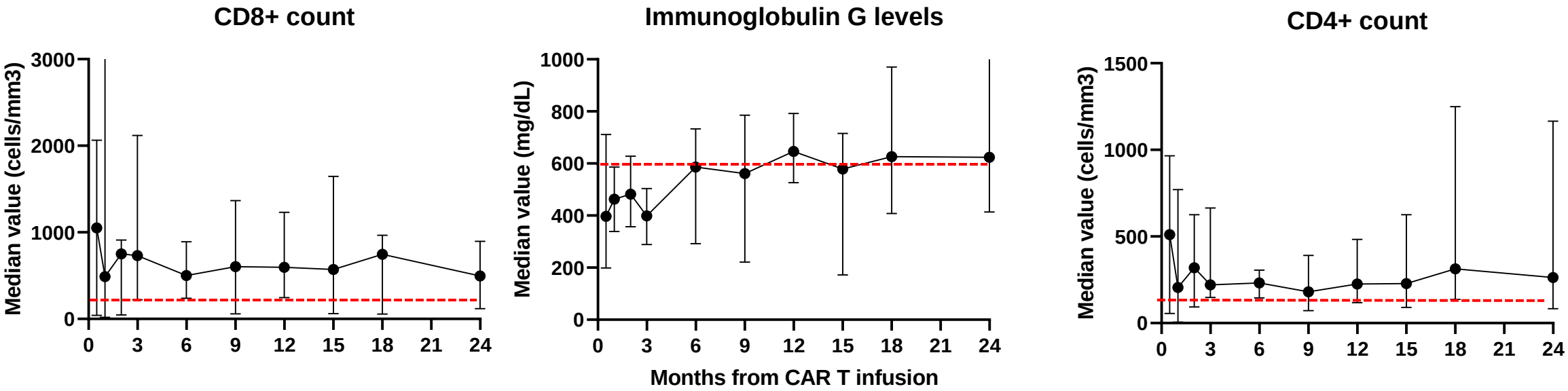


Persistent G3-4 cytopenias in 4/15 (27%) patients at 1 year and in 1/9 (11%) patients at 2 years

All patients had GCSF support; trasfusional support as needed

***Strati P et al**, Haematologica 2019*

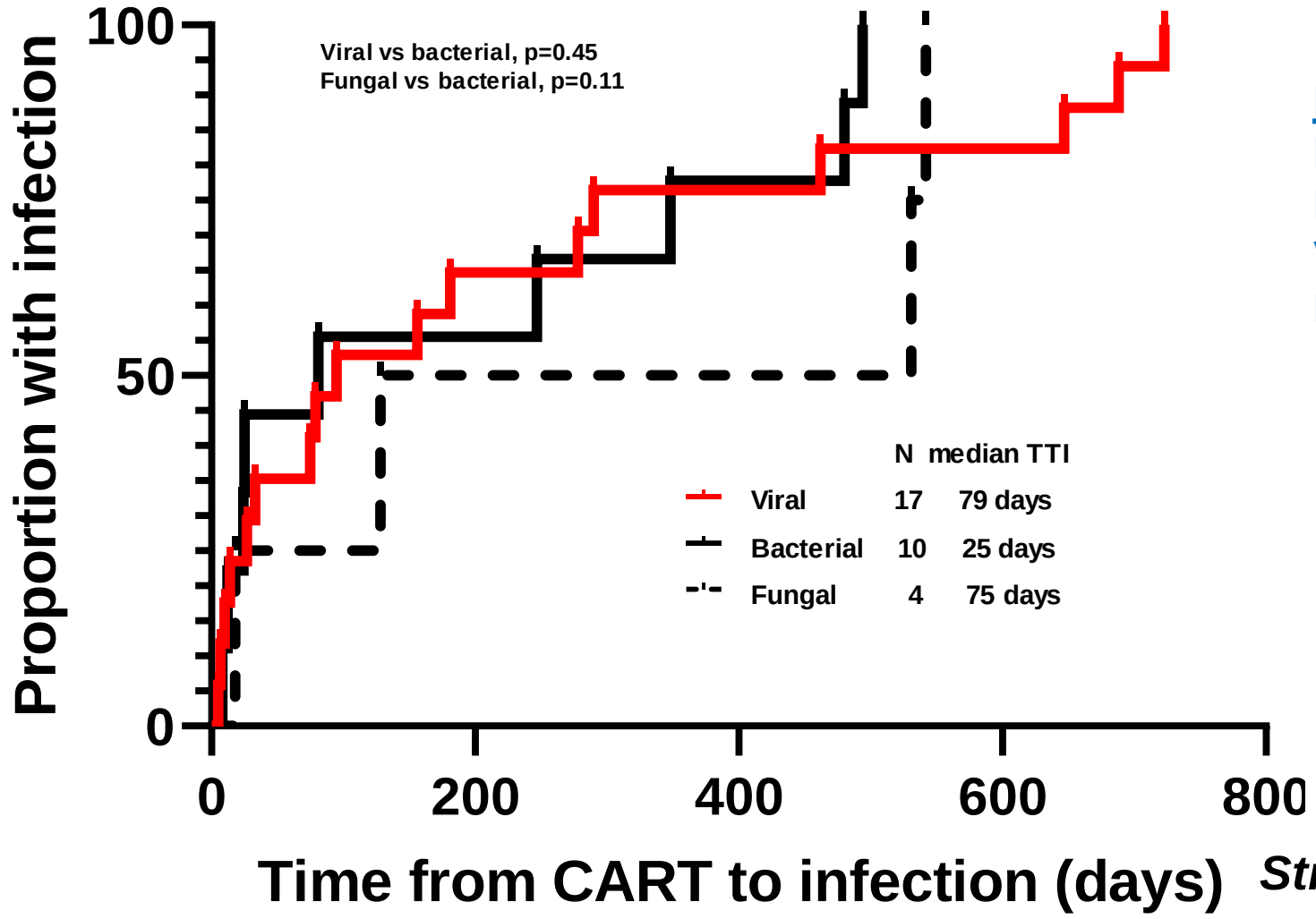
Immune recovery: CD4 T cells can remain low for prolonged time



