Chimeric Antigen Receptor T-cells therapy

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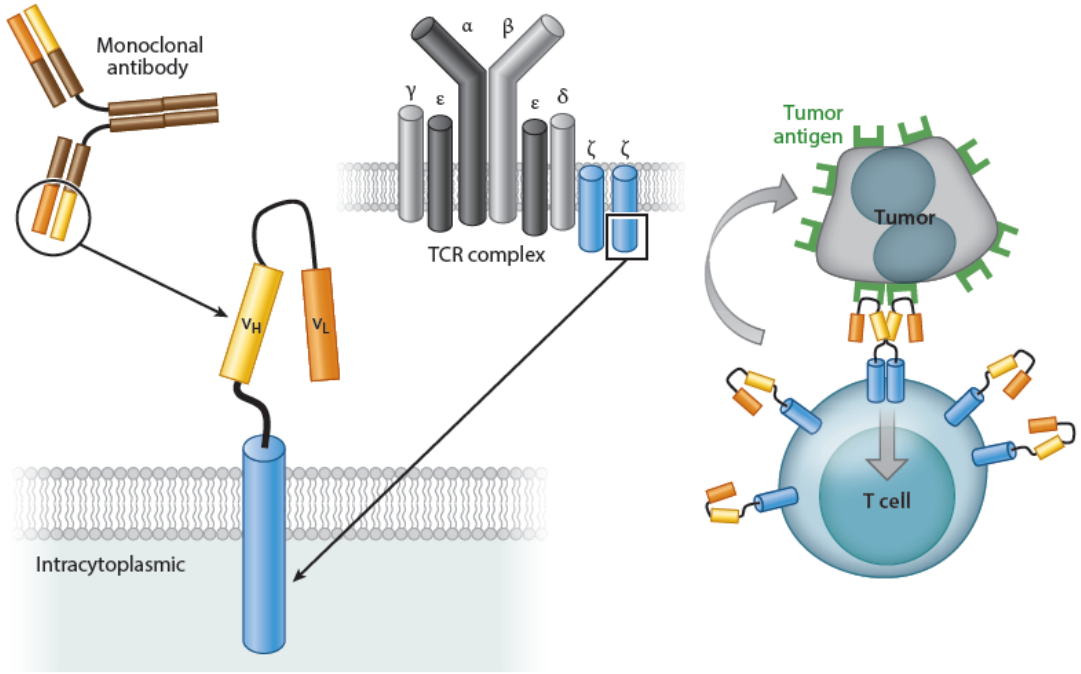
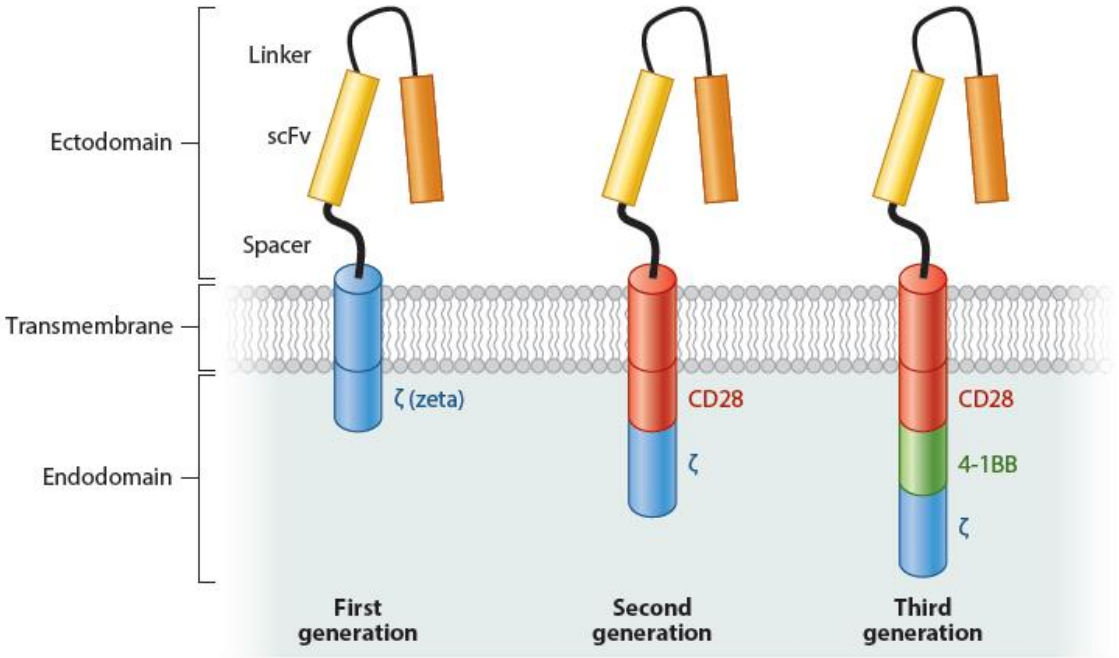
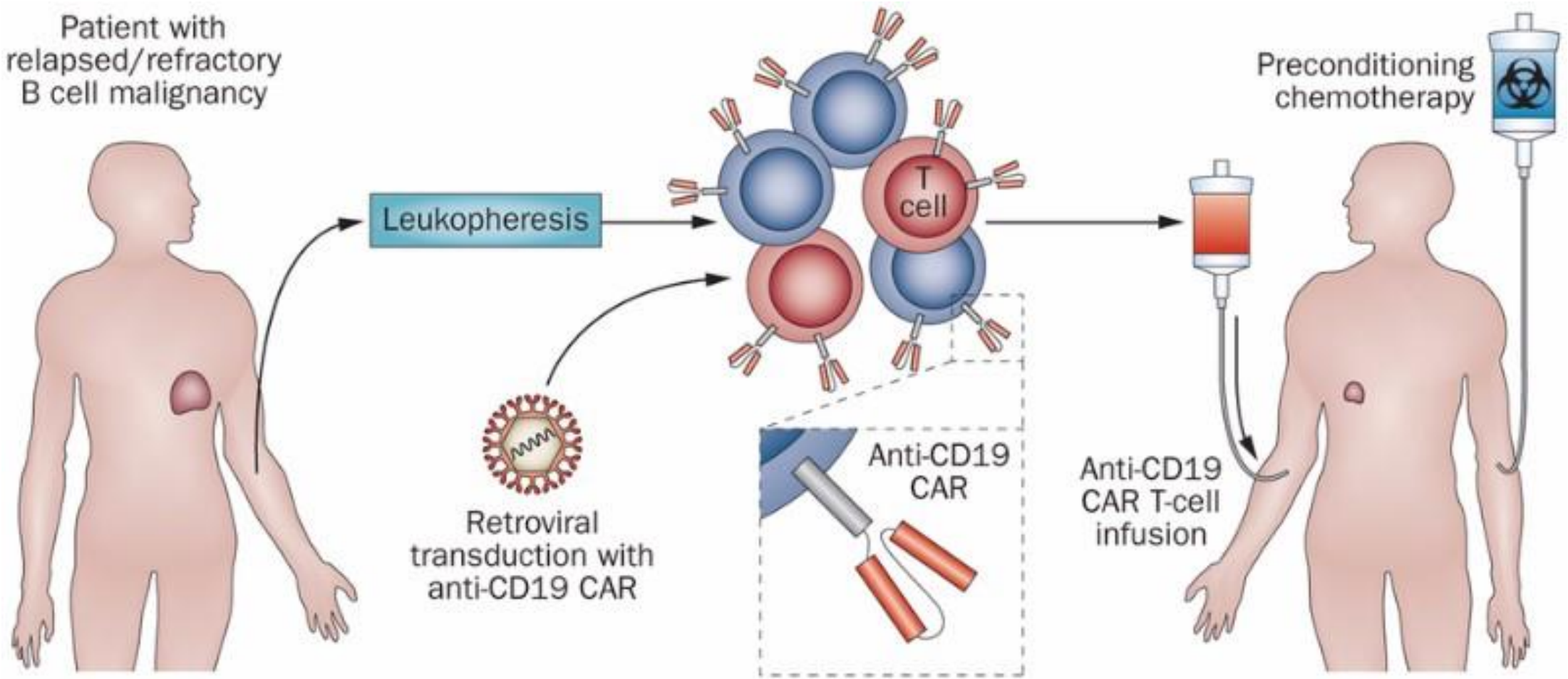
The Concept





Ramos CA, *et al.* *Ann Rev Med* 2016; 67: 6.1-6.19.

