Il monitoraggio immunologico dopo la reinfusione della terapia cellulare CAR-T è utile nella gestione clinica del paziente?

LE RAGIONI DEL NO

Mattia Algeri

IRCCS Ospedale Pediatrico Bambino Gesù, Roma

Disclosures

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

Disclosures – parte II

- **Membro di un centro da sempre forte promotore del monitoraggio immunologico dopo CAR-T**

- **Più volte utilizzatore del monitoraggio immunologico dopo CAR-T per guidare decisioni terapeutiche**

  (in un setting principalmente pediatrico)

LE RAGIONI DEL NO

MONITORAGGIO IMMUNOLOGICO E SCENARI CLINICI DOPO INFUSIONE DI CAR-T

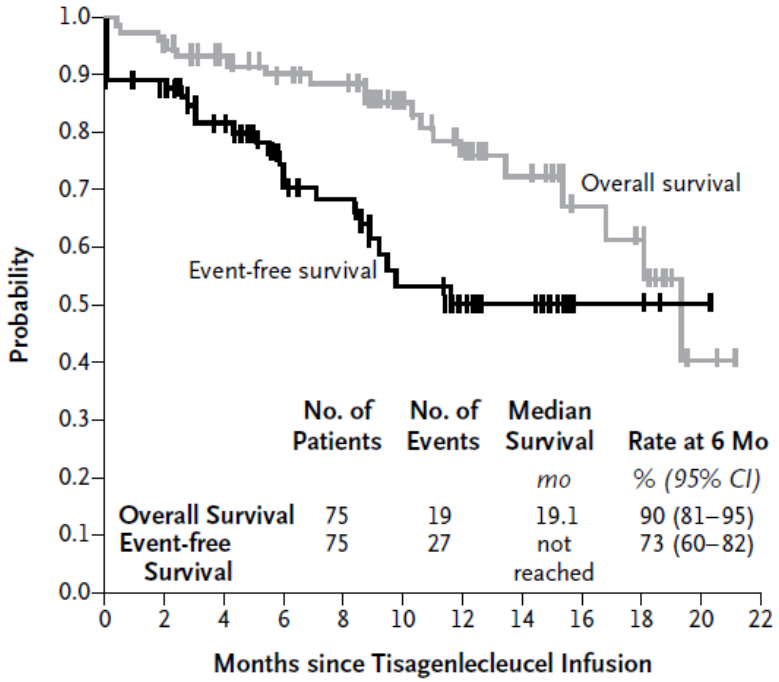
- **MIGLIORAMENTO/CONSOLIDAMENTO DELLA RISPOSTA**
- **GESTIONE TOSSICITA’**
- **IMMUNORICOSTITUZIONE**

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, P. Bader, M.R. Verneris, H.E. Stefanski, G.D. Myers, M. Qayed, B. De Moerloose, H. Hiramatsu, K. Schlis, K.L. Davis, P.L. Martin, E.R. Nemecek, G.A. Yanik, C. Peters, A. Baruchel, N. Boissel, F. Mechinaud, A. Balduzzi, J. Krueger, C.H. June, B.L. Levine, P. Wood, T. Taran, M. Leung, K.T. Mueller, Y. Zhang, K. Sen, D. Lebwohl, M.A. Pulsipher, and S.A. Grupp

B Event-free and Overall Survival



	No. of Patients	No. of Events	Median Survival (mo)	Rate at 6 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

Maude SL, et al. *NEJM 2018*.

TISAGENLECLEUCEL IN PEDIATRIC AND YOUNG ADULT PATIENTS (PTS) WITH RELAPSED/REFRACTORY (R/R) B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA (B-ALL): FINAL ANALYSES FROM THE ELIANA STUDY

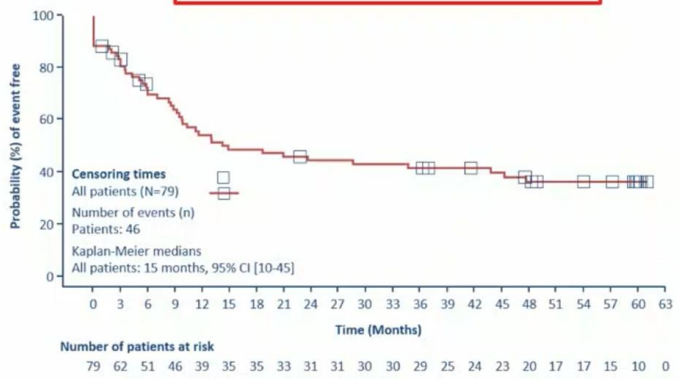
EHA EUROPEAN HEMATOLOGY ASSOCIATION

EHA2022 HYBRID VIRTUAL

Median EFS was 15 Months

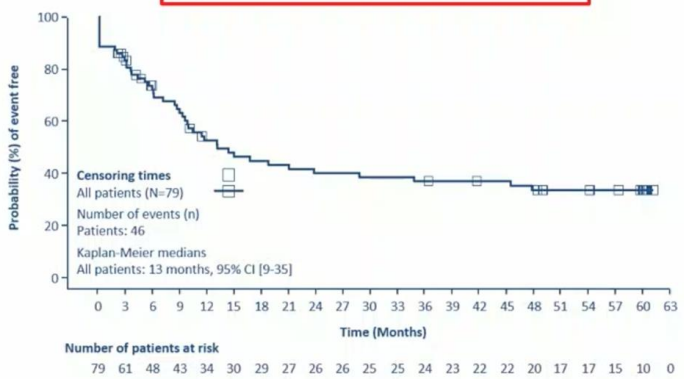
EFS Without Censoring for alloSCT

5-year EFS: 36% (95% CI, 25%-47%)



EFS With Censoring for alloSCT

5-year EFS: 34% (95% CI, 23%-45%)



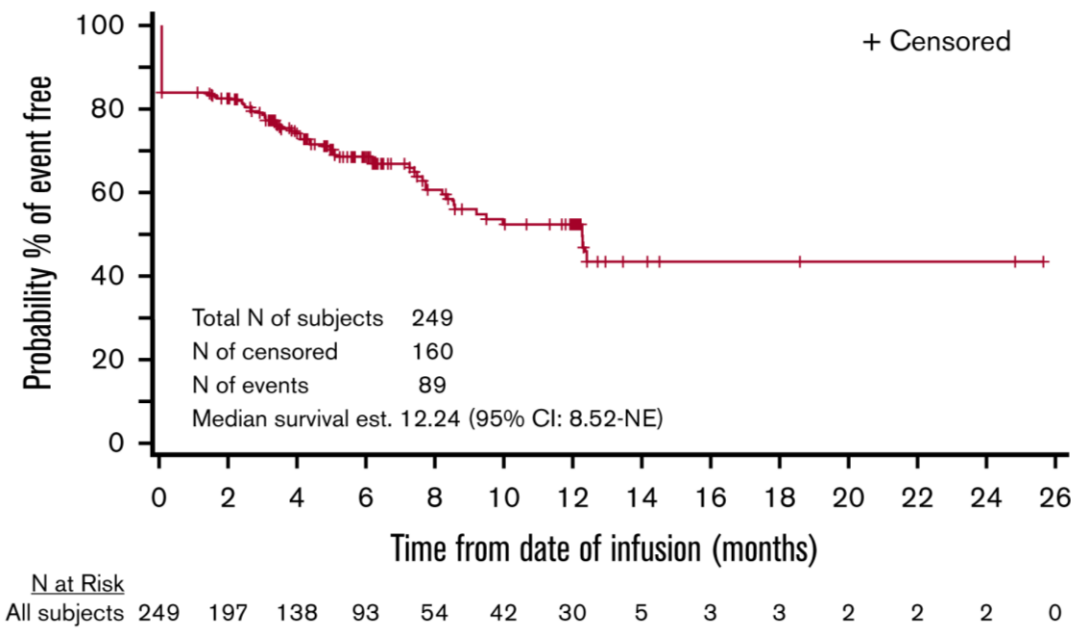
alloSCT, allogeneic stem cell transplantation; EFS, event-free survival; NE, not estimable.

12

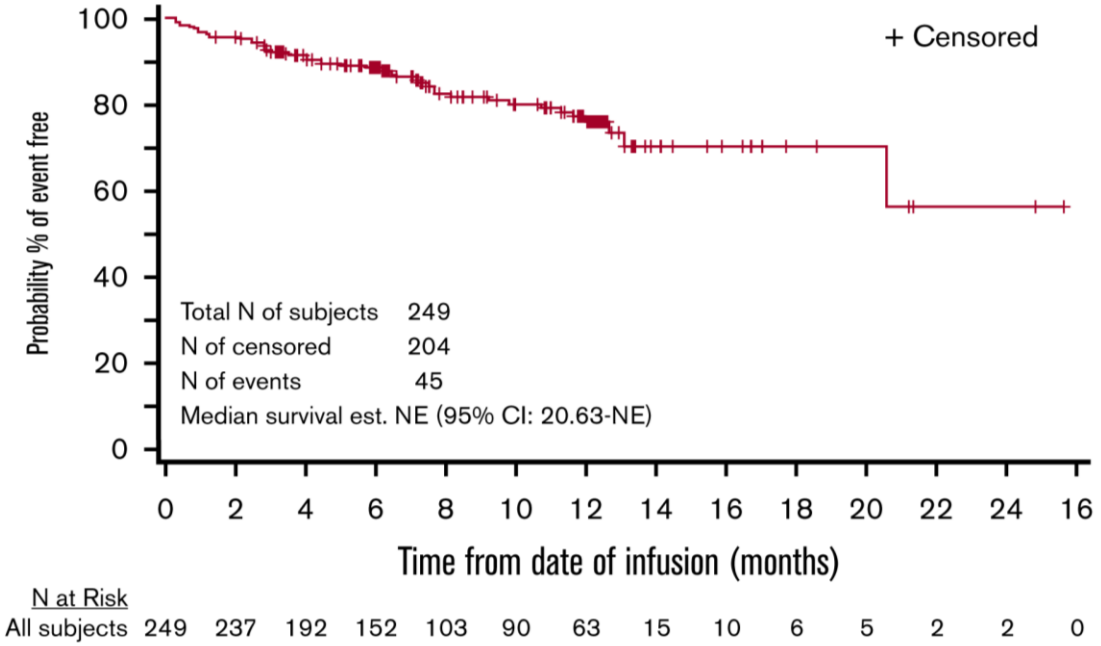
Rives S, et al. *EHA CONGRESS 2022*

Real-world evidence of tisagenlecleucel for pediatric B-ALL

EFS Rates Among All Infused Patients, % (95% CI) N = 249	
6 months	68.6 (62.0-74.4)
12 months	52.4 (43.4-60.7)



OS Rates Among All Infused Patients, % (95% CI) N = 249	
6 months	88.5 (83.6-92.0)
12 months	77.2 (69.8-83.1)



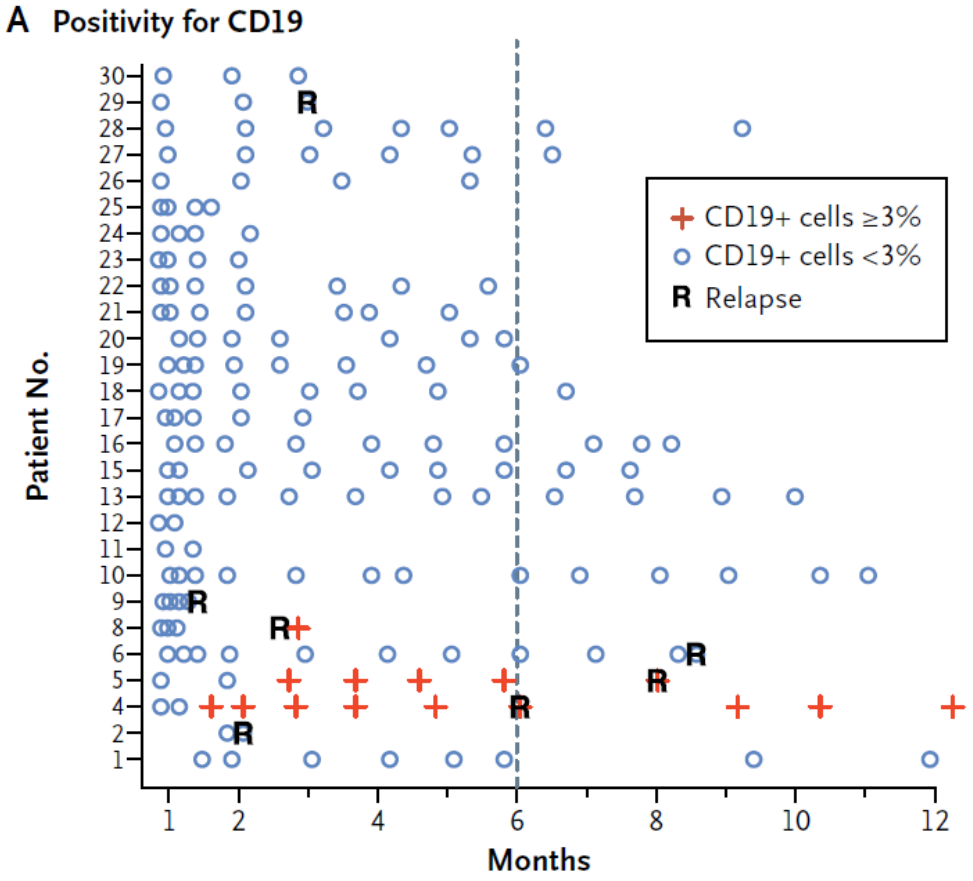
- **Prior alloSCT, n (%): 71 (27.8%)**
- **34 (16.1%) patients went on to HSCT after tisagenlecleucel while in remission**

Pasquini MC, et al. *Blood Adv*. 2020

Which patients given CAR T- cell therapy should be treated with HSCT?