CD8+ T cells normalized in 9/9 (100%) patients and IgG levels in 4/4 (100%; without IVIG) at 1 year
CD4+ T cells normalizated in 6/9 (67%) patients at 1 year and 5/7 (71%) at 2 years
13 (42%) received prophylactic IVIG and 4 (13%) therapeutic IVIG

***Strati P et al**, Haematologica 2019*

Infectious complications



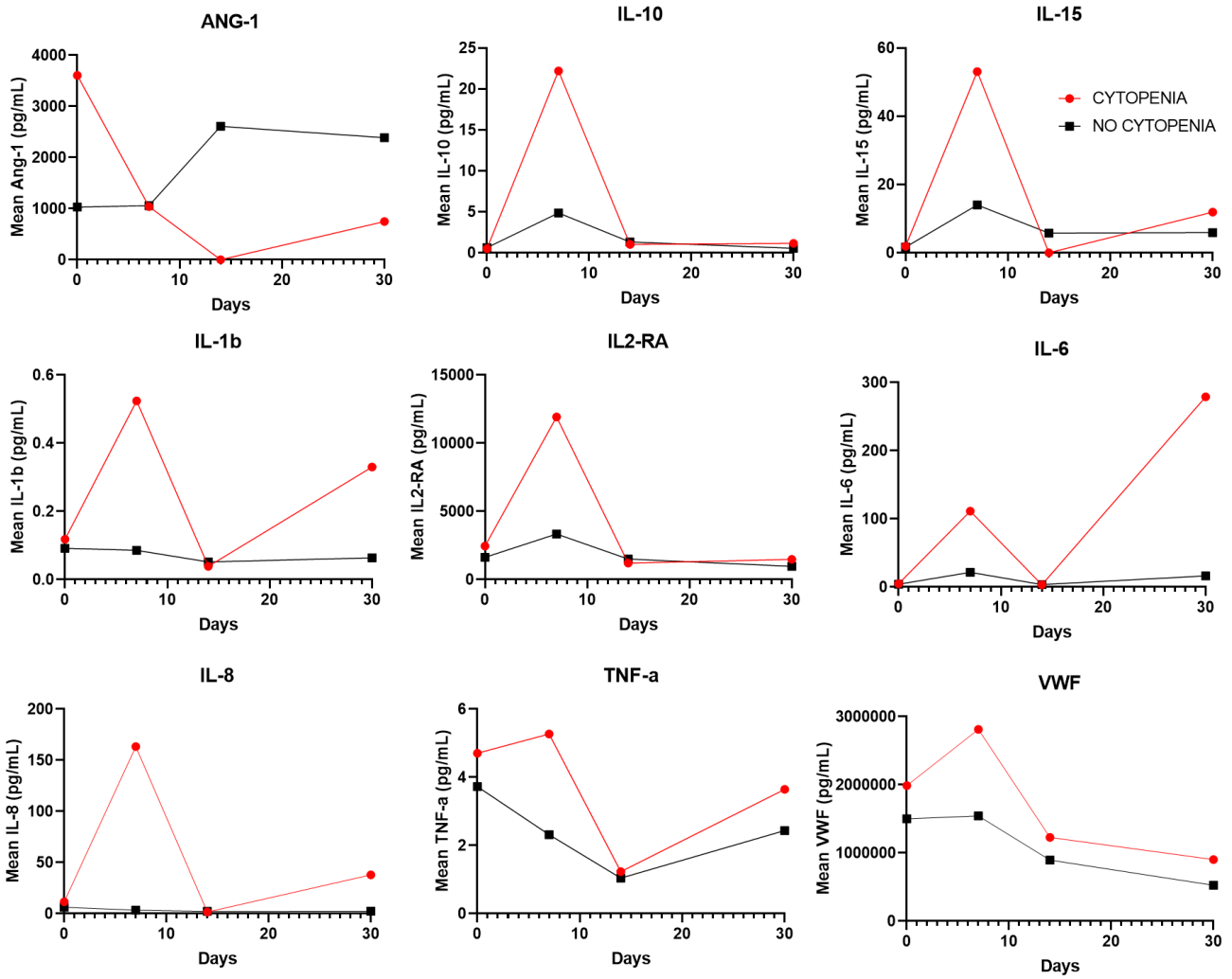
Prophylaxis
Bacterial: 2 (6%)
PJP: 13 (42%)
Viral: 22 (71%)
Fungal: none