The Concept


Patient with relapsed/refractory B cell malignancy
Leukopheresis
T cell
Retroviral transduction with anti-CD19 CAR
Anti-CD19 CAR
Preconditioning chemotherapy
Anti-CD19 CAR T-cell infusion

The Concept

Prefix

Suggest by manufacturer

Infixes

Manipulation:

- *gene* for transduced by a vector /virus
- *cabta* for cell expressed antibody and T cell activation

Cell type:

- *leuc* for leucocyte

Suffixes

Cel for Use for cell therapy

Axi-cabta/gene- Cila-Leu-

-

The Concept

- **Tisa-gene- Lec-leucel**
  - **KYMRIAH®**
    - **ALL**
- **Axi-cabtagene- Cila-Leucel**
  - **YESCARTA ®**
    - **Lymphome**
- **Lisa- cabtagene-Mara-Leucel**

NOVARTIS

Kite Pharma

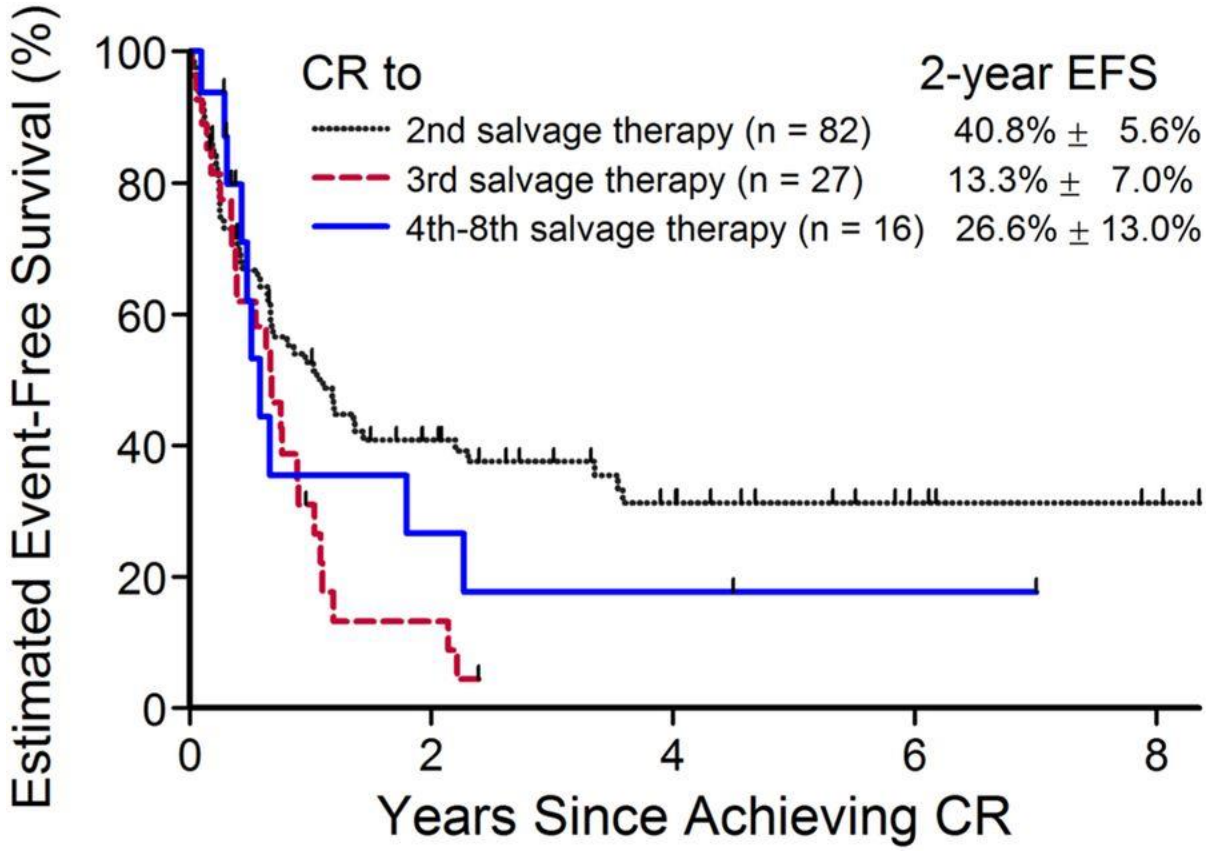
GILEAD

JUNO
THERAPEUTICS
A Celgene COMPANY

The Concept

- Indications and results in Hematology
- Toxicities
- Future development
- Issues

R/R Acute Lymphoblastic Leukemia



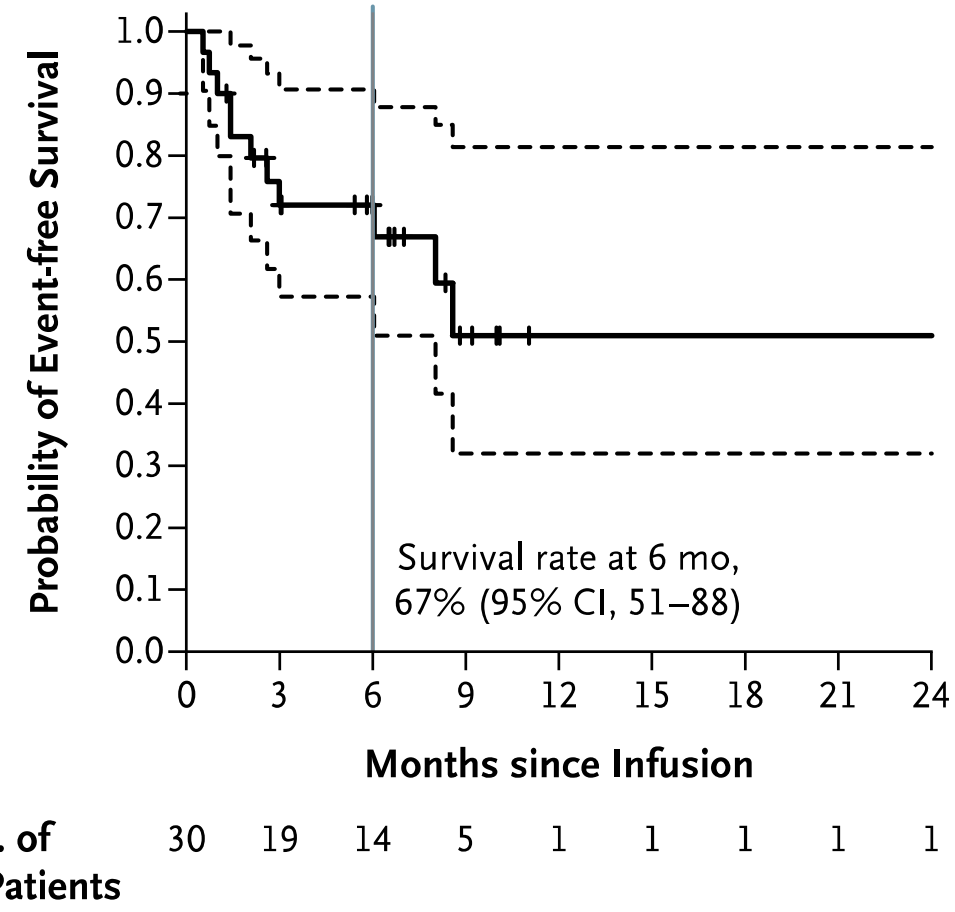
CAR-T anti CD19.

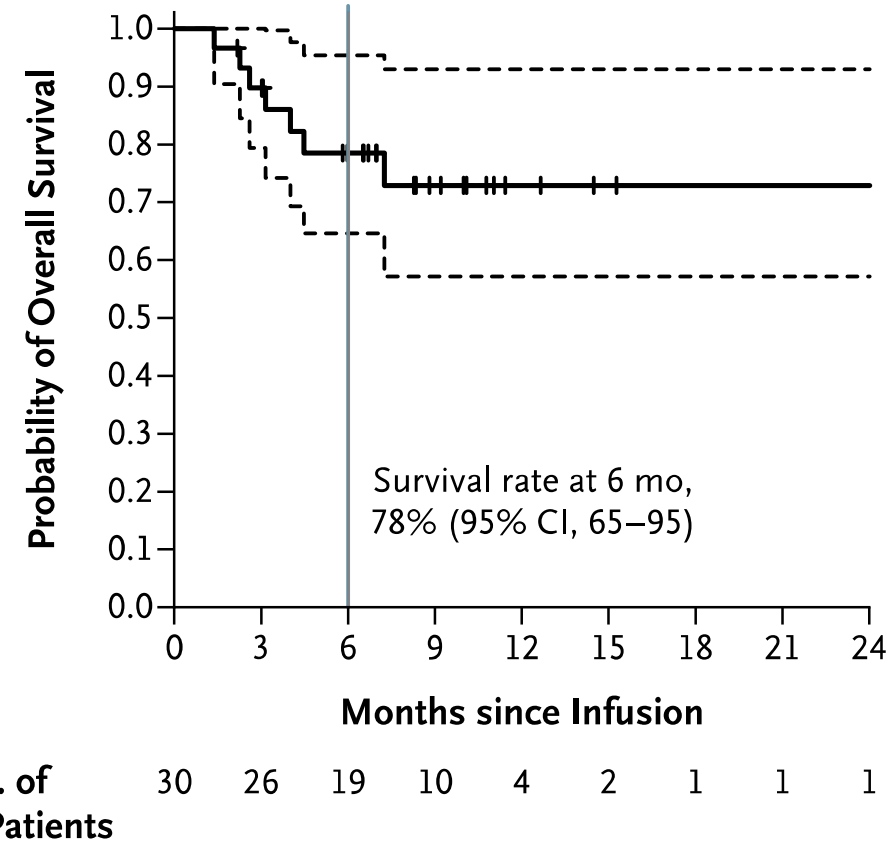
Maude SL et al. N Engl J Med. 2014; 371: 1507-17.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Pediatric Cohort (N = 25)	Adult Cohort (N = 5)	Total (N = 30)
Sex — no. (%)			
Female	11 (44)	1 (20)	12 (40)
Male	14 (56)	4 (80)	18 (60)
Age at infusion — yr			
Median	11	47	14
Range	5–22	26–60	5–60
Allogeneic transplantation — no. (%)	18 (72)	0	18 (60)
Primary refractory disease — no. (%)	0	3 (60)	3 (10)
Relapse — no. (%)			
1	3 (12)	2 (40)	5 (17)
≥2	22 (88)		22 (73)
Baseline burden of acute lymphoblastic leukemia — no. (%)			
Presence of detectable disease†	20 (80)	4 (80)	24 (80)
Morphologic remission‡		1 (20)	1 (3)
Absence of minimal residual disease	5 (20)		5 (17)
High-risk cytogenetic factors — no.			
BCR–ABL1	2		
IKZF1 deletion	2		
iAMP21	1		
MLL translocation	1		
Hypodiploidy	2		
CNS status — no.§			
CNS-1	23		
CNS-2	2		

R/R Acute Lymphoblastic Leukemia





CAR-T anti CD19.