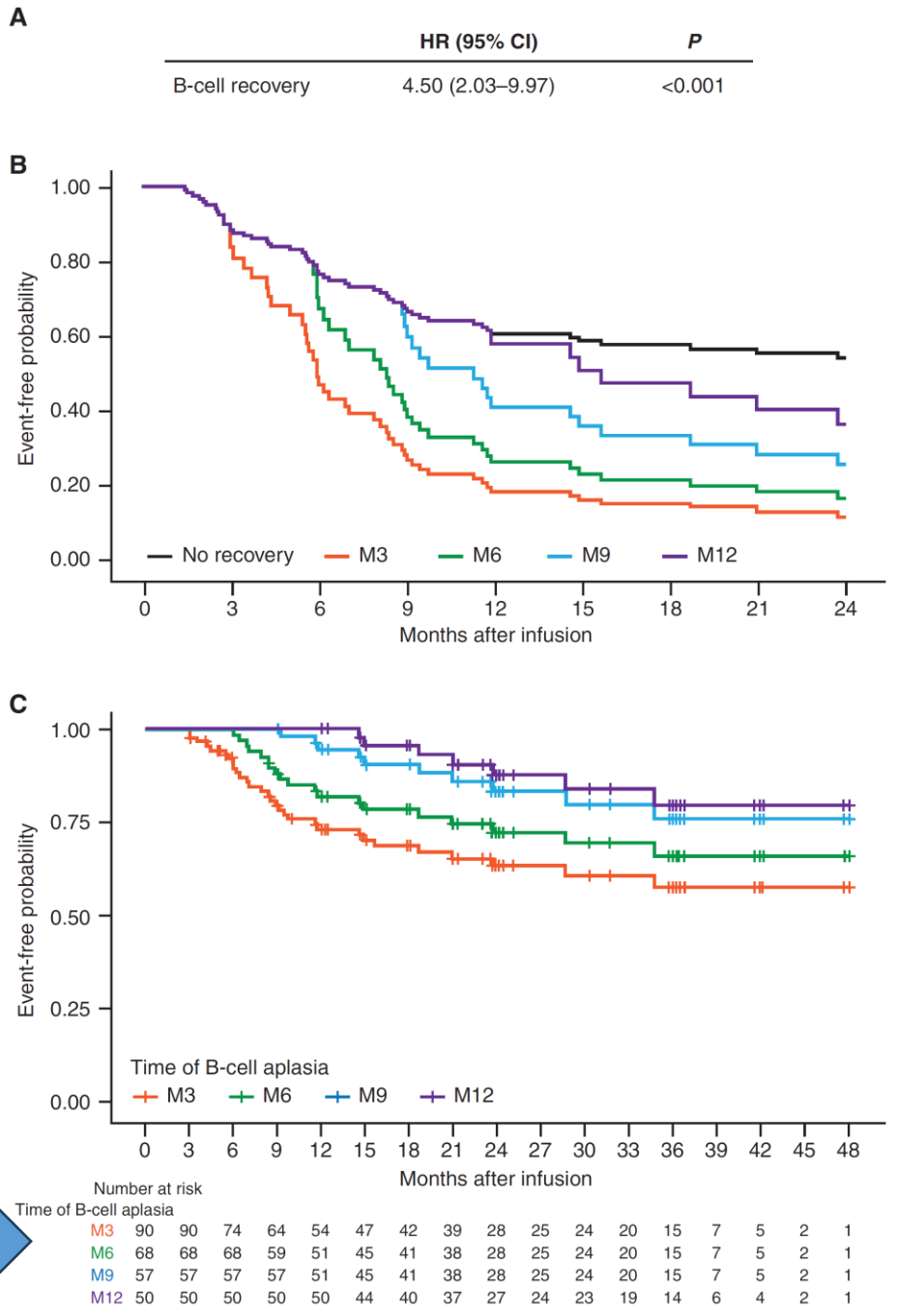
Is there a role for immune monitoring in the decision-making process?

Loss of B-cell aplasia



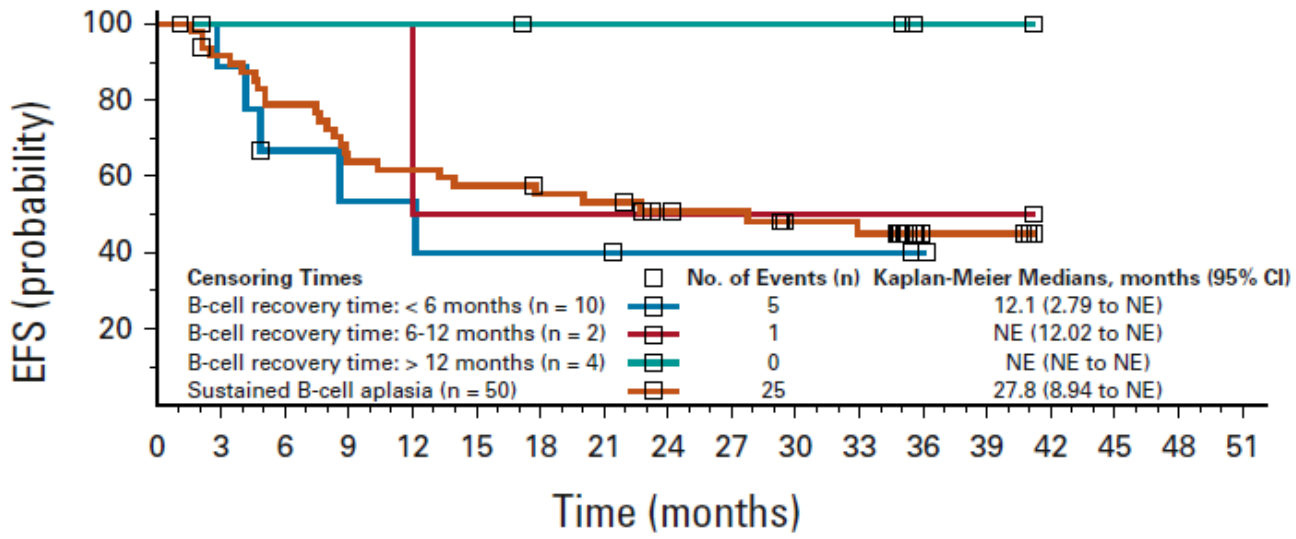
Maude SL, et al. *NEJM 2014*

For patients with persistence of BCA at 3, 6, 9, and 12 months the corresponding 2 years EFS were 63%, 72%, 83% and 88%, respectively.



Pulsipher MA, et al. *Blood Cancer Discovery* 2022

Loss of B-cell aplasia



No. at risk:

B-cell recovery time: < 6 months	10	8	5	4	4	3	3	3	2	2	2	2	1	0	
B-cell recovery time: 6-12 months	2	2	2	2	2	1	1	1	1	1	1	1	1	1	0
B-cell recovery time: > 12 months	4	4	4	4	4	4	3	3	3	3	3	3	1	1	0
Sustained B-cell aplasia	50	43	37	30	29	27	25	24	20	19	15	14	3	3	0

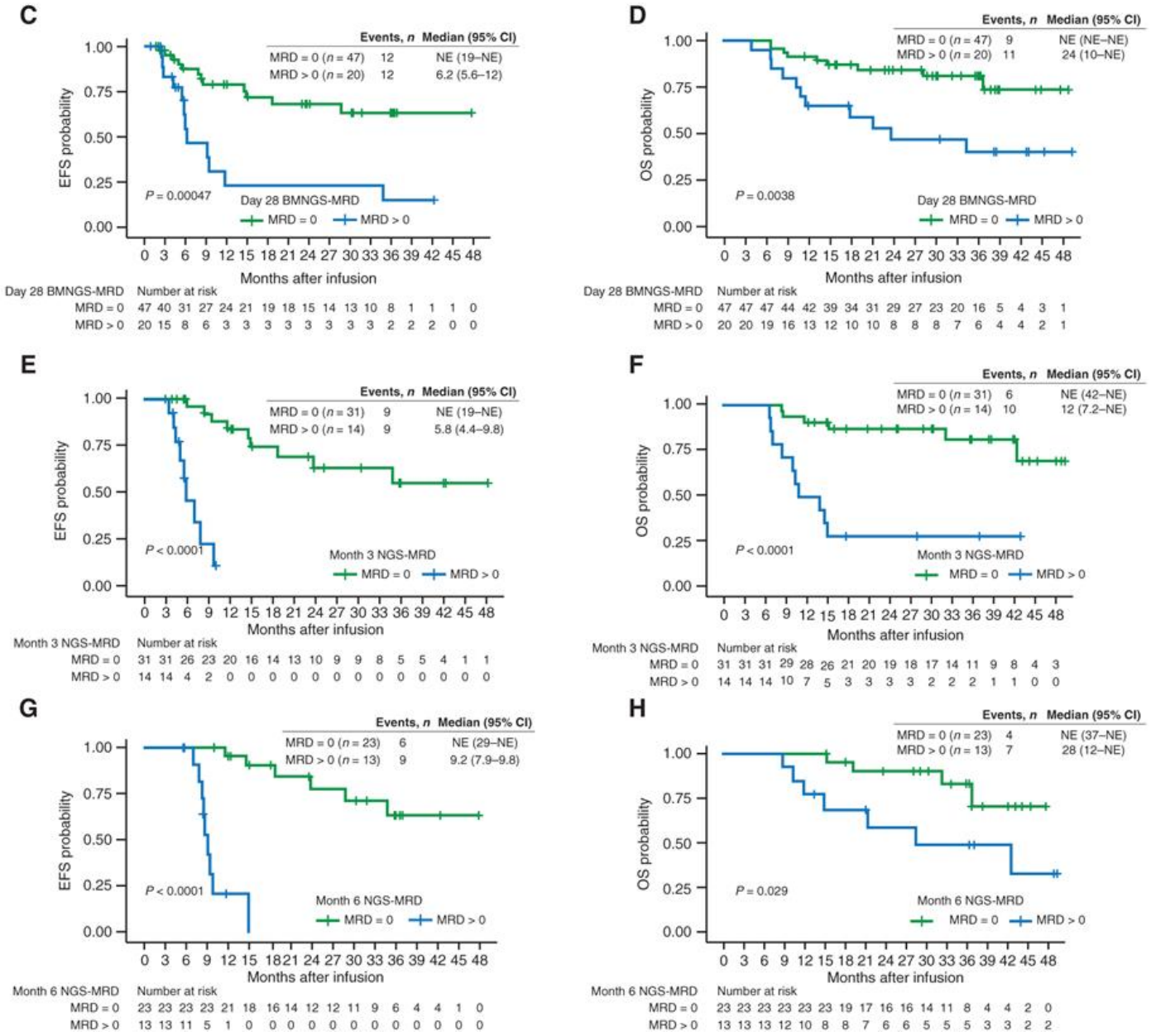
Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial

Theodore W. Laetsch, MD[1,2]; Shannon L. Maude, MD, PhD[1]; Susana Rives, MD, PhD[3]; Hidefumi Hiramatsu, MD, PhD[4]; Henrique Bittencourt, MD, PhD[5,6]; Peter Bader, MD[7]; André Baruchel, MD[8]; Michael Boyer, MD[9]; Barbara De Moerloose, MD, PhD[10]; Muna Qayed, MD[11]; Jochen Buechner, MD, PhD[12]; Michael A. Pulsipher, MD[13,14]; Gary Douglas Myers, MD[15]; Heather E. Stefanski, MD, PhD[16]; Paul L. Martin, MD, PhD[17]; Eneida Nemecek, MD[18]; Christina Peters, MD[19]; Gregory Yanik, MD[20]; Seong Lin Khaw, MBBS(Hons), PhD[21]; Kara L. Davis, DO[22]; Joerg Krueger, MD[23]; Adriana Balduzzi, MD[24]; Nicolas Boissel, MD, PhD[25]; Ranjan Tiwari, MSc[26]; Darragh O'Donovan, PhD[27]; and Stephan A. Grupp, MD, PhD[1,2]

The current analysis supports the recently published finding that B-cell recovery within the first 6 months after infusion predicts risk of relapse and may be an indicator for clinicians to consider subsequent therapy; ***however, B-cell recovery does not always precede relapse.***