Only G3-4 D30 lymphopenia associated with G3-4 infections (9/14 [64%] vs 4/17 [24%], p=0.03)

***Strati P et al**, Haematologica 2019*

Elevated AUC of myeloid-derived cytokines associate with D30 G3-4 cytopenia

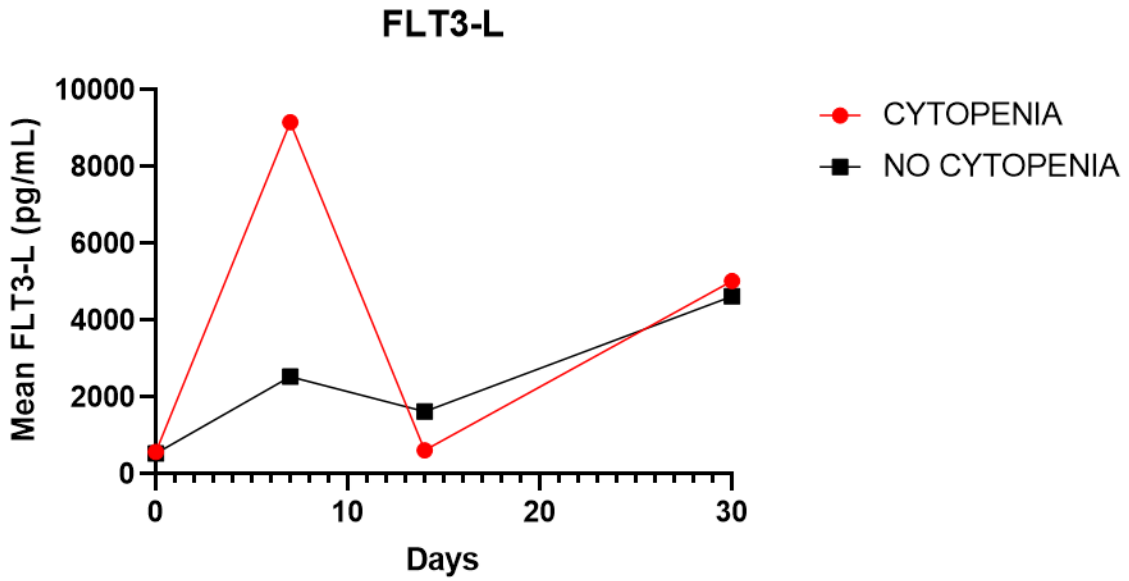
Area Under the Curve (AUC)			
Patients (N=19)	Day 30 G3-4 Cytopenia (n=9)	No Day 30 G3-4 Cytopenia (n=10)	p-value
IFN-γ	18768	1659	**0.02**
Ang-1	25916	60169	**0.0002**
Ang-2	149453	128440	0.44
EGF	12531	92879	**0.05**
FLT-3 ligand	113583	75376	**0.02**
G-CSF	108995	69112	**0.03**
GM-CSF	45.73	2.758	**0.04**
Granzyme-B	1527	1343	0.68
Gro-α	39207	2898	**0.03**
ITAC	8381	5065	0.18
IL-10	178.4	55.90	**0.01**
IL-15	473.7	217.6	**0.004**
IL-1Rα	78740	41921	**0.04**
IL-1α	15.05	15.94	0.79
IL-1β	7.169	2.025	**0.002**
IL-2	18.82	16.45	0.33
IL-2Rα	117887	54288	**0.006**
IL-3	1947	945.3	**0.03**
IL-5	134.4	131.5	0.93
IL-6	3068	338.1	**0.0009**
IL-8	1505	91.61	**0.01**
IP-10	100879	95079	0.83
M-CSF	864.8	436.3	**0.04**
MCP-1	40886	9777	**0.03**
MIG	192138	153374	0.40
MIP-1α	7637	8042	0.89
TNF-α	96.73	60.79	**0.002**
VEGF	1397	1395	0.99
VWF	47991016	30582100	**<0.001**