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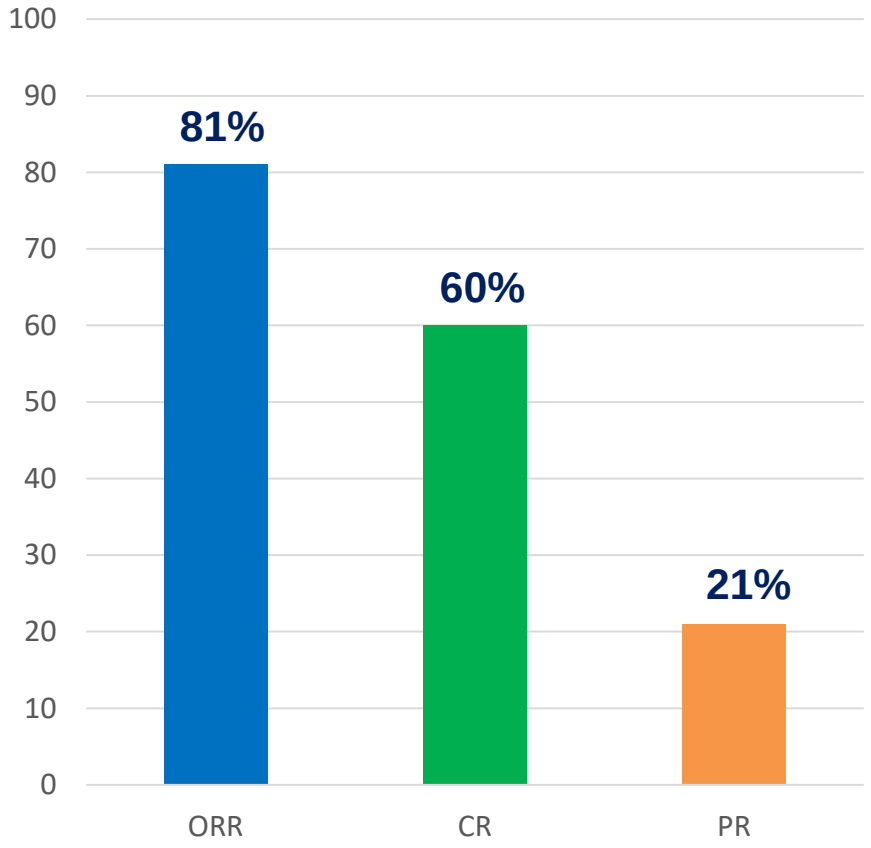
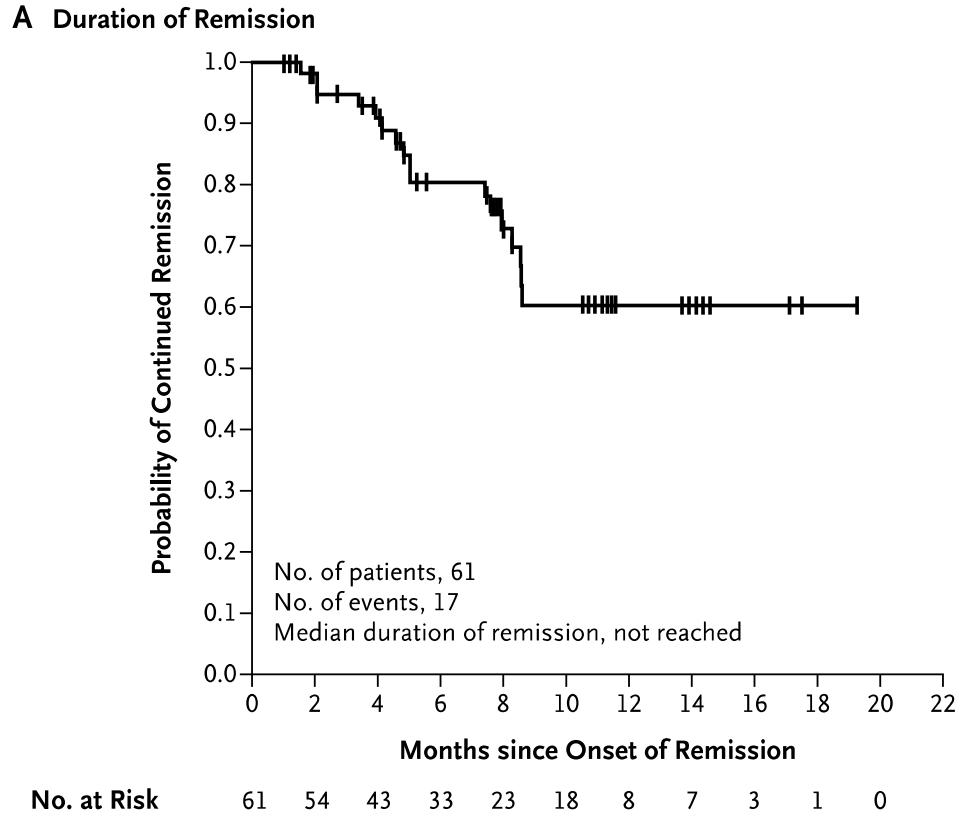
R/R Acute Lymphoblastic Leukemia





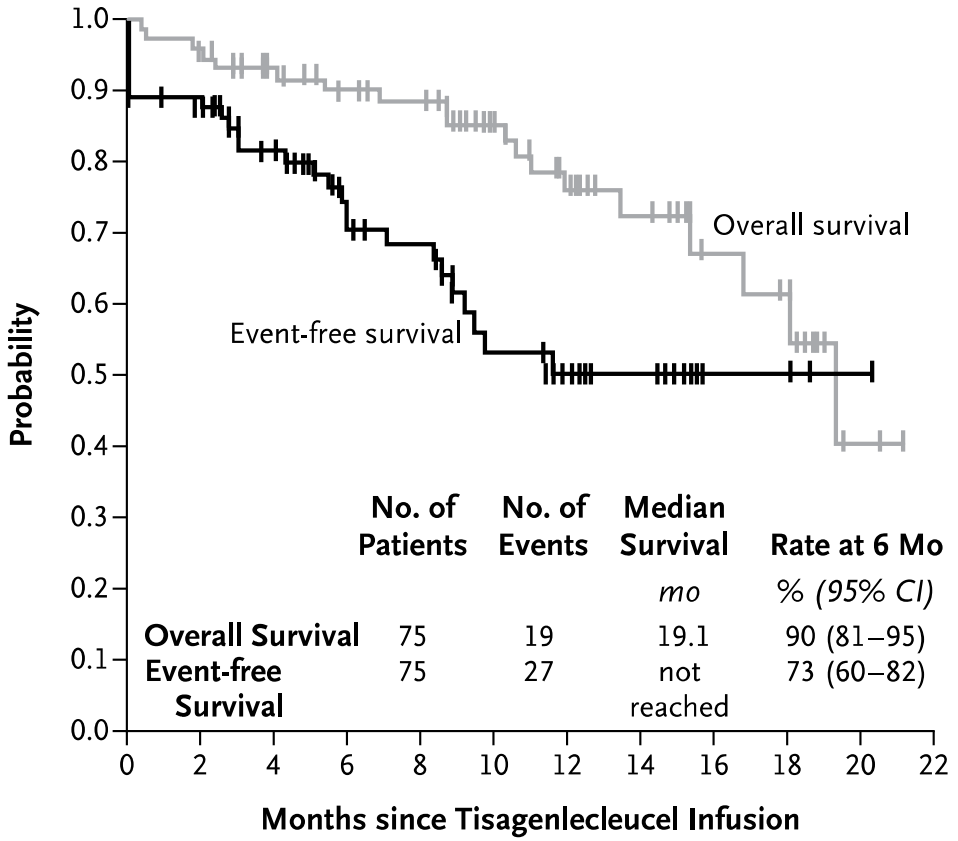
100% of CR patients had undetectable MRD.

CAR-T anti CD19.