Laetsch TW, et al. *J Clin Oncol* 2023

Next-generation sequencing measurable residual disease



Pulsipher MA, et al. *Blood Cancer Discovery* 2022

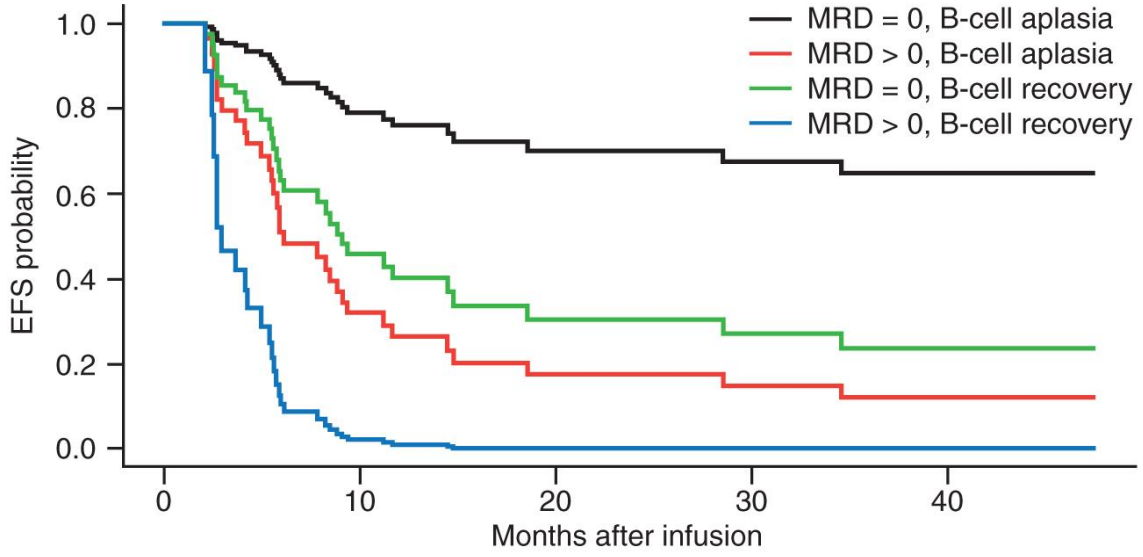
NGS-MRD and loss of B-cell aplasia

Multivariate and Combined Analysis Models

A

	HR (95% CI)	*P*
Day 28 NGS-MRD status		
MRD = 0	—	—
MRD > 0	4.87 (2.18–10.8)	<0.001
B-cell recovery	3.33 (1.44–7.69)	0.005

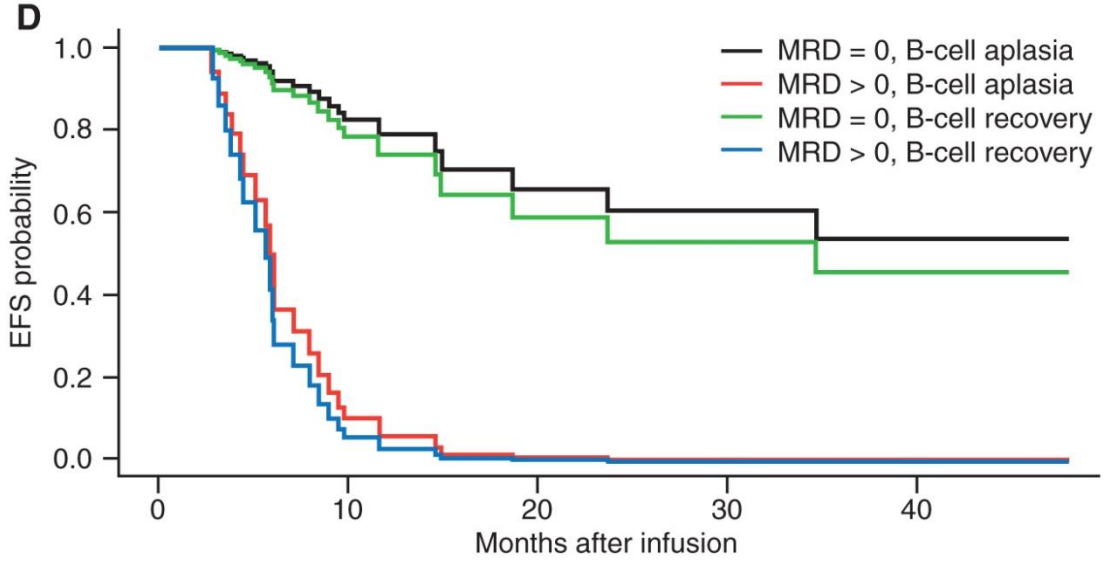
B



C

	HR (95% CI)	*P*
Month 3 NGS-MRD status		
MRD = 0	—	—
MRD > 0	12.0 (2.87–50.0)	<0.001
B-cell recovery	1.27 (0.33–4.79)	0.7

D



Pulsipher MA, et al. *Blood Cancer Discovery* 2022

original reports

Disease Burden Affects Outcomes in Pediatric and Young Adult B-Cell Lymphoblastic Leukemia After Commercial Tisagenlecleucel: A Pediatric Real-World Chimeric Antigen Receptor Consortium Report

Liora M. Schultz, MD[1]; Christina Baggott, PhD[2]; Snehit Prabhu, PhD[3]; Holly L. Pacenta, MD[4,5]; Christine L. Phillips, MD[6,7]; Jenna Rossoff, MD[8]; Heather E. Stefanski, MD, PhD[9]; Julie-An Talano, MD[10]; Amy Moskop, MD[10]; Steven P. Margossian, MD, PhD[11]; Michael R. Verneris, MD[12]; Gary Douglas Myers, MD[13]; Nicole A. Karras, MD[14]; Patrick A. Brown, MD[15]; Muna Qayed, MD, MSc[16]; Michelle Hermiston, MD, PhD[17]; Prakash Satwani, MD[18]; Christa Krupski, DO, MPH[6,7]; Amy K. Keating, MD[12]; Rachel Wilcox, BS[13]; Cara A. Rabik, MD, PhD[19]; Vanessa A. Fabrizio, MD, MS[20,21]; Rayne H. Rouce, MD[22]; Vasant Chinnabhandar, MD[9]; Michael Kunicki, BS[2]; Valentin V. Barsan, MD[1]; A. Yasemin Goksenin, MD, PhD[17]; Yimei Li, PhD[23]; Sharon Mavroukakis, MS[2]; Emily Egeler, PhD[2]; Kevin J. Curran, MD[20,21]; Crystal L. Mackall, MD[24,25]; and Theodore W. Laetsch, MD[4,26,27]

Leukapheresis and cell shipment for planned standard-of-care tisagenlecleucel treatment (N = 200)

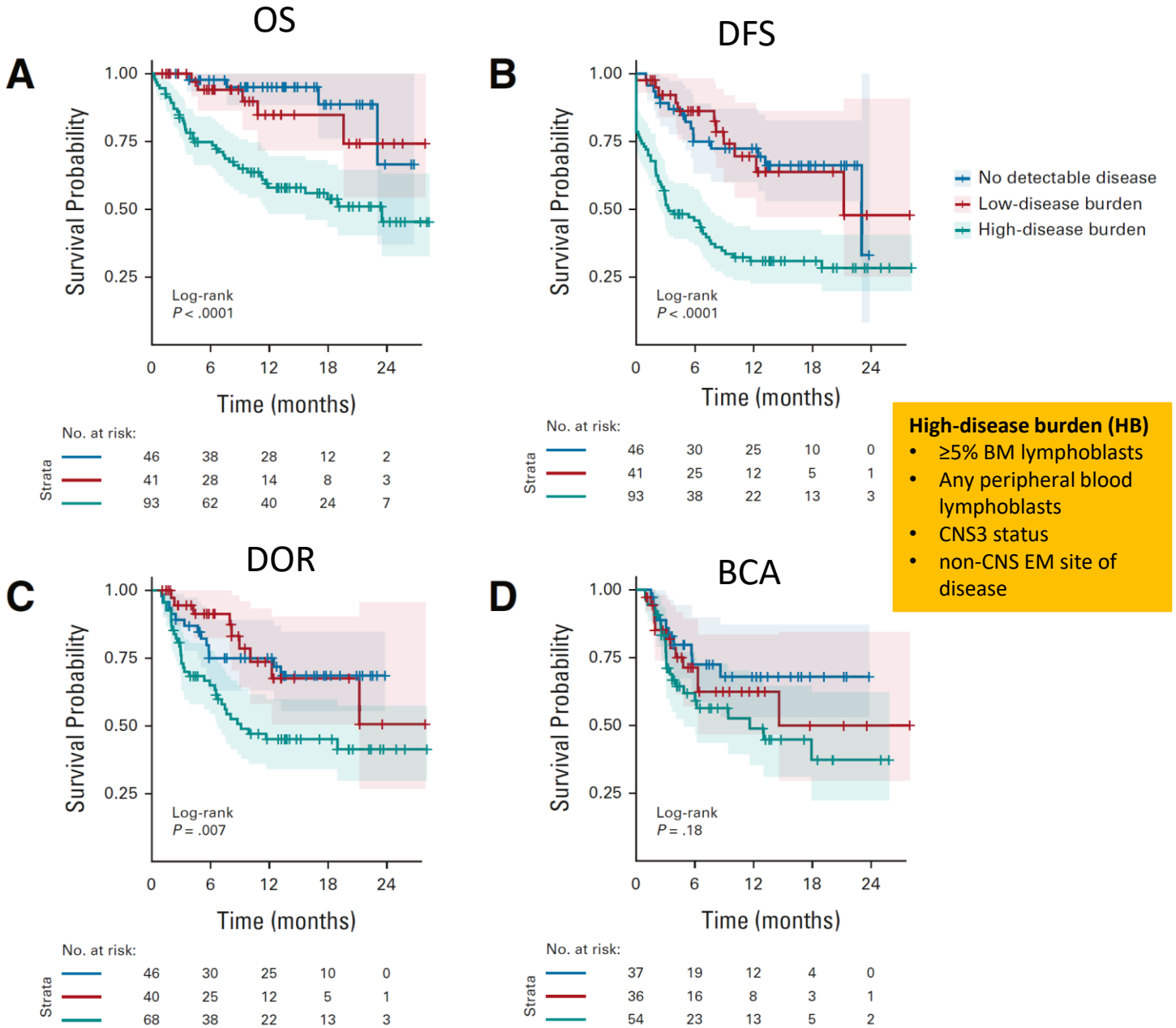
48% of patients had low-disease burden (<5% bone marrow lymphoblasts, no CNS3, or other extramedullary disease), or undetectable disease, pre-tisagenlecleucel.

Tisagenlecleucel CAR T-cell infusion (n = 185)

Standard of care	(n = 161)
Managed access program/single-patient IND	(n = 24)

Evaluable for[b]

Response and survival	(n = 184)
CAR-mediated toxicity	
CRS	(n = 182)
Neurotoxicity	(n = 179)