After adjusting for FDR

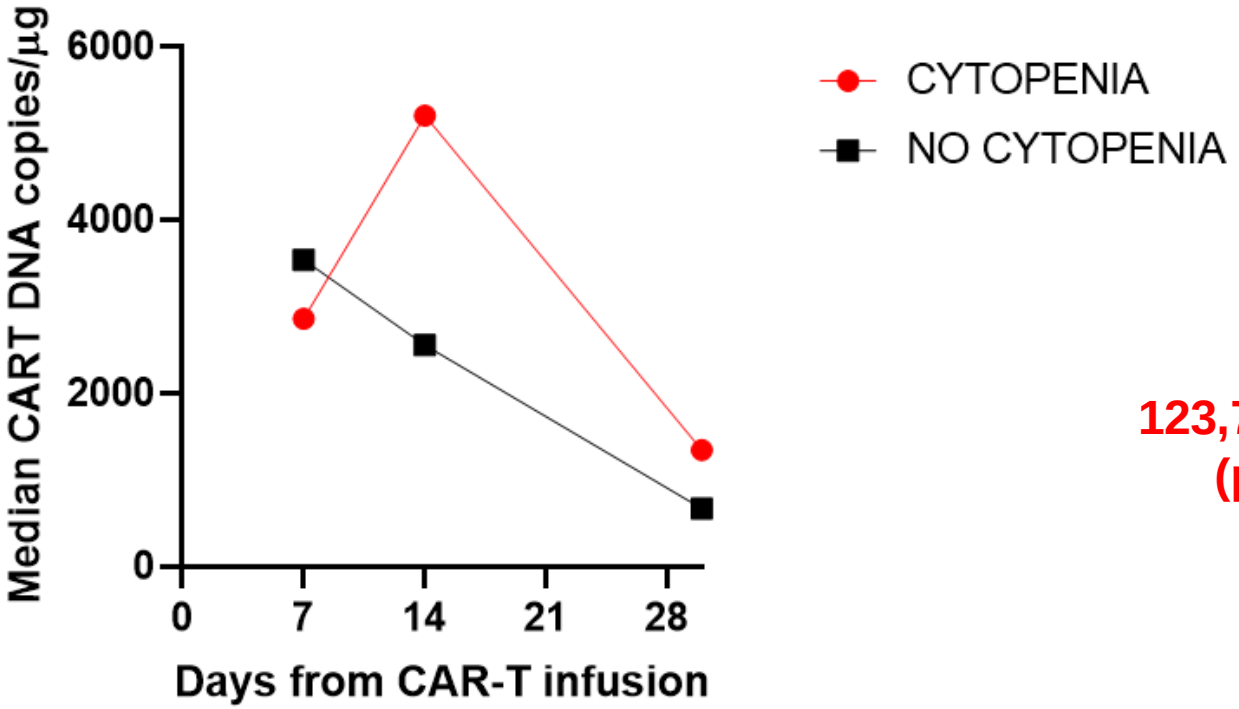
Elevated peak at day 7 of FLT-3 (a myeloid-derived cytokine) associates with D30 G3-4 cytopenia

	Mean peak (pg/mL)		
Patients (N=19)	Day 30 G3-4 Cytopenia (n=9)	No Day 30 G3-4 Cytopenia (n=10)	p-value
IFN-γ	2327	85	**0.03**
Ang-1	1041	1057	0.17
Ang-2	15212	6843	0.07
EGF	1.3	2.7	**0.005**
FLT-3 ligand	9165	2536	**<0.001**
G-CSF	11610	6676	**0.02**
GM-CSF	6.2	0.1	**0.03**
Granzyme-B	210	133	0.45
Gro-α	5035	188	**0.03**
ITAC	892	256	0.06
IL-10	22	4.7	**0.01**
IL-15	53	14	0.10
IL-1Rα	9314	3137	0.11
IL-1α	0.7	0.4	0.26
IL-1β	0.5	0.1	**0.03**
IL-2	1	0.7	0.29
IL-2Rα	11931	3348	**0.05**
IL-3	216	50	**0.03**
IL-5	13	7	0.08
IL-6	111	22	**0.04**
IL-8	163	3.5	**0.03**
IP-10	10230	8328	0.68
M-CSF	90	23	**0.04**
MCP-1	4584	401	**0.03**
MIG	20625	12802	0.31
MIP-1α	795	304	0.11
TNF-α	5.3	2.3	0.06
VEGF	30	27	0.33
VWF	2812534	1543357	0.19



After adjusting for FDR

Elevated AUC of CAR T-cell amplification associates with D30 G3-4 cytopenia



123,794 vs 71,548 DNA copies/µg
(p=0.57, small simple size)

How can we improve efficacy?