Maude SL et al. N Engl J Med. 2018; 378: 439-48.

R/R Acute Lymphoblastic Leukemia

B **Event-free and Overall Survival**



	No. of Patients	No. of Events	Median Survival	Rate at 6 Mo
			mo	*% (95% CI)*
Overall Survival	75	19	19.1	90 (81–95)
Event-free Survival	75	27	not reached	73 (60–82)

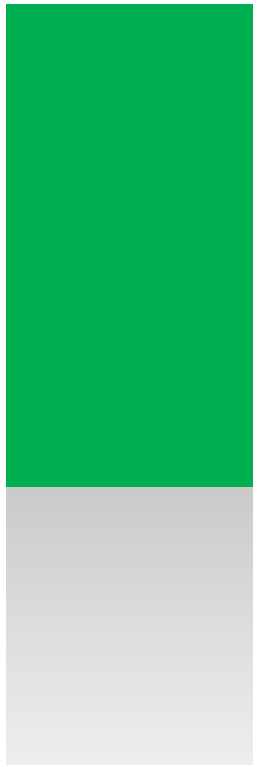
No. at Risk

Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

CAR-T anti CD19.

Maude SL et al. N Engl J Med. 2018; 378: 439-48.

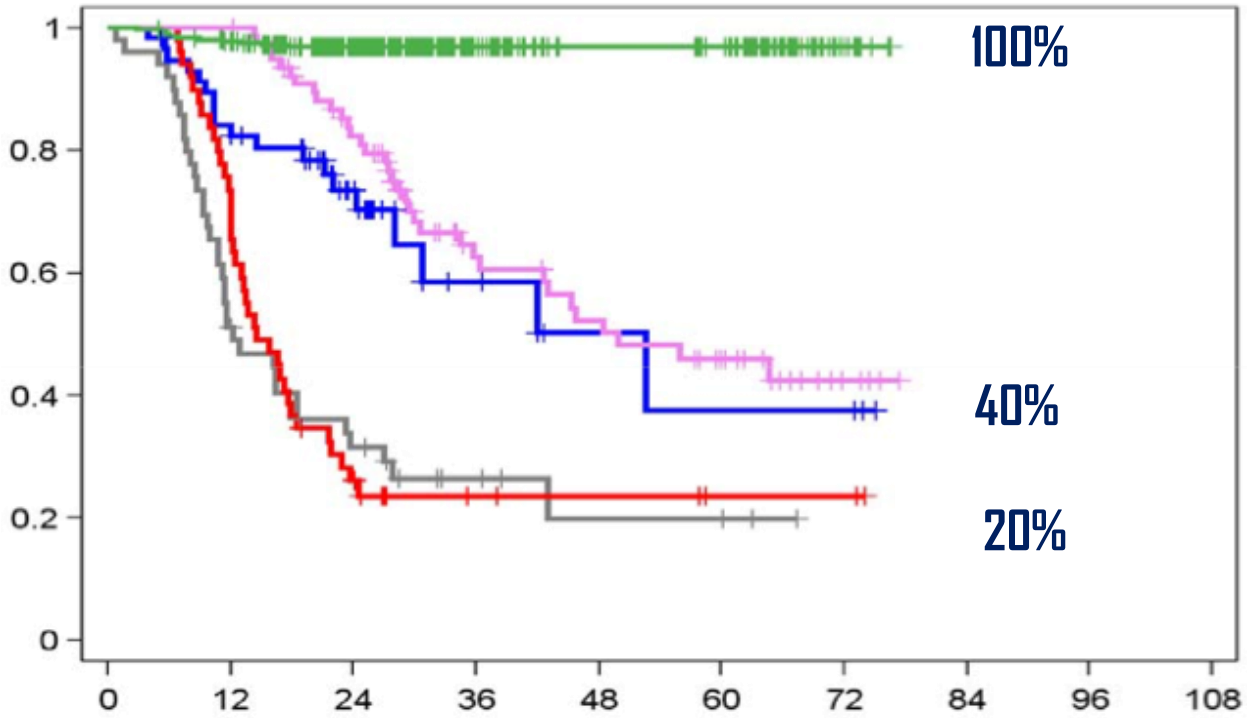
Refractory DLBCL



Cured with R-CHOP
(50-60%)

Late Relapse or PR after chemotherapy
(25 to 35%)

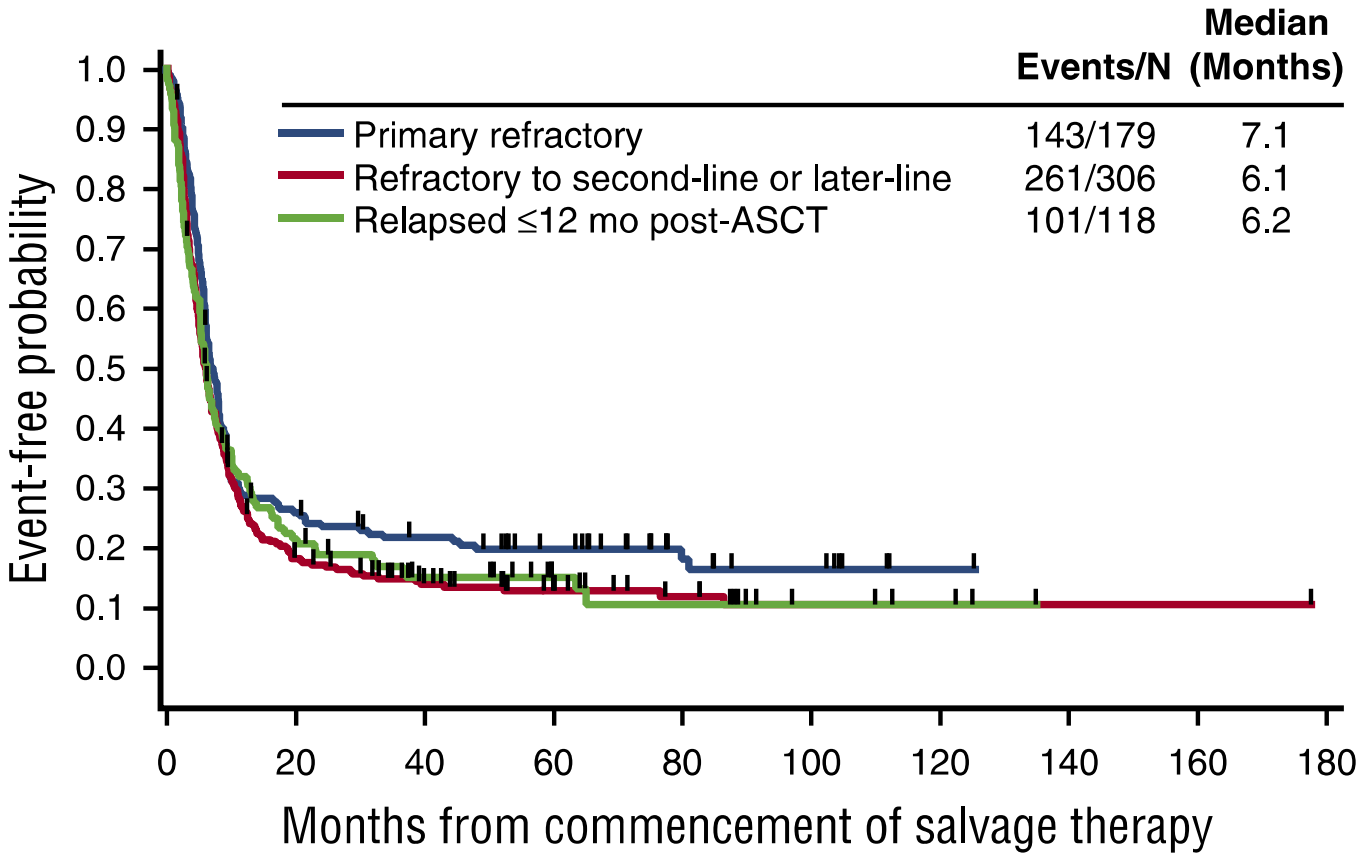
Refractory and early relapse
(15 to 25%)



Adapted from Coiffier B et al., Hematology Am Soc Hematol Educ Program 2016: 366-371 and Coiffier et al. ICML 2008

Refractory DLBCL

SCHOLAR-1



- ORR : 26%
- CR: 7%
- mOS: 6.3 mo

- **Refractory disease: PD or SD as best response at anytime of treatment or relapsed < 12 mo post-ASCT**
- **N=636**

Crump M et al. Blood. 2017; 130: 1800-1808.