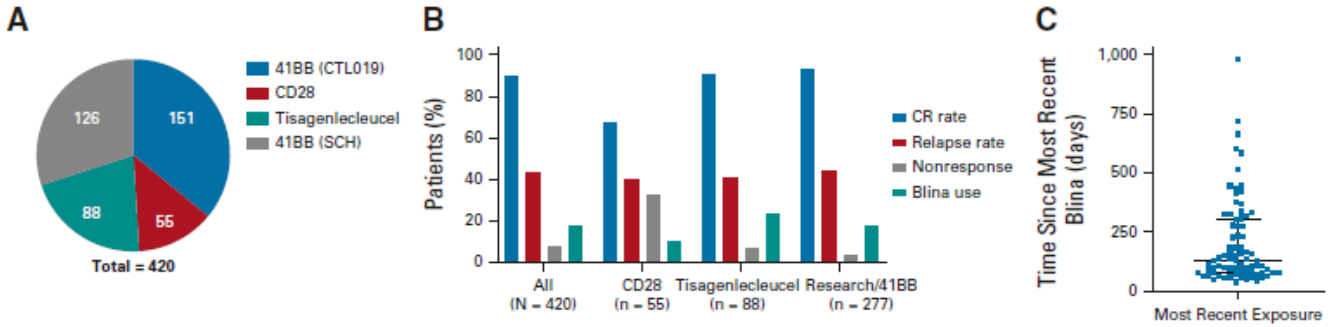


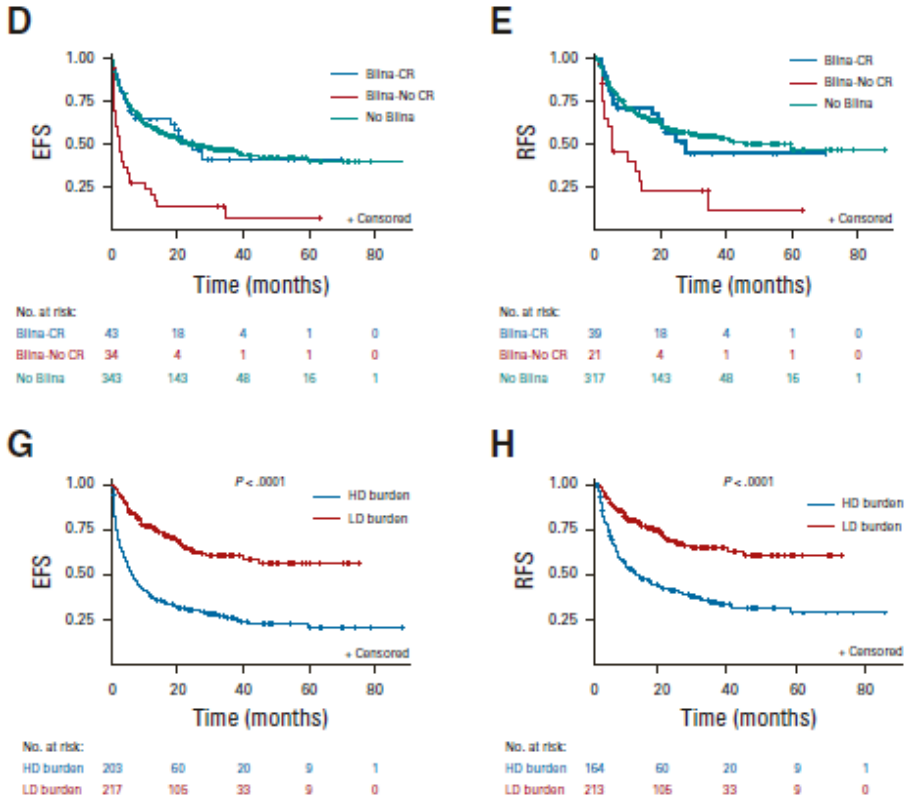
High-disease burden (HB)
- ≥5% BM lymphoblasts
- Any peripheral blood lymphoblasts
- CNS3 status
- non-CNS EM site of disease

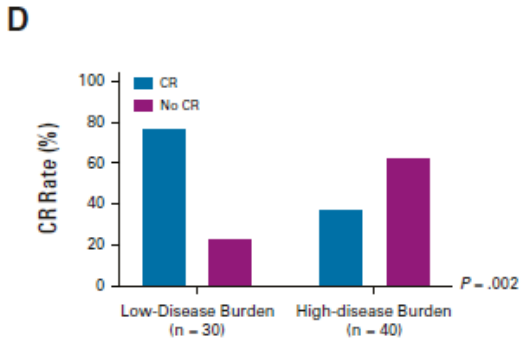
Schultz LM, et al. *J Clin Oncol* 2022

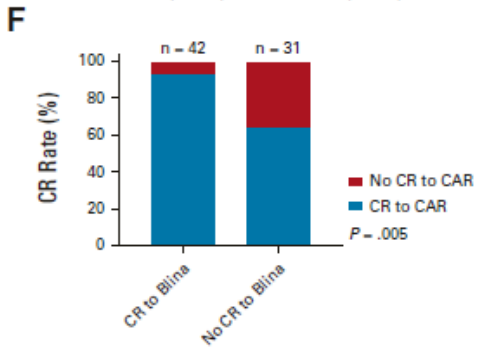
Blinatumomab Nonresponse and High-Disease Burden Are Associated With Inferior Outcomes After CD19-CAR for B-ALL

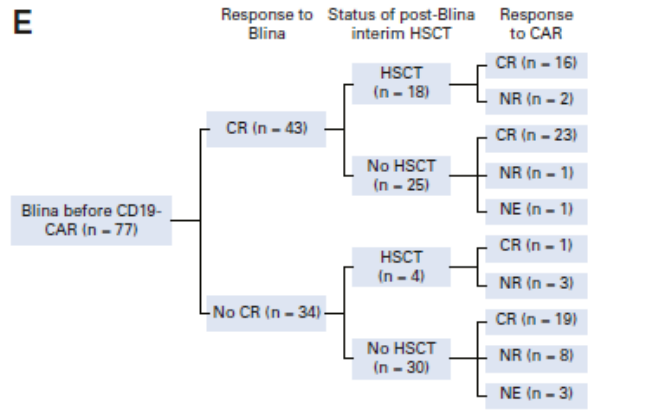
Regina M. Myers, MD[1]; Agne Taraseviciute, MD[2,3]; Seth M. Steinberg, PhD[4]; Adam J. Lamble, MD[5]; Jennifer Sheppard, RN[6]; Bonnie Yates, PNP[7]; Alexandra E. Kovach, MD[2]; Brent Wood, MD[2]; Michael J. Borowitz, MD, PhD[8]; Maryalice Stetler-Stevenson, MD, PhD[9]; Constance M. Yuan, MD, PhD[9]; Vinodh Pillai, MD, PhD[1]; Toni Foley, RN[7]; Perry Chung, BS[1]; Lee Chen, BA[2]; Daniel W. Lee, MD[10]; Colleen Annesley, MD[5]; Amanda DiNofia, MD[1]; Stephan A. Grupp, MD, PhD[1]; Samuel John, MD[6]; Deepa Bhojwani, MD[11]; Patrick A. Brown, MD[12]; Theodore W. Laetsch, MD[1,6]; Lia Gore, MD[13]; Rebecca A. Gardner, MD[5]; Susan R. Rheingold, MD[1]; Michael A. Pulsipher, MD[2]; and Nirali N. Shah, MD, MHSc[7]

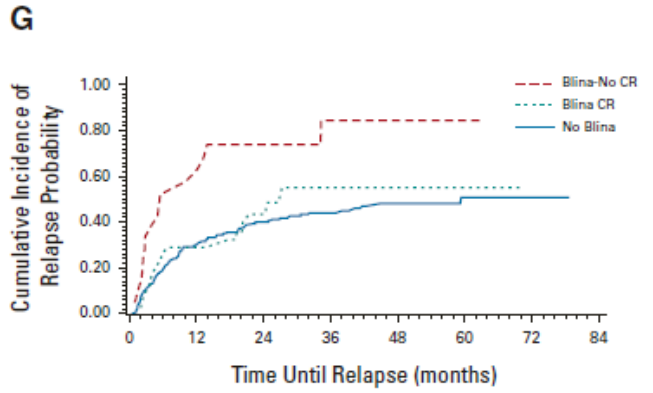












Myers RM, et al. *J Clin Oncol 2022*

CLINICAL TRIALS AND OBSERVATIONS

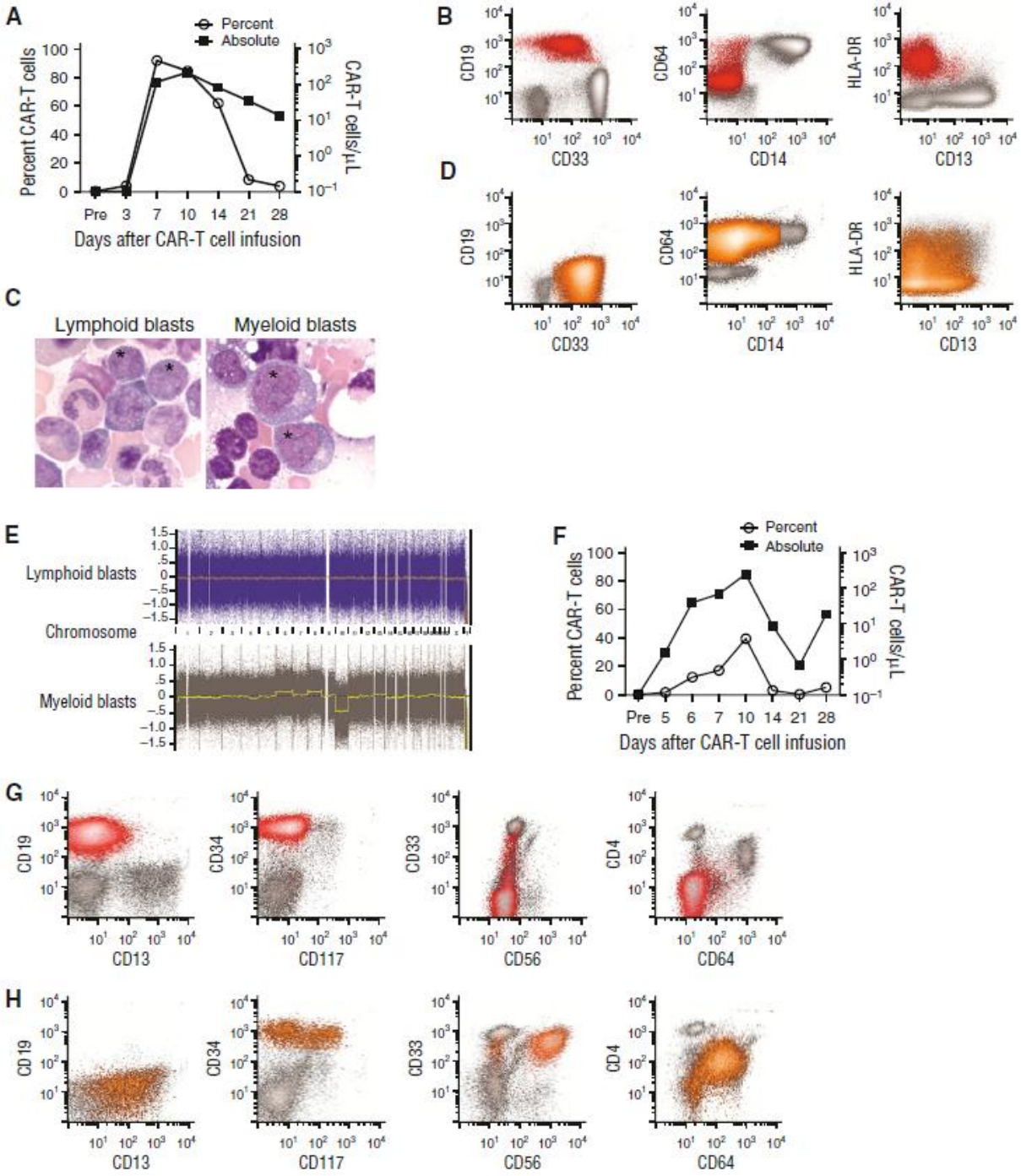
Acquisition of a CD19-negative myeloid phenotype allows immune escape of *MLL*-rearranged B-ALL from CD19 CAR-T-cell therapy

Rebecca Gardner,[1,2] David Wu,[3] Sindhu Cherian,[3] Min Fang,[3] Laïla-Aïcha Hanafi,[4] Olivia Finney,[1] Hannah Smithers,[1] Michael C. Jensen,[1,2] Stanley R. Riddell,[4,5] David G. Maloney,[4,5] and Cameron J. Turtle[4,5]

[1]Seattle Children's Research Institute, [2]Department of Pediatrics, and [3]Department of Laboratory Medicine, University of Washington, Seattle, WA; [4]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; and [5]Department of Medicine, University of Washington, Seattle, WA

Key Points

- CD19-targeted CAR-T-cell therapy of patients with *MLL*-rearranged B-ALL effectively induced marrow remission of B-ALL.
- Patients with *MLL*-rearranged B-ALL who attain CR after CD19 CAR-T-cell therapy may be at risk for relapse with clonally related AML.