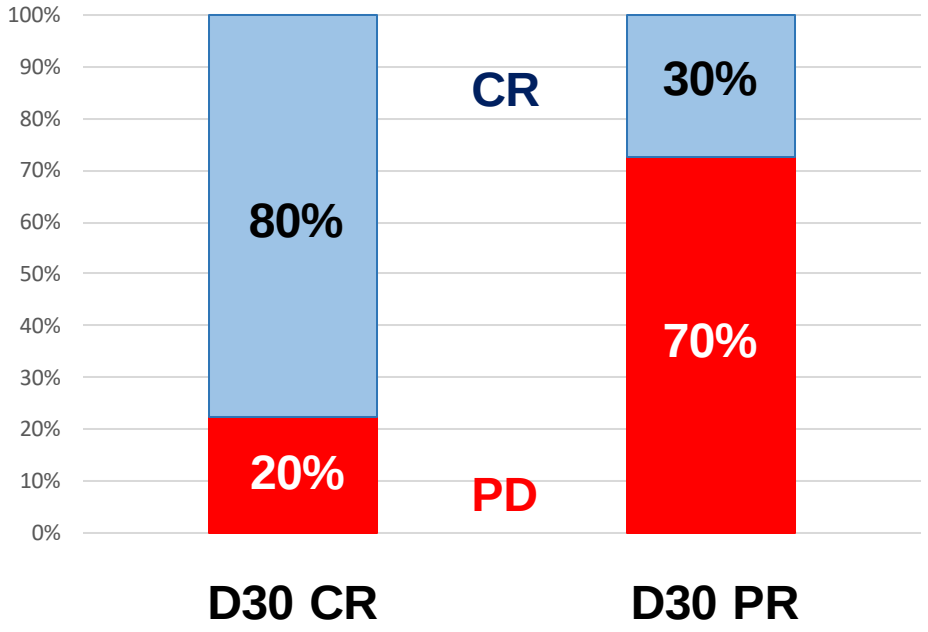
CART
High CCR7+/CCR7− T cell
Early CD4+ CAR T cells

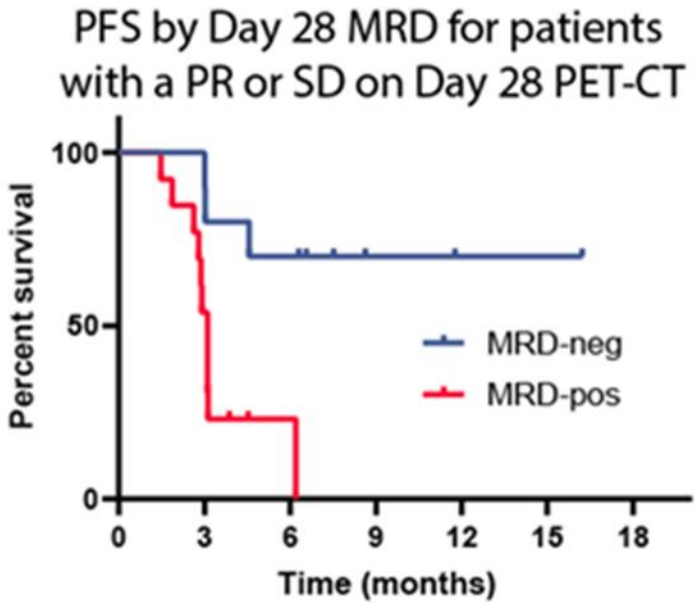
Microenvironment
Low myeloid cells
Low PD-1 expression