ZUMA-1: Baseline Characteristics

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

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

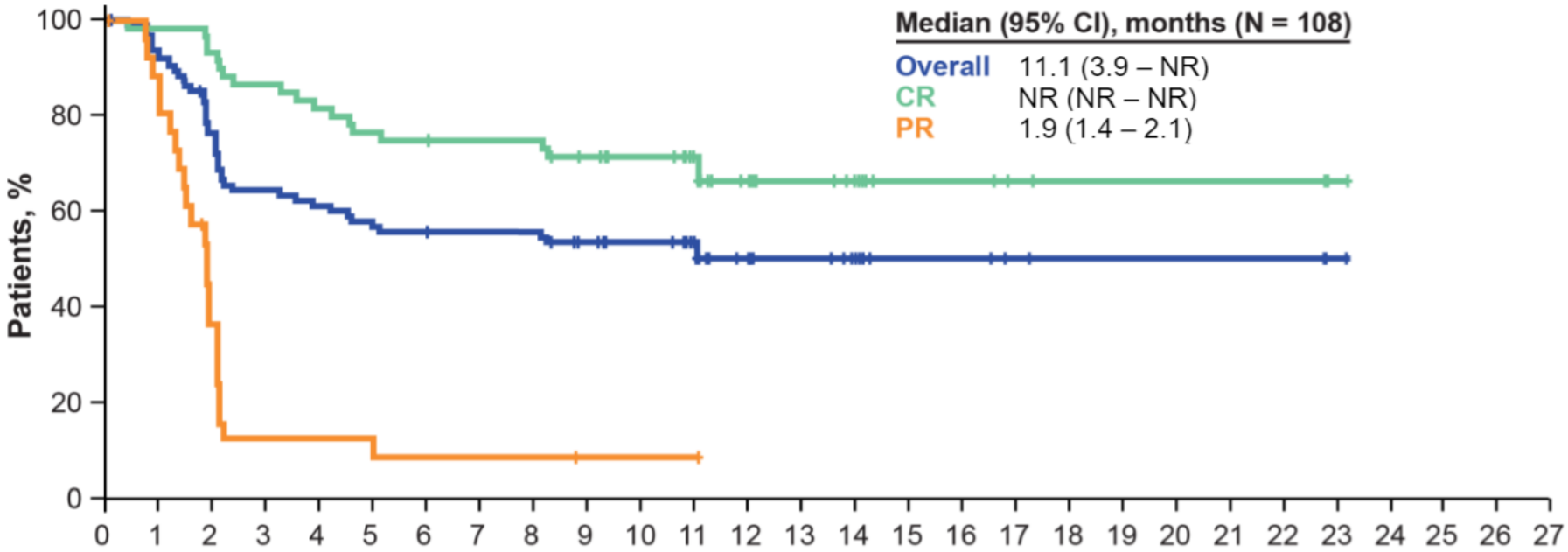
ZUMA-1: Objective Response

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days

Response was evaluated by investigator assessment.
CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

ZUMA-1: Duration of Response by Best Objective Response



Patients at Risk

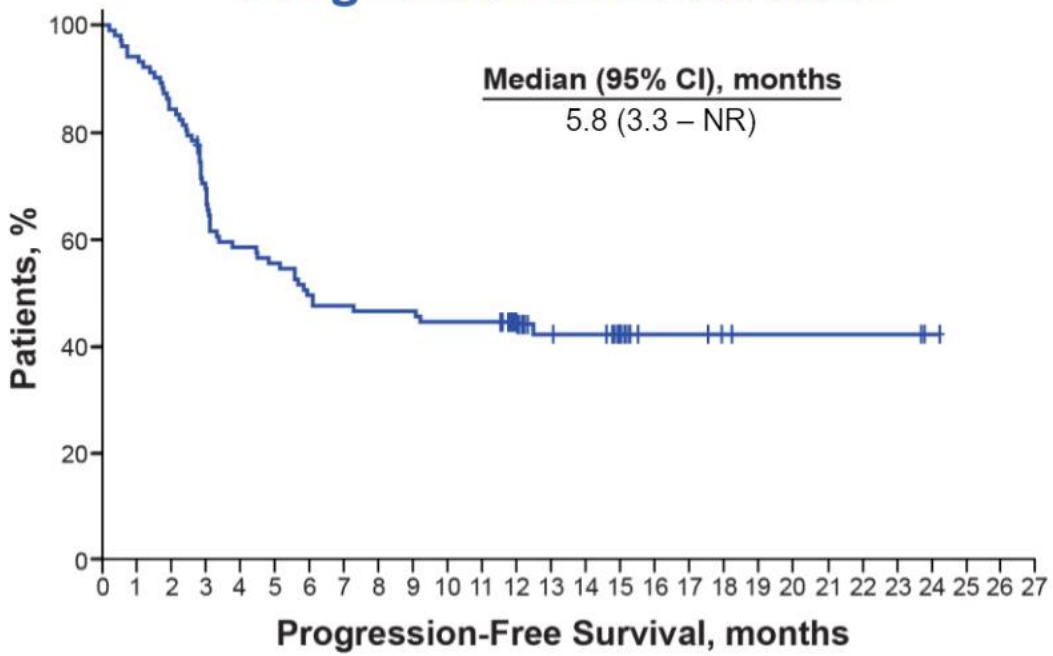
Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	1	0
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	1	0
PR	26	21	9	3	3	2	2	2	2	1	1	1	0												

- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients have ongoing CR at 24 months

CR, complete response; NR, not reached; PR, partial response.