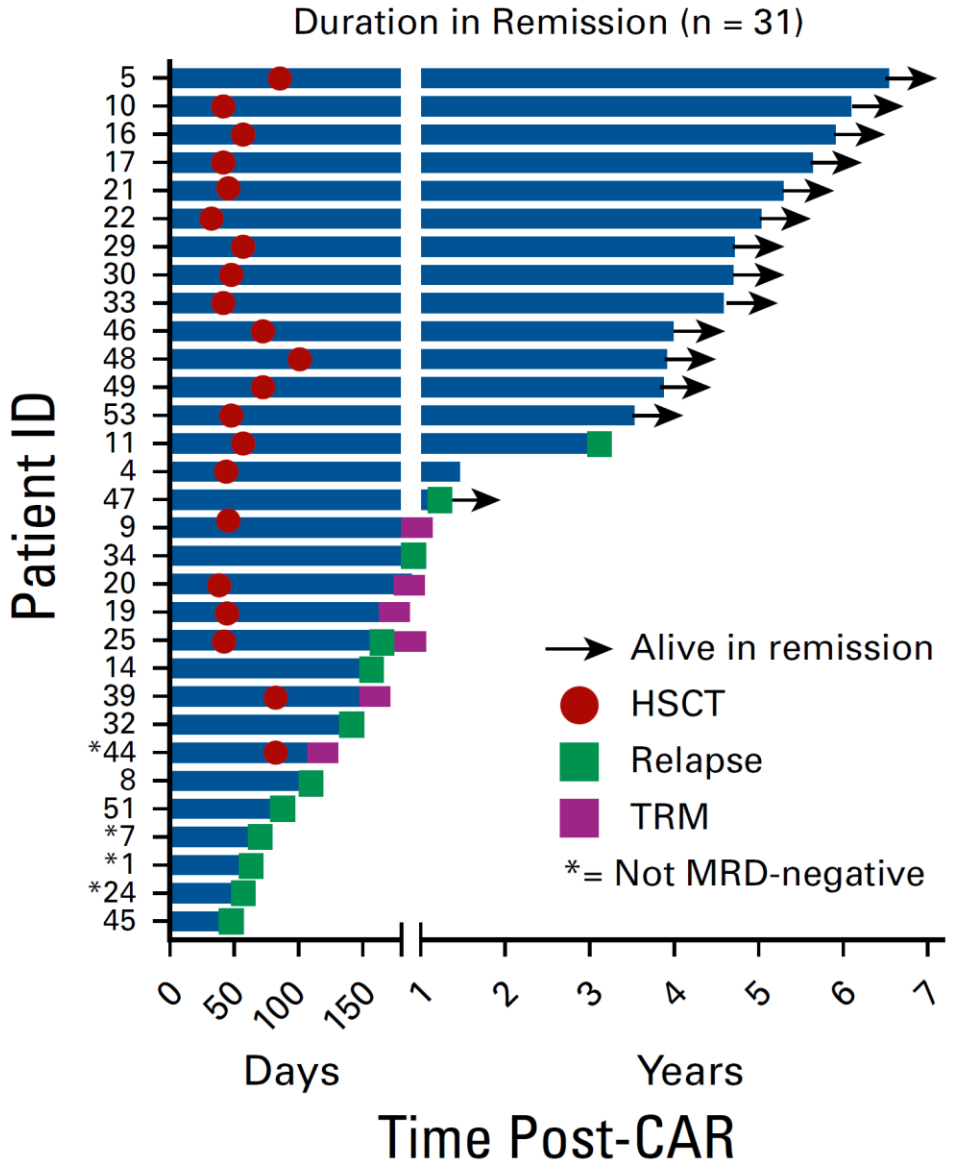


Gardner R, et al. *Blood* 2017.

Long-Term Follow-Up of CD19-CAR T-Cell Therapy in Children and Young Adults With B-ALL

Nirali N. Shah, MD[1]; Daniel W. Lee, MD[1,2]; Bonnie Yates, CNP[1]; Constance M. Yuan, MD, PhD[3,4]; Haneen Shalabi, DO[1]; Staci Martin, PhD[1]; Pamela L. Wolters, PhD[1]; Seth M. Steinberg, PhD[5]; Eva H. Baker, MD, PhD[6]; Cindy P. Delbrook, RN[1]; Maryalice Stetler-Stevenson, MD, PhD[3,4]; Terry J. Fry, MD[1,7]; David F. Stroncek, MD[8]; and Crystal L. Mackall, MD[1,9,10,11]

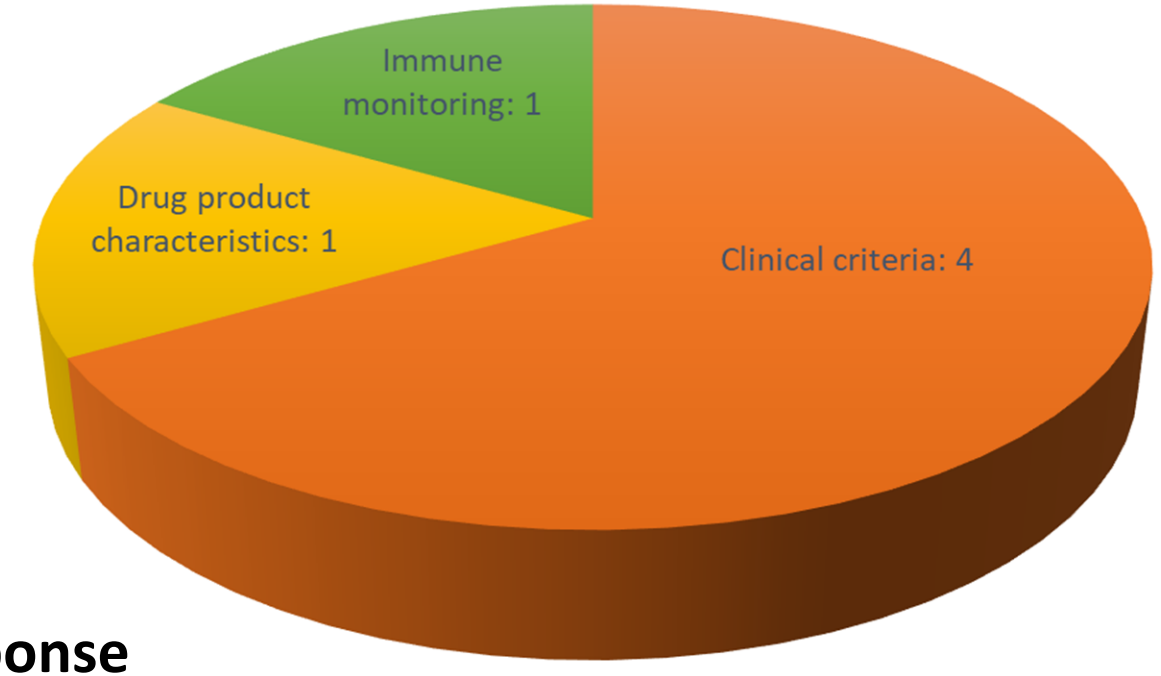
- 28 pediatric and young subjects who achieved an MRD negative CR following CD19/28z CAR-T
- Improved LFS for the 21 patients who received consolidative HSCT
- 5-year EFS: 61.9%
- Cumulative incidence of Relapse: 4.8%.
- All 7 patients who did not undergo HSCT relapsed



Shah NN, et al. *JCO* 2020

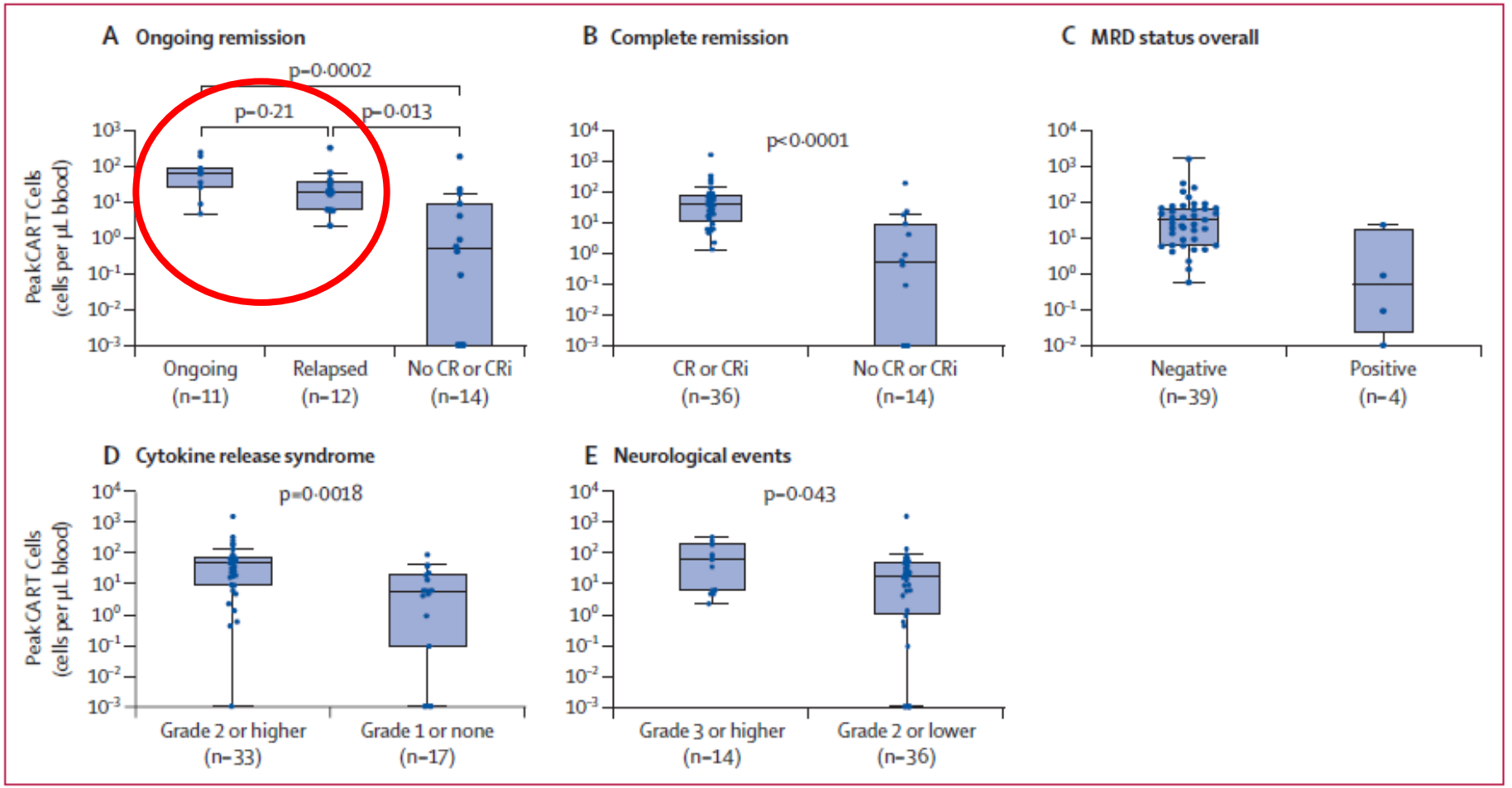
Which patients given CAR T- cell therapy should be treated with HSCT?

- In patients experiencing early B-cell recovery
- In case of persistence/reappearance of MRD
- In those who do have high leukemia burden
- In those with previous blinatumomab nonresponse
- In those with KMT2a gene rearrangement
- In patients who receive CAR-T with limited persistence (independently of immune monitoring…)



KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study

Bijal D Shah, Armin Ghobadi, Olalekan O Oluwole, Aaron C Logan, Nicolas Boissel, Ryan D Cassaday, Thibaut Leguay, Michael R Bishop, Max S Topp, Dimitrios Tzachanis, Kristen M O'Dwyer, Martha L Arellano, Yi Lin, Maria R Baer, Gary J Schiller, Jae H Park, Marion Subklewe, Mehrdad Abedi, Monique C Minnema, William G Wierda, Daniel J DeAngelo, Patrick Stiff, Deepa Jeyakumar, Chaoling Feng, Jinghui Dong, Tong Shen, Francesca Milletti, John M Rossi, Remus Vezan, Behzad Kharabi Masouleh, Roch Houot