Early predictors
Day 30 PET
ctDNA

Name	Phase	Population	Product
Axicabtagene Ciloleucel			
NCT02348216 (ZUMA-1)	I/II	Failed 2 lines	Axicabtagene Ciloleucel
NCT02926833 (ZUMA-6)	I/II	Failed 2 lines	Axicabtagene Ciloleucel + atezolizumab
NCT03391466 (ZUMA-7)	III	Failed 1 line	Axicabtagene Ciloleucel vs ASCT
NCT03153462 (ZUMA-9)	EA	Failed 2 lines	Axicabtagene Ciloleucel (suboptimal)
NCT03704298 (ZUMA-11)	I/II	Failed 2 lines	Axicabtagene Ciloleucel + Utomilumab
NCT03761056 (ZUMA-12)	II	Previously untreated	Axicabtagene Ciloleucel
NCT04002401 (ZUMA-14)	II	Failed 2 lines	Axicabtagene Ciloleucel + rituximab Axicabtagene Ciloleucel + lenalidomide
Tisagenlecleucel			
NCT04134117	I	PCNSL	Tisagenlecleucel
NCT03630159 (PORTIA)	I	Failed 2 lines	Tisagenlecleucel + pembrolizumab
NCT03876028	I	Failed 2 lines	Tisagenlecleucel + ibrutinib
NCT04161118 (TIGER)	II	Failed 1 line (elderly)	Tisagenlecleucel
NCT02445248 (JULIET)	II	Failed 2 lines	Tisagenlecleucel
NCT03570892 (BELINDA)	III	Failed 1 line	Tisagenlecleucel vs ASCT
NCT04094311	IIIB	Failed 2 lines	Tisagenlecleucel (suboptimal)
Lisocabtagene Maraleucel			
NCT02631044 (TRANSCEND)	I	Failed 2 lines	Lisocabtagene Maraleucel
NCT03310619 (PLATFORM)	I/II	Failed 2 lines	Lisocabtagene Maraleucel + CC-122 Lisocabtagene Maraleucel + durvalumab
NCT03744676 (OUTREACH)	II	Failed 2 lines	Lisocabtagene Maraleucel
NCT03483103 (PILOT)	II	Failed 1 line	Lisocabtagene Maraleucel
NCT03575351 (TRANSFORM)	III	Failed 1 line	Lisocabtagene Maraleucel vs ASCT

Majority of patients with D30 PR/SD progress: how to predict who?



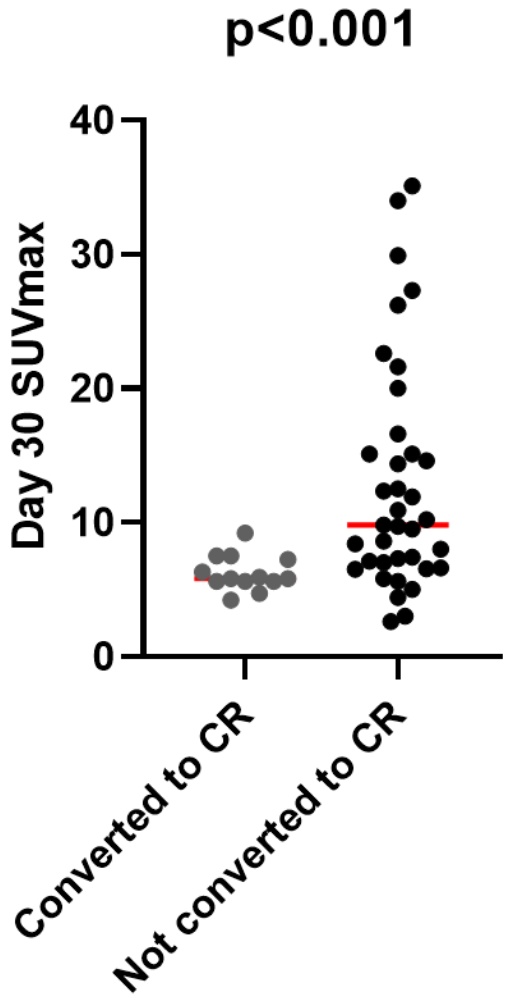


ctDNA data; no tissue biopsy data

Nastoupil J et al. JCO 2020; **Frank MJ** et al, Blood 2020

D30 SUV_{max} associated with conversion D30 PR/SD to CR

Total (N=50)	Median [range]		
	Converted to CR (N=13)	Not converted to CR (N=37)	p-value
ANC (10^9/L)	1.47[0.27-7]	1.4[0-10]	0.19
ALC (10^9/L)	0.34[0.13-1.75]	0.45[0-2.5]	0.50
AMC (10^9/L)	0.44[0.21-1]	0.32[0-0.9]	0.93
Hemoglobin (g/dL)	11.3[9.2-12.4]	9.7[5.7-15.2]	1
PLT count (10^9/L)	95[17-162]	63[1-270]	1
CRP (mg/L)	1.69[0.39-47]	2.86[0.15-211]	0.68
Ferritin (mg/L)	579[7.14-1412]	1042[20-30833]	0.20
LDH (U/L)	214[130-425]	216[107-3693]	0.52
SUV_{max}	5.8 [4.2-9.2]	9.8 [3-35.1]	0.001