ZUMA-1 at Median Follow-Up of 15.4 Months: 42% Progression-Free and 56% Alive

Progression-Free Survival

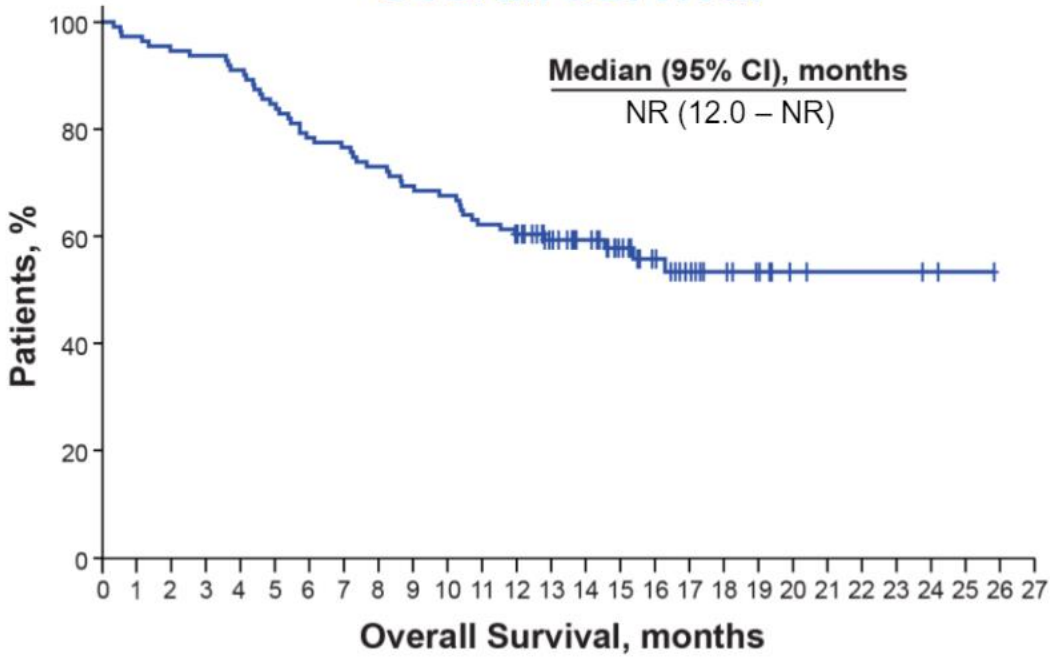


Patients at Risk

108 90 61 52 49 47 34 20 6 4 3 3 1

Landmark	PFS
6-month	49
12-month	44
18-month	41

Overall Survival



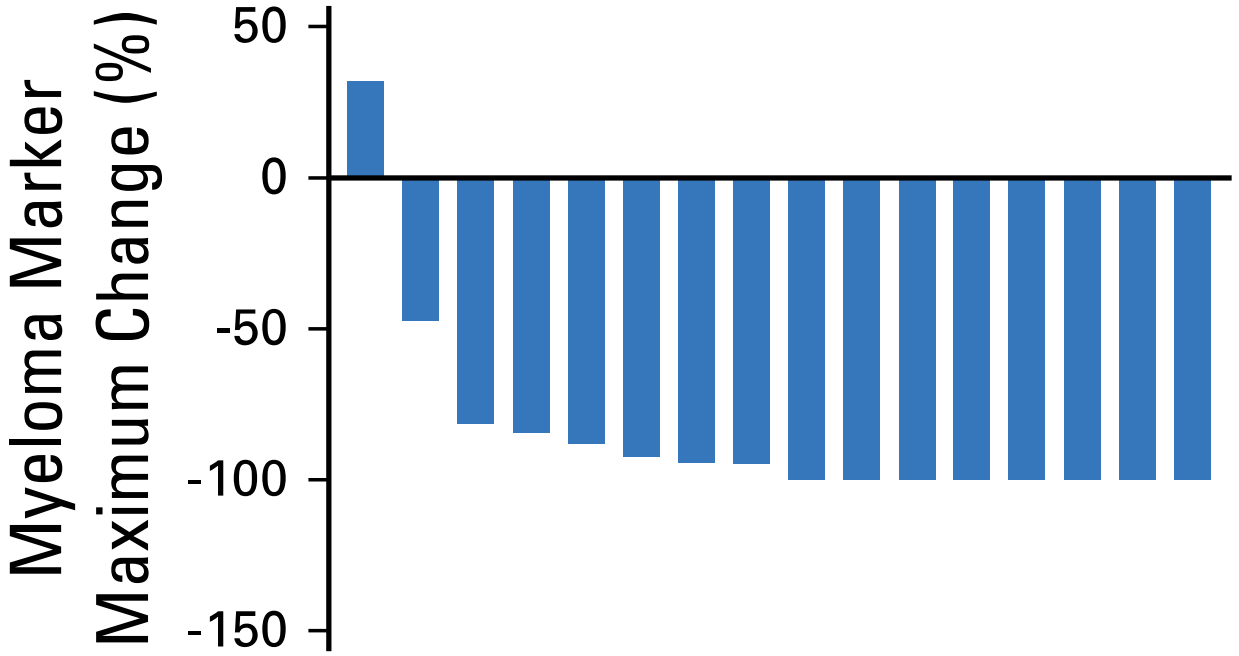
Patients at Risk

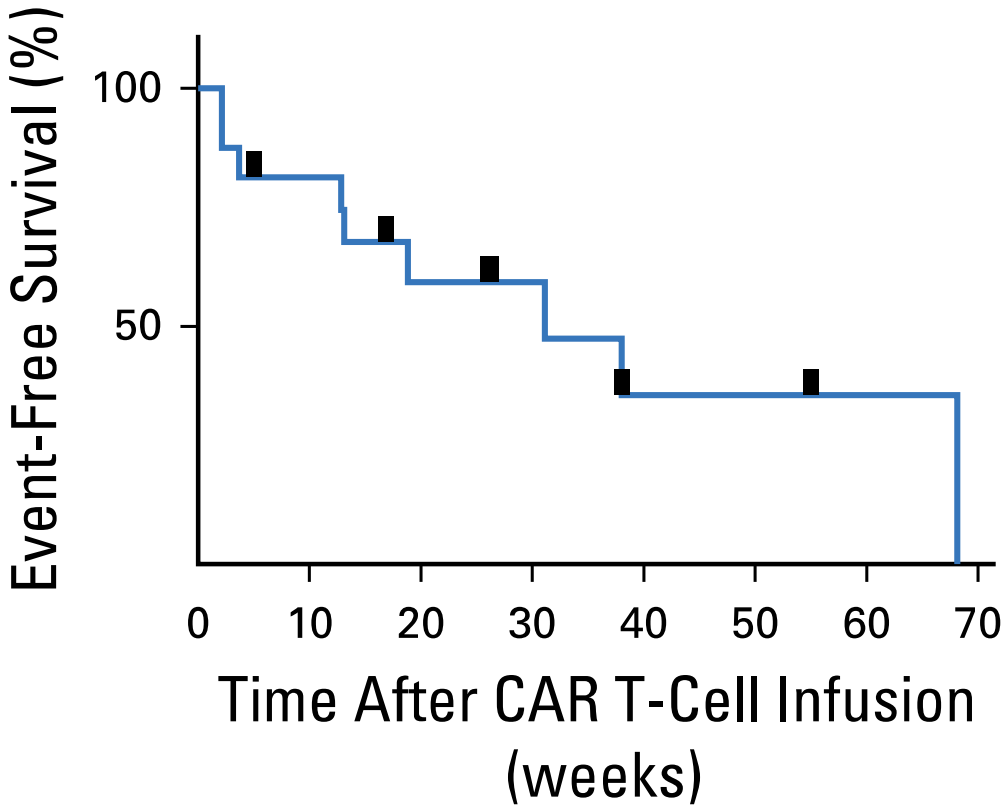
108 102 98 84 78 72 63 40 23 11 4 3 2 0

Landmark	OS
6-month	78
12-month	59
18-month	52

NR, not reached; OS, overall survival; PFS, progression-free survival.

R/R Multiple Myeloma





CAR-T anti B Cell Maturation Antigen.

Brudno JN et al. J Clin Oncol. 2018; May 29.

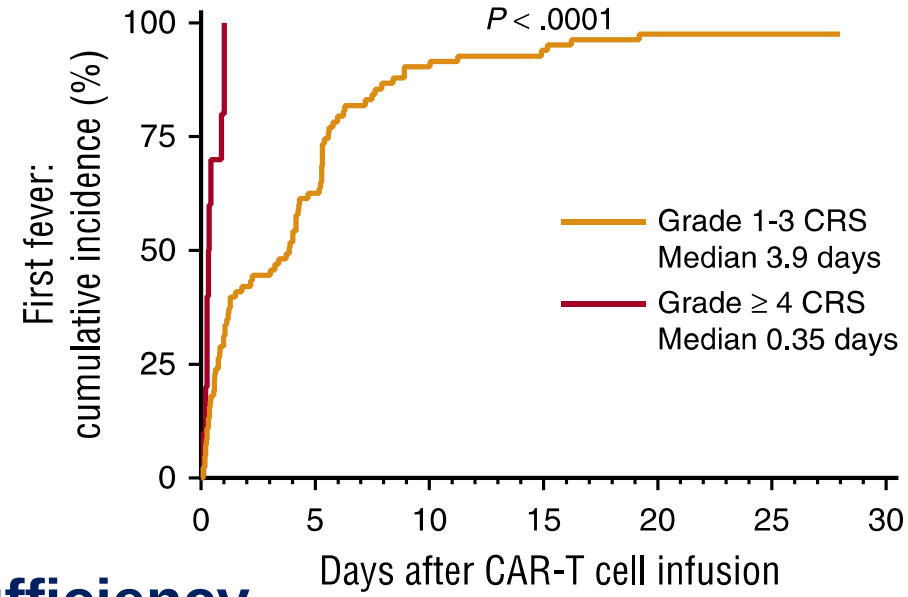
Toxicities

Cytokines Release Syndrome (CRS)

Neurotoxicities

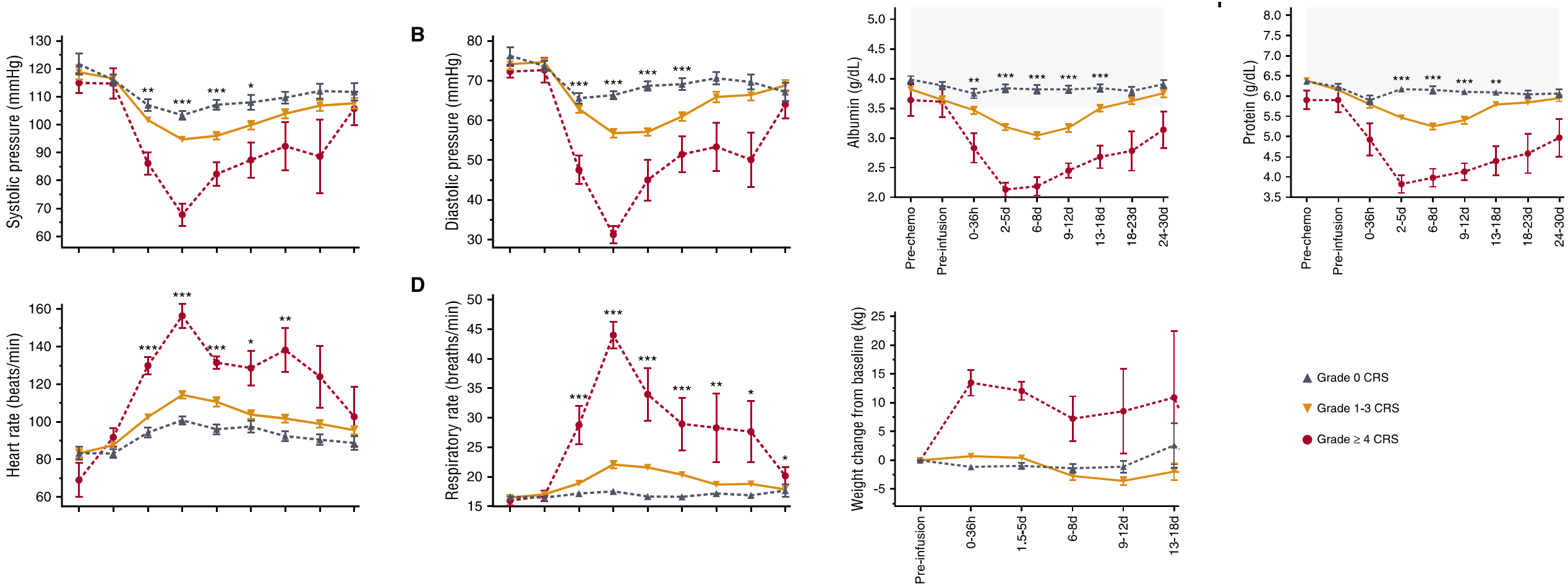
Cytokines Release Syndrome

- **Symptoms**
  - **Fever**
  - **Hypotension**
  - **Coagulopathy**
  - **Capillary leak**
  - **Respiratory and Cardiovascular insufficiency**
  - **More frequent in ALL/NHL**