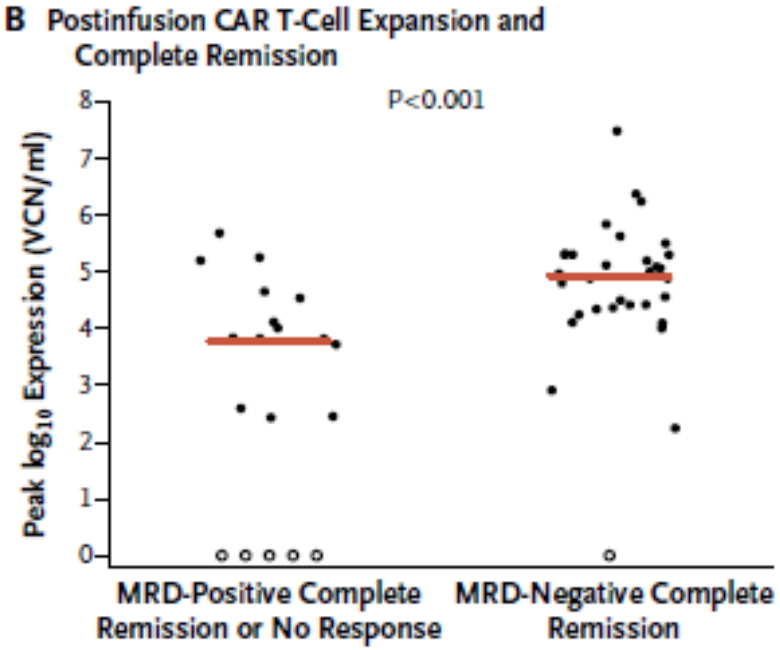
Shah BD, et al. *Lancet* 2021

Park JH, et al. *NEJM 2018*

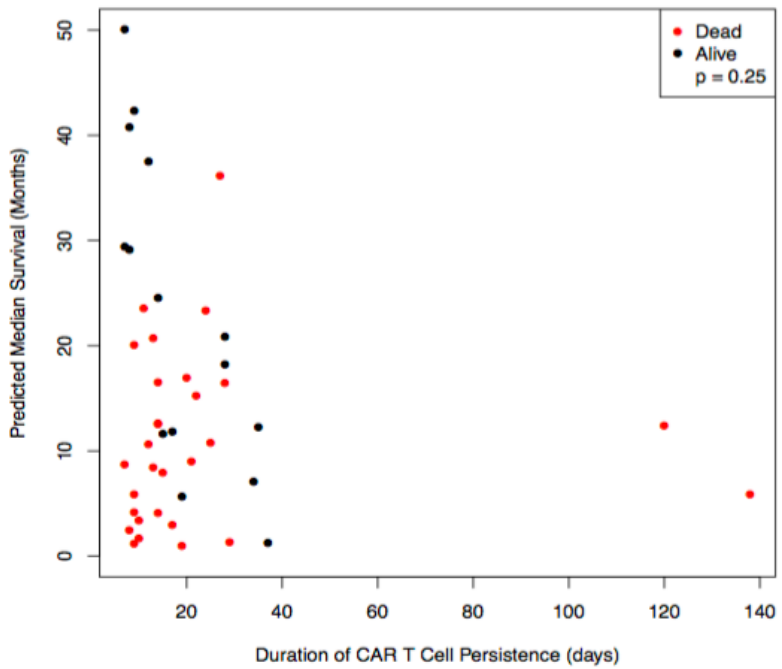
ORIGINAL ARTICLE

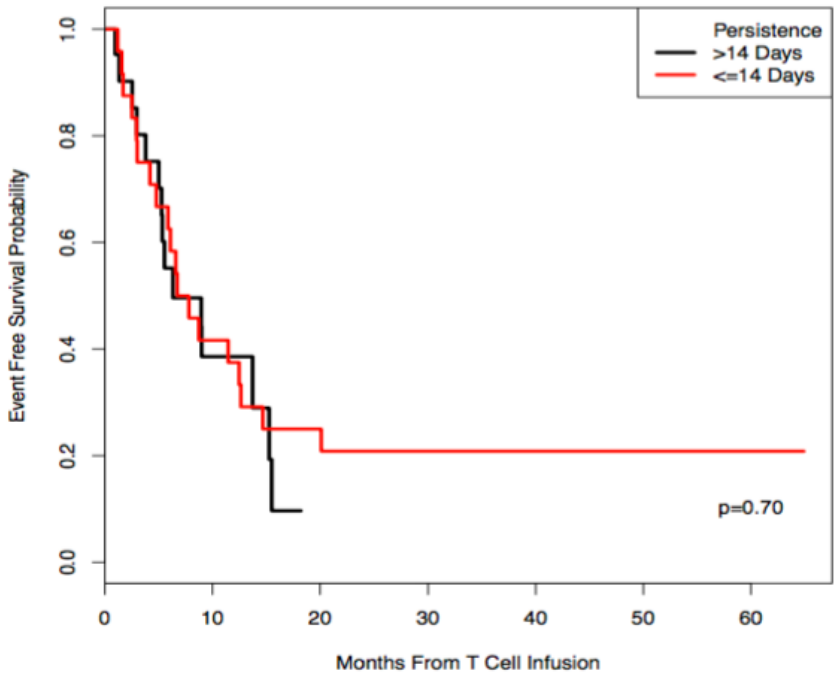
Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

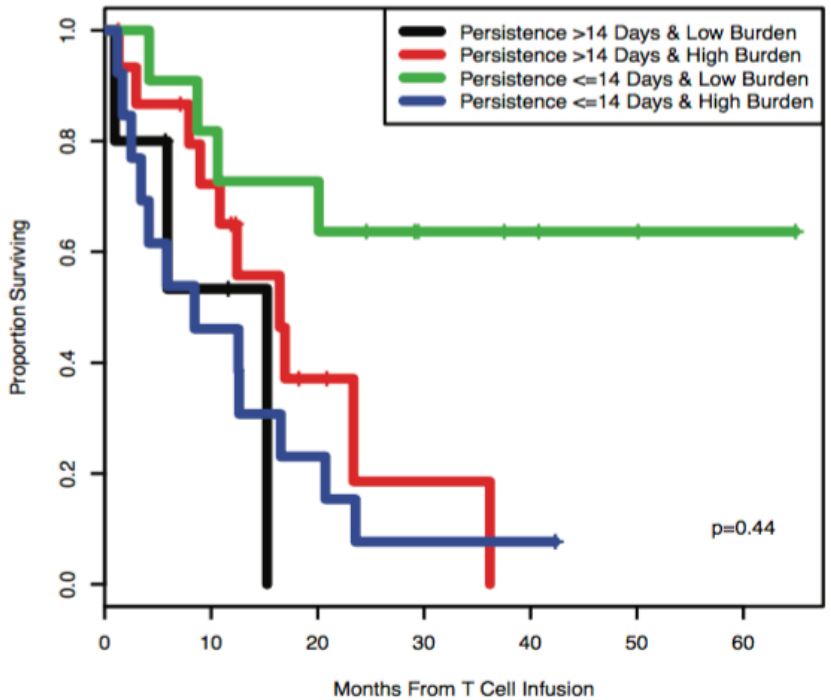
Jae H. Park, M.D., Isabelle Rivière, Ph.D., Mithat Gonen, Ph.D., Xiuyan Wang, Ph.D., Brigitte Sénéchal, Ph.D., Kevin J. Curran, M.D., Craig Sauter, M.D., Yongzeng Wang, Ph.D., Bianca Santomasso, M.D., Ph.D., Elena Mead, M.D., Mikhail Roshal, M.D., Peter Maslak, M.D., Marco Davila, M.D., Ph.D., Renier J. Brentjens, M.D., Ph.D., and Michel Sadelain, M.D., Ph.D.



B 53 adults who received 19-28z CAR T cells that were manufactured at MSKCC





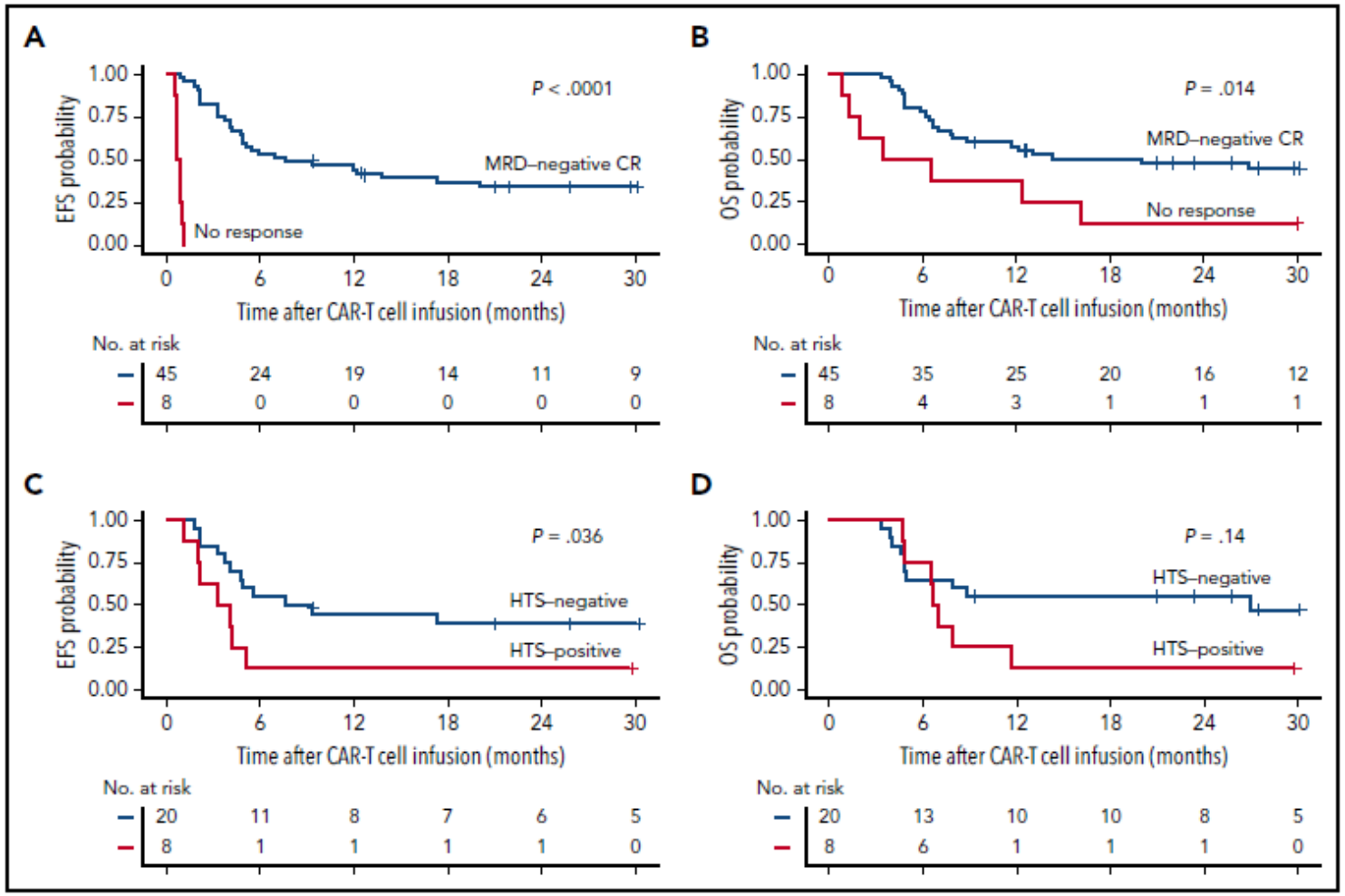


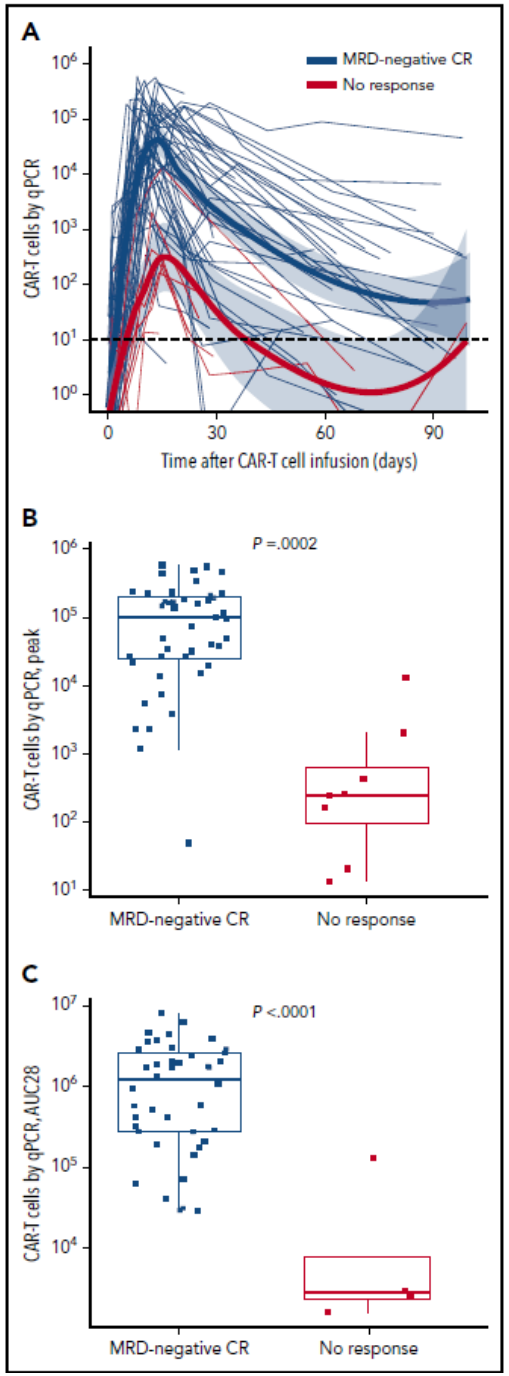
IMMUNOBIOLOGY AND IMMUNOTHERAPY

Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy

Kevin A. Hay,[1,2] Jordan Gauthier,[1] Alexandre V. Hirayama,[1] Jenna M. Voutsinas,[1] Qian Wu,[1] Daniel Li,[3] Ted A. Gooley,[1] Sindhu Cherian,[4] Xueyan Chen,[4] Barbara S. Pender,[1] Reed M. Hawkins,[1] Aesha Vakil,[1] Rachel N. Steinmetz,[1] Gary Schoch,[1] Aude G. Chapuis,[1,5] Brian G. Till,[1,5] Hans-Peter Kiem,[1,5] Jorge D. Ramos,[1,5] Mazyar Shadman,[1,5] Ryan D. Cassaday,[1,5] Utkarsh H. Acharya,[1,5] Stanley R. Riddell,[1,5] David G. Maloney,[1,5] and Cameron J. Turtle[1,5]