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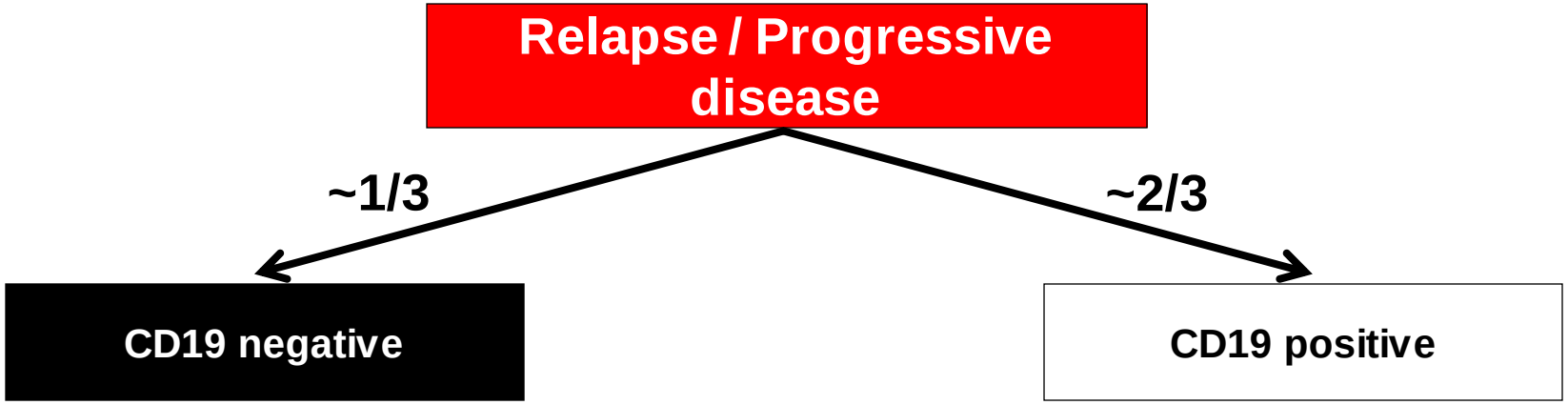
CART failure: no standard available

CLINICAL TRIALS!!!!!



Target other antigens

- CD79b: polatuzumab
- XPO1: selinexor

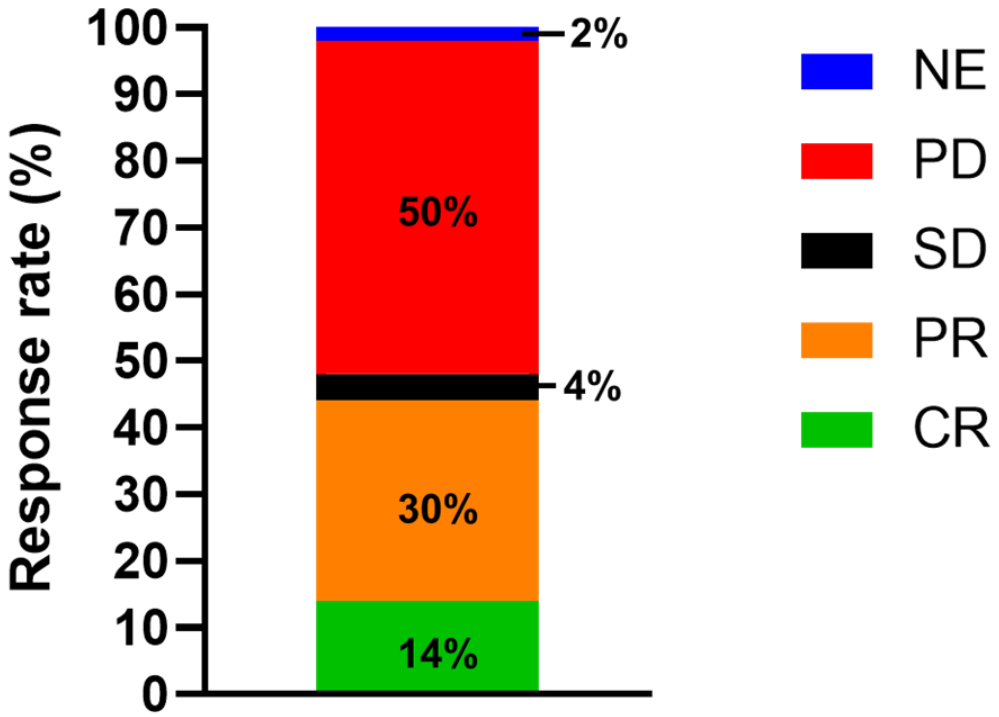
Target more CD19

- Tafasitamab + lenalidomide
- Lonca T

Manipulate the microenvironment

- Lenalidomide
- Pembrolizumab

Response to PV after CAR T-cell therapy



Treatment discontinuation	Number (%)
Overall	52 (91%)
Progression	40 (70%)
CR/patient decision	7 (13%)
Allogenic SCT	3 (6%)
Clinical Trial	1 (2%)
Toxicity	1 (2%)