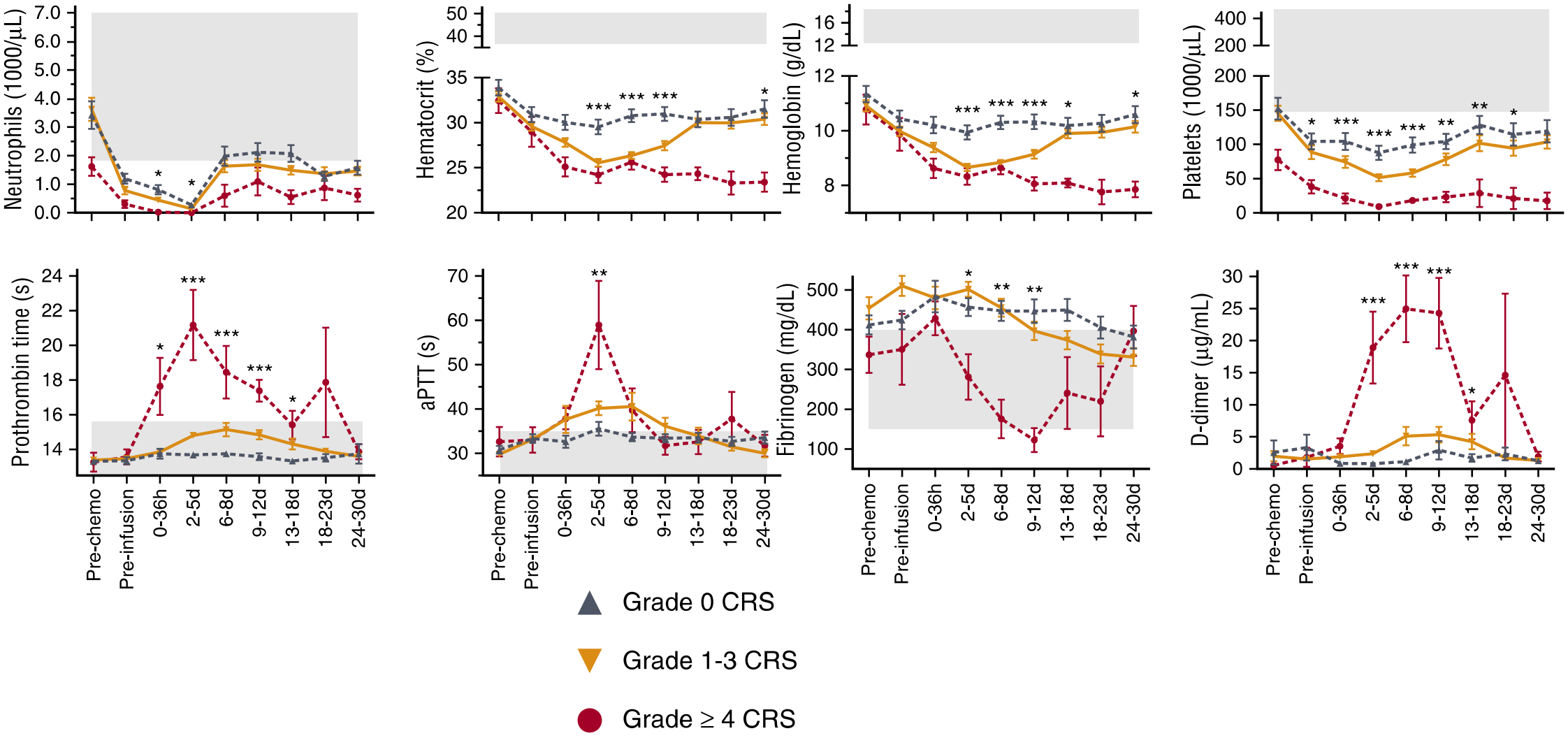
Hay KA et al. Blood. 2017; 130: 2295-06.

Cytokines Release Syndrome: symptoms



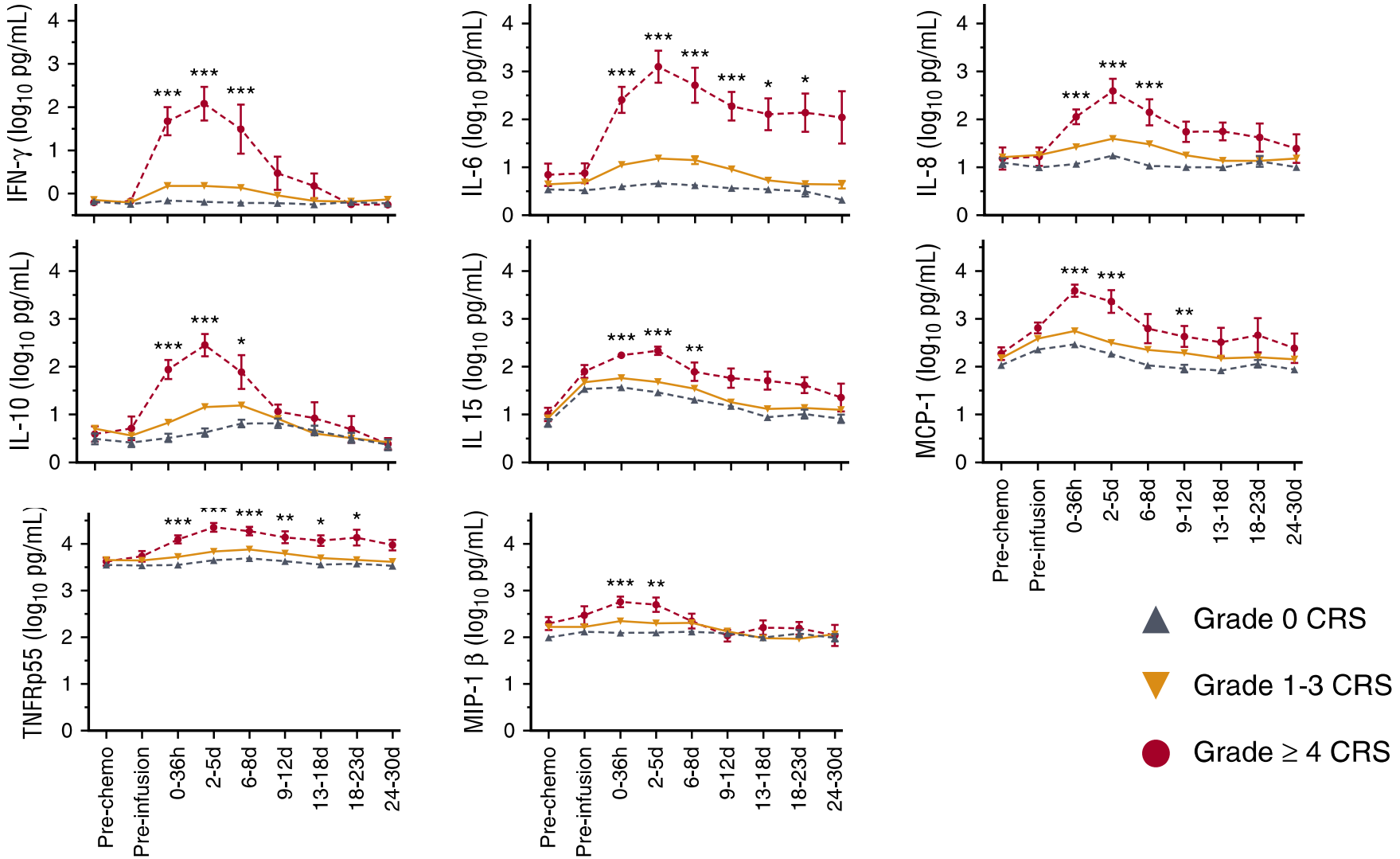
Hay KA et al. Blood. 2017; 130: 2295-06.

Cytokines Release Syndrome: biology



Hay KA et al. Blood. 2017; 130: 2295-06.

Cytokines Release Syndrome: cytokine profile



Hay KA et al. Blood. 2017; 130: 2295-06.

Cytokines Release Syndrome: risk factors

Risk factors
Marrow disease burden
Platelet count
CD8+ selection method
CPM-FDR lymphodepletion
CAR-T cells dose

Hay KA et al. Blood. 2017; 130: 2295-06.

Cytokines Release Syndrome: treatment by tocilizur...ab

Characteristics and treatment	CTL019 series ($n = 45$) n (%)	KTE-C19 series ($n = 15$) n (%)
Baseline CRS grade		
Grade 3	10 (22.2)	14 (93.3)
Grade 4	35 (77.8)	1 (6.7)
CRS duration prior to tocilizumab		
0–4 days	23 (51.1)	12 (80.0)
>4 days	22 (48.9)	3 (20.0)
Number of tocilizumab doses		
1 dose	25 (55.5)	6 (40.0)
2 doses	13 (28.9)	5 (33.3)
≥3 doses	7 (15.6)	4 (26.7)
Number of tocilizumab doses daily		
Single daily dose	43 (95.6)	10 (66.7)
Multiple doses per day	2 (4.4)	5 (33.3)
First tocilizumab dose level[a]		
8 mg/kg	38 (84.4)	15 (100)
12 mg/kg	7 (15.6)	0

[a]

Analyses	CTL019 series ($n = 45$) responders n (%, 95% CI)	KTE-C19 series ($n = 15$) responders n (%, 95% CI)
Primary analysis:		
Response by day 14	31 (68.9, 53.4–81.8)	8 (53.3, 26.6–78.7)
Additional analyses		
Response by day 2	9 (20.0, 9.6–34.6)	3 (20.0, 4.3–48.1)
Response by day 7	26 (57.8, 42.2–72.3)	8 (53.3, 26.6–78.7)
Response by day 21	31 (68.9, 53.4–81.8)	8 (53.3, 26.6–78.7)

Abbreviation: CI, confidence interval.