Lisocabtagene Maraleucel: 4-1BB costimulation, defined CD4:CD8 subsets



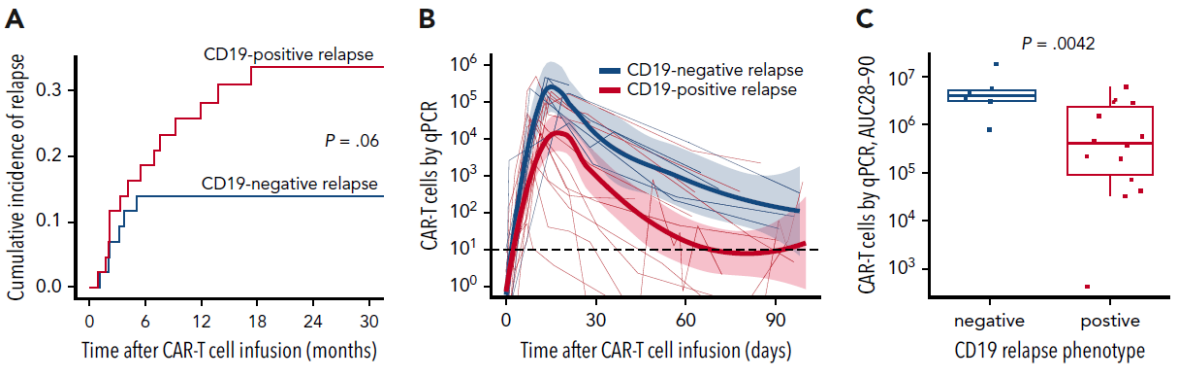


Hay KA et al. *Blood* 2019

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy

Kevin A. Hay,[1,2] Jordan Gauthier,[1] Alexandre V. Hirayama,[1] Jenna M. Voutsinas,[1] Qian Wu,[1] Daniel Li,[3] Ted A. Gooley,[1] Sindhu Cherian,[4] Xueyan Chen,[4] Barbara S. Pender,[1] Reed M. Hawkins,[1] Aesha Vakil,[1] Rachel N. Steinmetz,[1] Gary Schoch,[1] Aude G. Chapuis,[1,5] Brian G. Till,[1,5] Hans-Peter Kiem,[1,5] Jorge D. Ramos,[1,5] Mazyar Shadman,[1,5] Ryan D. Cassaday,[1,5] Utkarsh H. Acharya,[1,5] Stanley R. Riddell,[1,5] David G. Maloney,[1,5] and Cameron J. Turtle[1,5]



Hay KA et al. *Blood* 2019

Table 2. Univariable and multivariable analyses for factors that had in impact on EFS in patients who achieved MRD-negative CR

Variable	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
LDH (per 100 U/L, prelymphodepletion)	1.49	1.22-1.80	<.0001	1.39	1.12-1.74	.003
Bridging systemic therapy*	5.66	2.56-12.5	<.0001	—†		—
Platelet count (per 50 000/μL, prelymphodepletion)	0.57	0.42-0.76	.0002	0.65	0.47-0.88	.006
Extramedullary disease	3.57	1.66-7.65	.001	—		—
Fludarabine added to lymphodepletion	0.30	0.13-0.66	.003	0.34	0.15-0.78	.011
IL-6 (pg/mL, prelymphodepletion)	1.02	1.01-1.03	.005	—		—
Marrow blasts by flow cytometry, %	1.01	1.00-1.03	.006	—		—
High-risk cytogenetics‡	2.48	1.12-5.50	.03	—		—
Neutrophil count (1000/μL, prelymphodepletion)	0.73	0.55-0.97	.03	—		—
Soluble TNFRp55 (day 0), pg/mL	4.84	1.07-21.8	.04	—§		—
IL-2 (day 0), pg/mL	3.24	1.05-10.0	.04	—		—
IL-8 (pg/mL, prelymphodepletion)	1.78	1.00-3.15	.05	—		—
Soluble TIM-3 (ng/mL; prelymphodepletion)	1.05	1.00-1.11	.06	—		—
Dose level (2×10^5 vs 2×10^6 CAR T cells per kg)	0.51	0.24-1.11	.09	—		—
No. of previous regimens	1.13	0.97-1.32	.1	—		—
Previous allogeneic HCT	1.65	0.79-3.44	.2	—		—
Previous blinatumomab therapy	1.27	0.52-3.12	.6			
ECOG PS	1.18	0.62-2.26	.6	—		—
Age, y	1.00	0.98-1.01	.7	—		—
Time from leukapheresis to lymphodepletion, d	1.52	0.64-3.62	.3			
CD4+:CD8+ CAR T-cell ratio (peak expansion)	1.20	0.86-1.68	.3			
CD4+:CD8+ CAR T-cell ratio (AUC from day 0 to day 28)	1.09	0.76-1.55	.6			
CD4+:CD8+ CAR T-cell ratio (fold change from infusion product to peak expansion)	1.21	0.81-1.81	.4			
CAR T-cell counts (transgene $\log_{10}$ copies/μg of DNA; AUC28)	0.98	0.56-1.71	.9	—		—

ORIGINAL ARTICLE

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators*

No differences between patients who had a response and those who did not in:

- Mean *in vivo* expansion and concentration–time profiles of tisagenlecleucel, measured as transgene level;
- Median time to maximum transgene level;
- Mean area under the concentration– time curve from day 0 to day 28 (AUC0–28d);

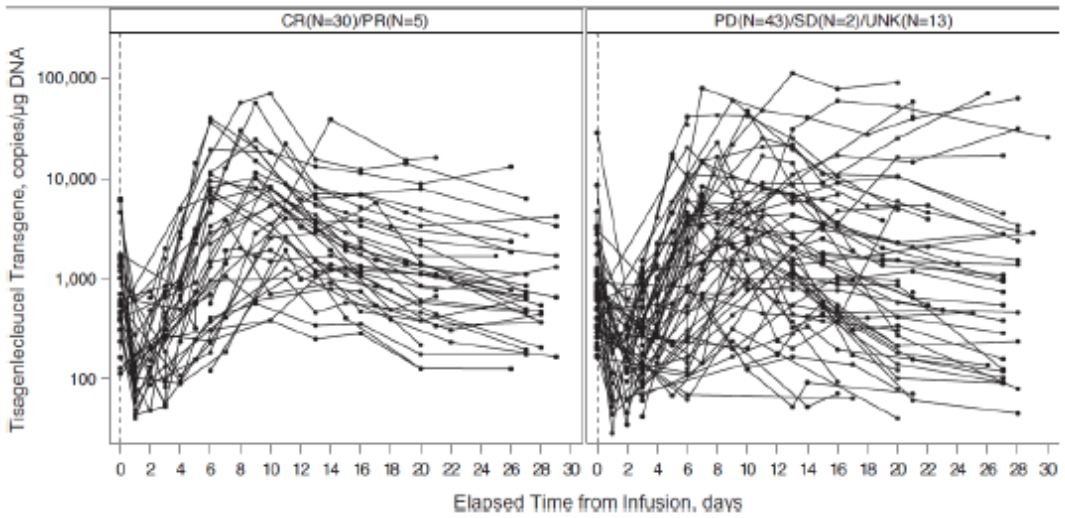


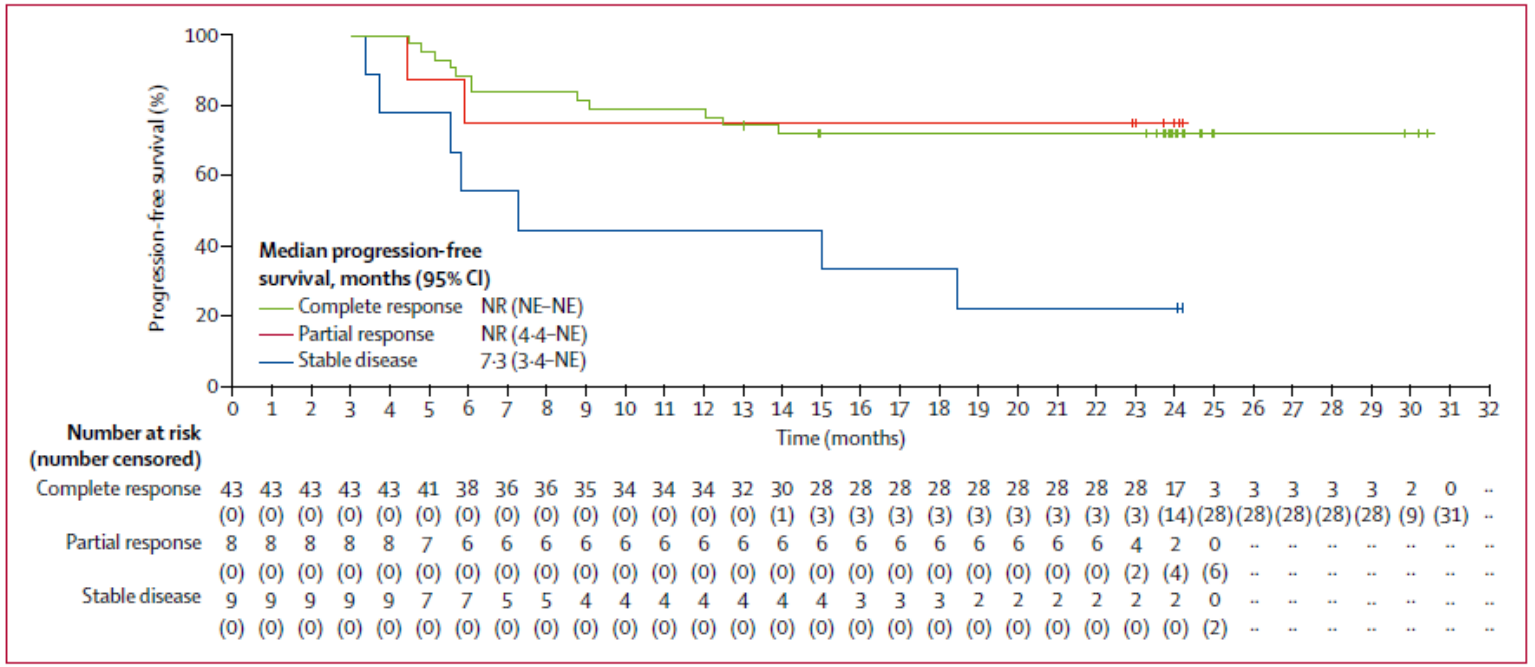
Table S7. Summary of Cellular Kinetic Parameters by Response at Month 3

Parameter	Statistics	CR/PR (N=35)	SD/PD/Unknown* (N=58)	All Patients (N=93)
$AUC_{0\text{-}28d}$, copies/µg × days	n	33	42	75
	Geometric mean	64,300	64,800	64,600
	Geo-CV%	156	301	227
	Fold difference (responders over nonresponders)	1		
C_{max}, copies/µg	n	35	51	86
	Geo-mean	6210	5100	5530
	Geo-CV%	226	373	303
	Fold difference (responders over nonresponders)	1		
T_{max}, days	n	35	51	86
	Median	10	9	9
	Min, max	6, 17	3, 28	3, 28
T_{last}, days†	n	35	48	83
	Median	289	57	92
	Min, max	18, 693	16, 374	16, 693

Schuster SJ, et a. *NEJM* 2019

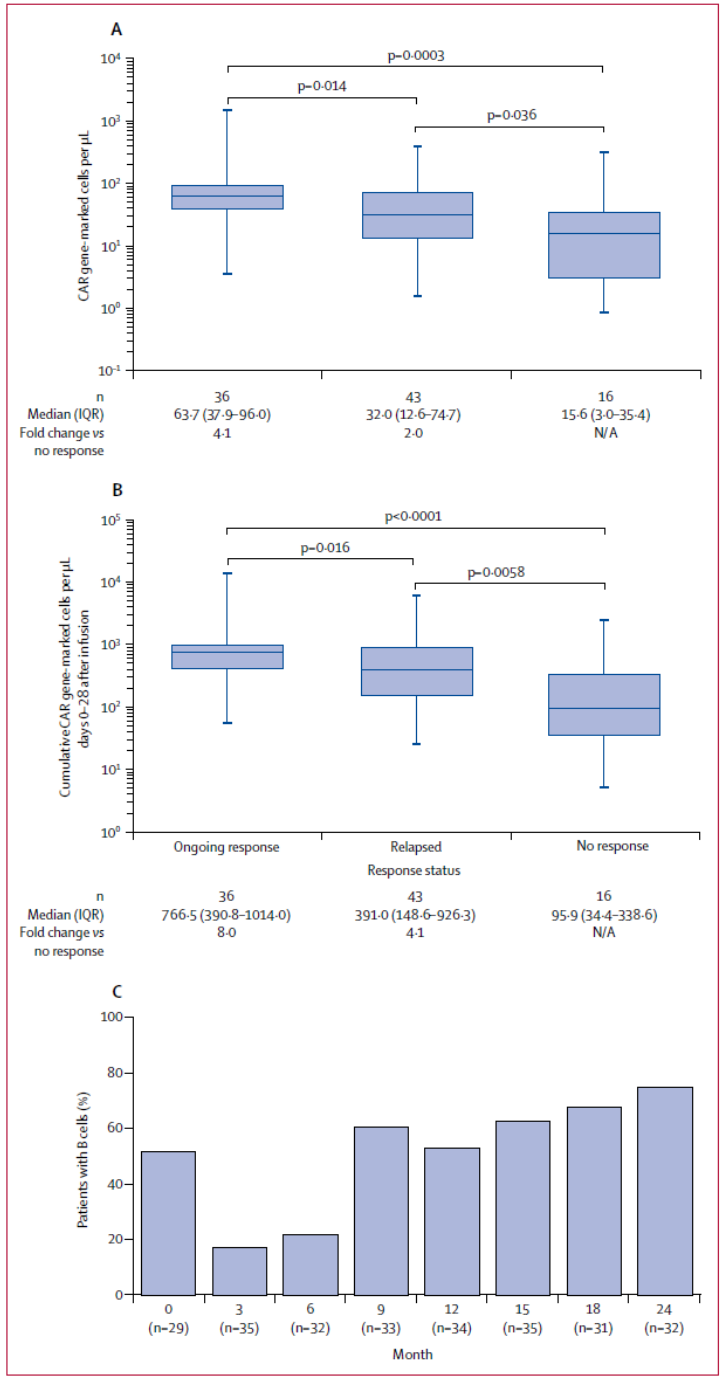
Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

Frederick L Locke, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wiezorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu**



Post-hoc analysis of CAR T-cell and B-cell concentrations

CAR T cell exposure by peak concentrations of CAR T cells in peripheral blood (A) or area under the curve (B) and proportion of patients with responses at 24 months with detectable B cells (C).