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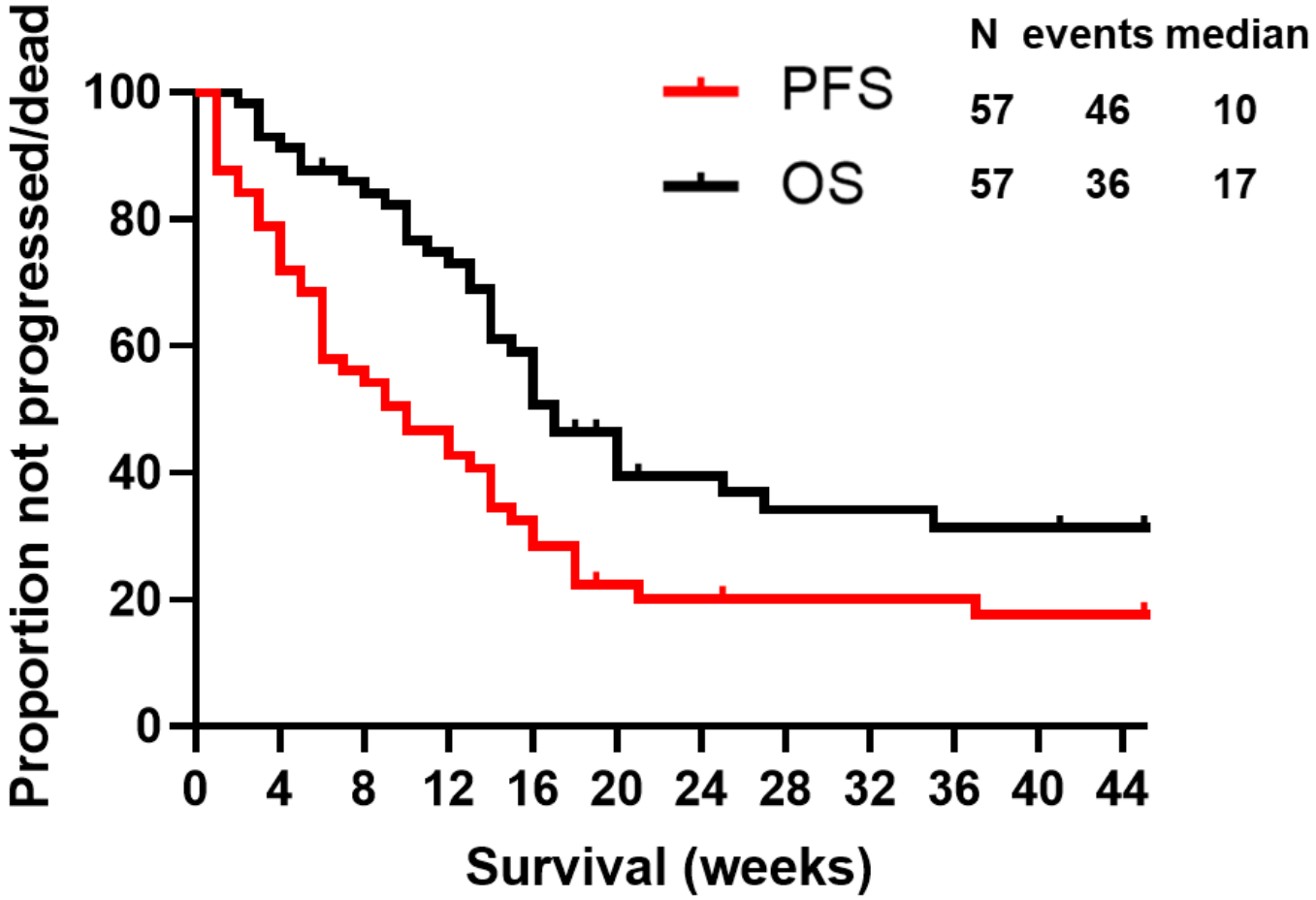
Survival with PV after CAR-T



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Other pathways to target post-CART

- Macrophages: CC-95251, 5F9
- Apoptosis: AZD4573, Selinexor, CPI-613
- B-cell receptor: LOXO-305, CG-806, HMPL-523

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Misha C Hawkins
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