Le QR et al. Oncologist. 2018; 23: 1-5.

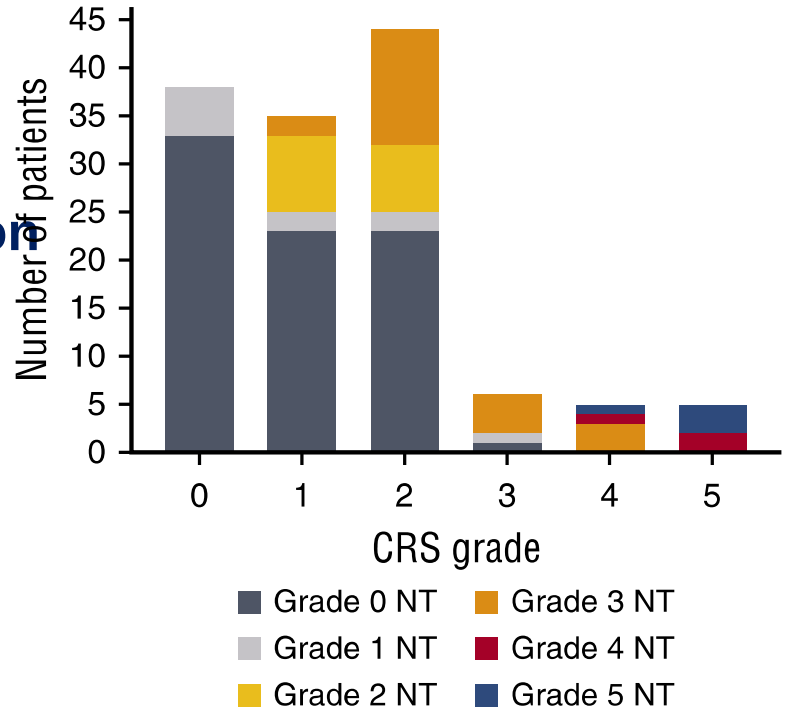
Neurotoxicity: Symptoms

- Delirium
- Headache
- Decrease level of conscience or speech impairment
- Focal neurologic deficits
- Seizure
- Acute cerebral edema
- Usually after the onset of CRS or after its resolution
- More frequent in ALL/NHL

Gauthier J et al. Curr Res Transl Med? 2018; 66: 50-52.

Neurotoxicity: mechanisms

- **Unknown**
- **Secondary to CRS:**
  - **Endothelial activation and vascular dysfunction**
    - **Hypotension, capillary leak, consumptive coagulopathy**



Hay KA et al. Blood. 2017; 130: 2295-06.

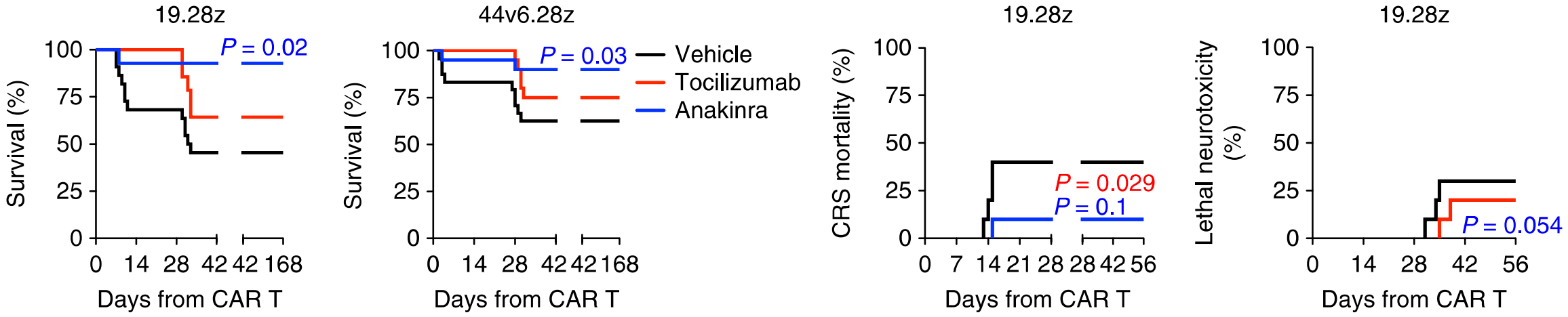
Neurotoxicity: treatment

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0036-4

Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells



Norelli M et al. Nature Med. 2018; May

Future developments

- **In Hematology**
  - **Multiple Myeloma (CD19, BCMA)**
  - **New targets: WT1, Survivin, PRAME**
- **In Oncology**
  - **Targets: EGFR/HER2, Mesothelin…**
- **Virus**
  - **HBsAg, CMV…**

Future development

IMMUNOTHERAPY

Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease

Christoph T. Ellebrecht,[1] Vijay G. Bhoj,[2] Arben Nace,[1] Eun Jung Choi,[1] Xuming Mao,[1] Michael Jeffrey Cho,[1] Giovanni Di Zenzo,[3] Antonio Lanzavecchia,[4] John T. Seykora,[1] George Cotsarelis,[1] Michael C. Milone,[2]*† Aimee S. Payne[1]*†

Science 2016; 353: 179-84

GASTROENTEROLOGY 2013;145:456–465

T Cells Expressing a Chimeric Antigen Receptor That Binds Hepatitis B Virus Envelope Proteins Control Virus Replication in Mice

KARIN KREBS,[1,*] NINA BÖTTINGER,[1,*] LI–RUNG HUANG,[2] MARKUS CHMIELEWSKI,[3] SILKE ARZBERGER,[1] GEORG GASTEIGER,[1] CLEMENS JÄGER,[1] EDGAR SCHMITT,[4] FELIX BOHNE,[1] MICHAELA AICHLER,[5] WOLFGANG UCKERT,[6] HINRICH ABKEN,[3] MATHIAS HEIKENWALDER,[1] PERCY KNOLLE,[2] and ULRIKE PROTZER[1]

[1]Institute of Virology, Technische Universität München/Helmholtz Zentrum München, München; [2]Institute of Molecular Medicine, University of Bonn, Bonn; [3]Department of Internal Medicine I, University Hospital Cologne, Köln; [4]Institute for Immunology, University of Mainz, Mainz; [5]Institute of Pathology, Helmholtz Zentrum München,

Issues

- **Longer follow-up**
  - **Efficacy**
  - **Toxicity**
- **How to prevent CRS and NT**
  - **Role of number of CAR-T infused**
  - **CD4/CD8 ratio**
  - **Role of chemotherapy**
  - **New generations of CAR-T**
- **Cost**

How to compare CAR-T cell therapies?

	JULIET	ZUMA	JUNO	BR-Pola
CAR-T	ScFvCD19 CD28/4-1BB/CD3z	ScFvCD19 CD28/CD3z	ScFvCD19 CD28/4-1BB/CD3z	
Ratio of enrollment (%)	**67**	**91**	**77**	**100**
Median of availability (d)	**39**	**17**		
Bridging chemotherapy (%)	Yes (90)	No		
Lymphodepletion	Ph Choice	Fu: 30mg/$m^{2,}$ D1-D3 CPM 500 mg/$m^{2,}$ D1-D3	Fu: 30mg/$m^{2,}$ D1-D3 CPM 300 mg/$m^{2,}$ D1-D3	
Number of infused cells	Median 5.10^8	2.10^6/kg	1.10^8	

Sehn L, et al. ASH 2017 Abst 2821. Shuster S, et al ASH 2017 Abst 577, Neelapu N et al ASH 2017, Abst 578; Abrahamson JS et ak. ASH 2017, Abst 579

How to compare CAR-T cell therapies?

	JULIET	ZUMA	JUNO	BR-Pola
n	99	108	91	40
FU		15.4	6.3	11.1
Histology	DLBCL/FL	DLBCL/T-FL/PMBL	DLBCL/t-FL/MZL/FL	DLBCL
Pior ASCT (%)	47	23	42	
>= 3 prior therapies	50	70		
CR at 6 months (%)	**54**	**58**	**50**	**48**
DOR for CR	**NR**	**NR**	**NR**	
DOR for CR/PR		11.1	9.2	8.8
Death (%)	**3.6**	**3**	**1**	
CRS grade ¾ (%)	**18**	**13**	**1**	
Onset/duration (d)	3/7	2/8	5/	
NeuroTox grade ¾ (%)	**11**	**28**	**12**	
Onset/duration		5/17	10/	

Sehn L, et al. ASH 2017 Abst 2821. Shuster S, et al ASH 2017 Abst 577, Neelapu N et al ASH 2017, Abst 578; Abrahamson JS et ak. ASH 2017, Abst 579