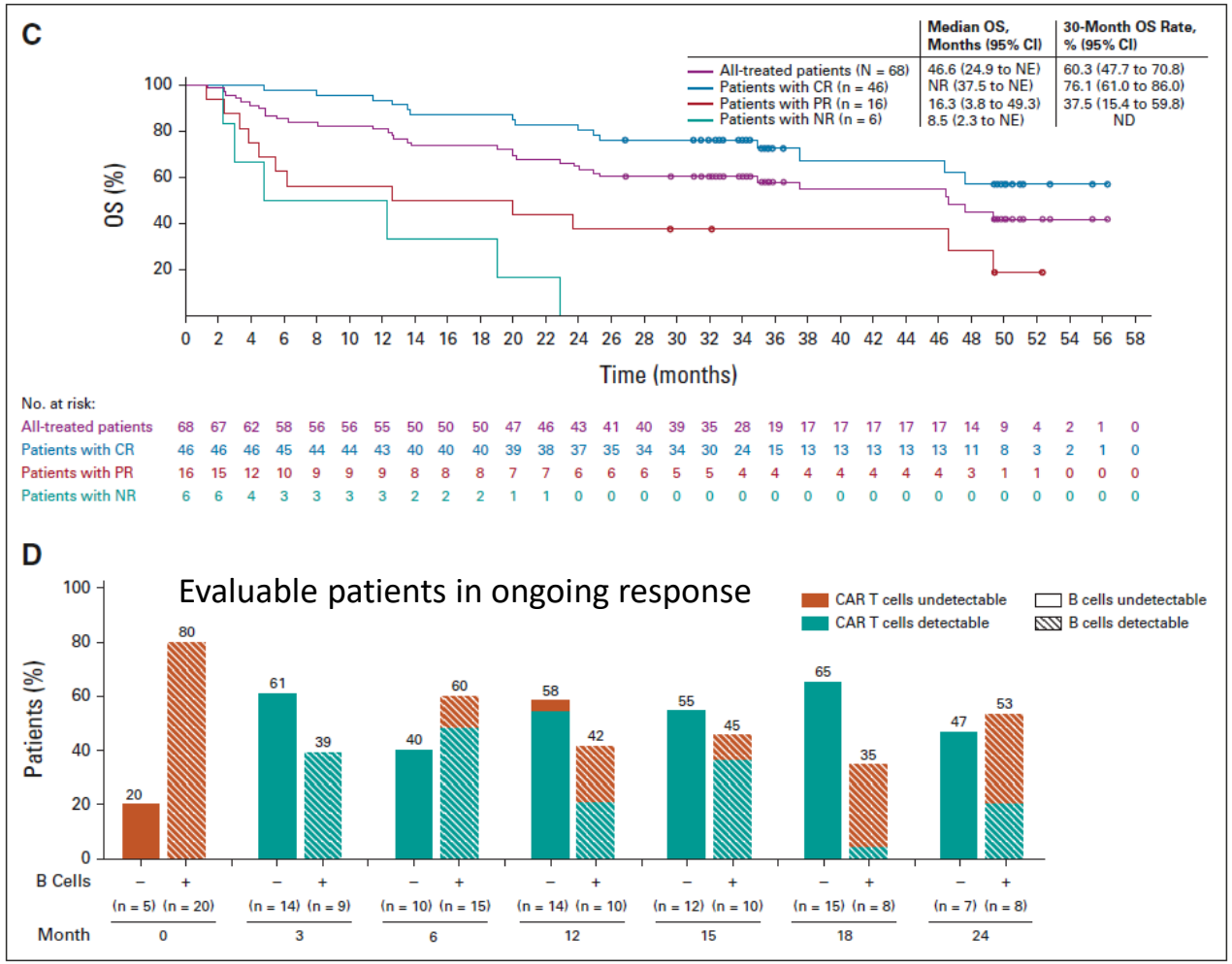
Locke FL, et a. *Lancet Oncol* 2019

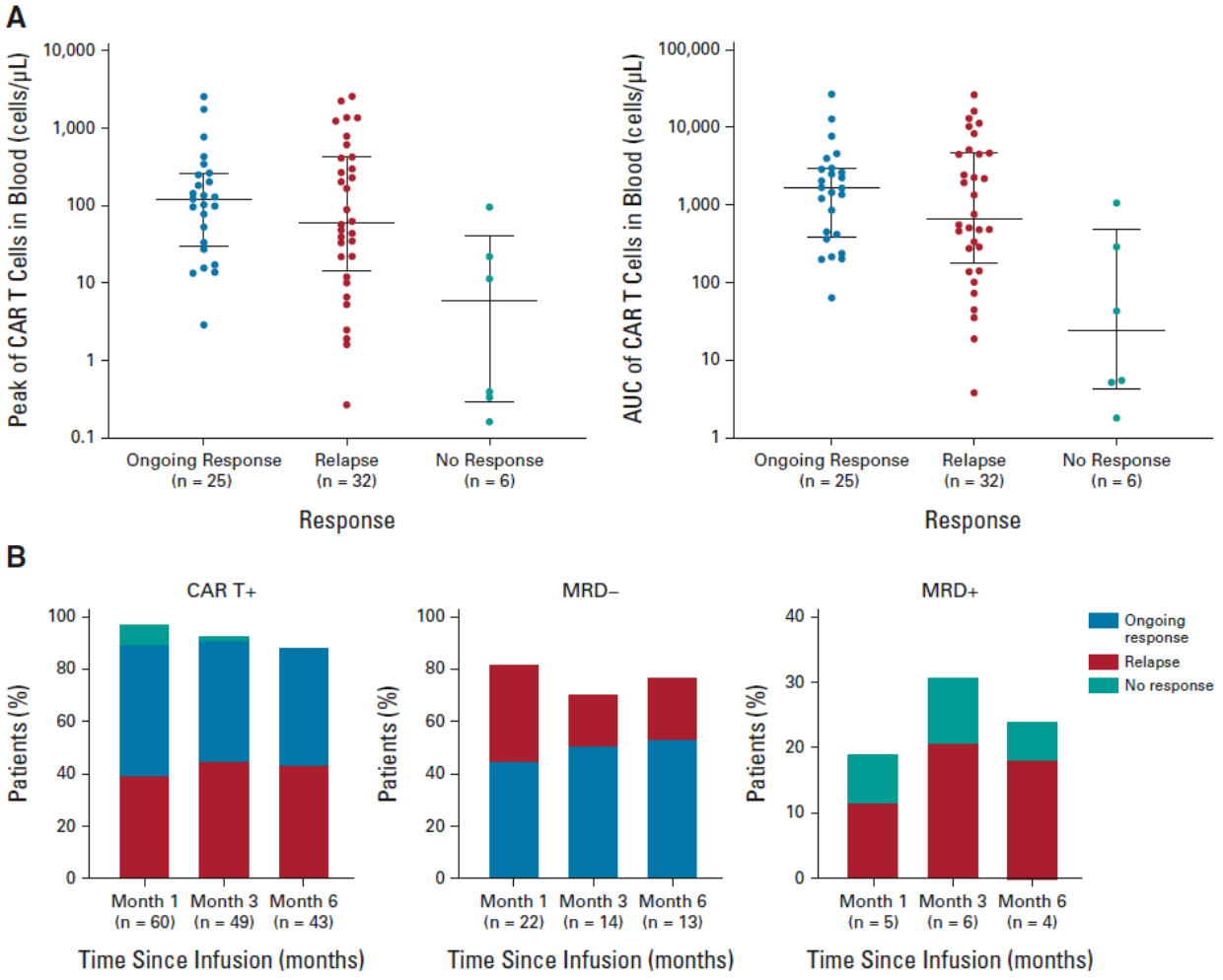
Immune monitoring after CAR-T in Mantle Cell Lymphoma

original reports

Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study

Michael Wang, MD[1]; Javier Munoz, MD, MS, MBA[2]; Andre Goy, MD, MS[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA[8]; Samantha Jaglowski, MD[9]; Ian W. Flinn, MD, PhD[10]; Peter A. McSweeney, MB, ChB[11]; David B. Miklos, MD, PhD[12]; John M. Pagel, MD, PhD, DSc[13]; Marie José Kersten, MD, PhD[14]; Krimo Bouabdallah, MD[15]; Rashmi Khanal, MD[16]; Max S. Topp, MD[17]; Roch Houot, MD, PhD[18]; Amer Beitinjaneh, MD[19]; Weimin Peng, PhD[20]; Xiang Fang, PhD[20]; Rhine R. Shen, PhD[20]; Rubina Siddiqi, PhD[20]; Ioana Kloos, MD[20]; and Patrick M. Reagan, MD[21]





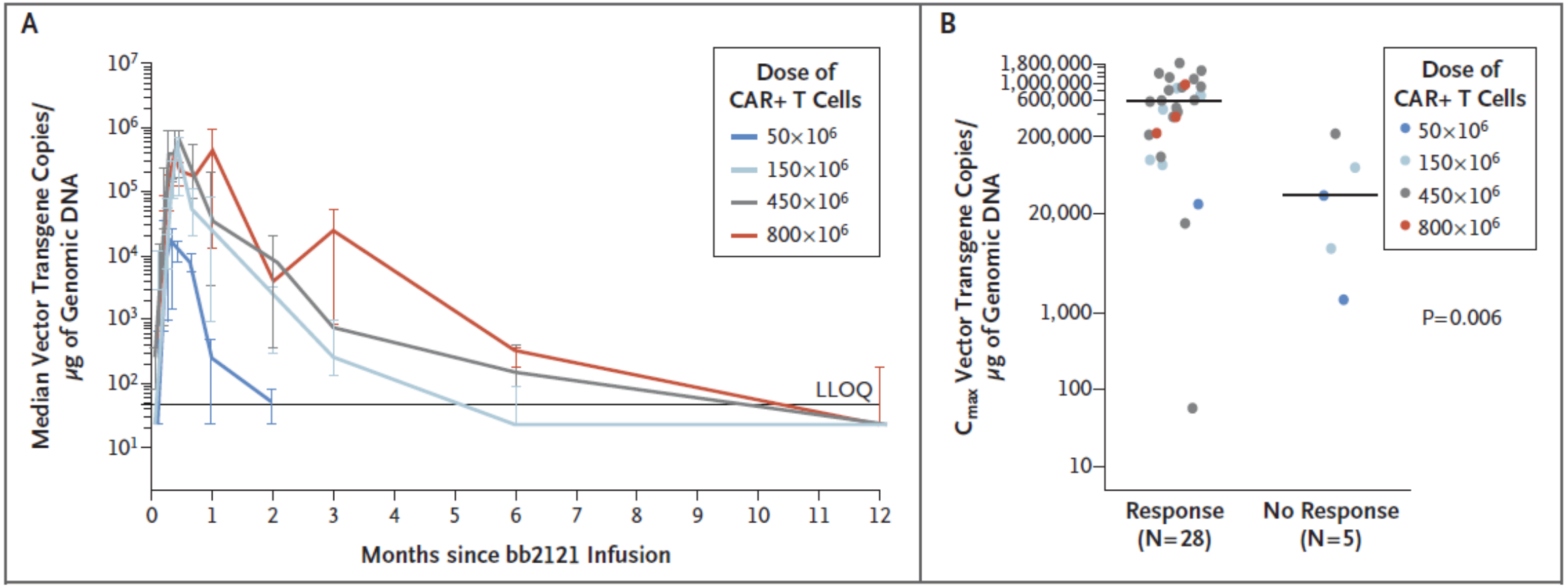
Wang M, et al. *J Clin Oncol 2022*

Immune monitoring and anti-BCMA CAR T cell therapy

ORIGINAL ARTICLE

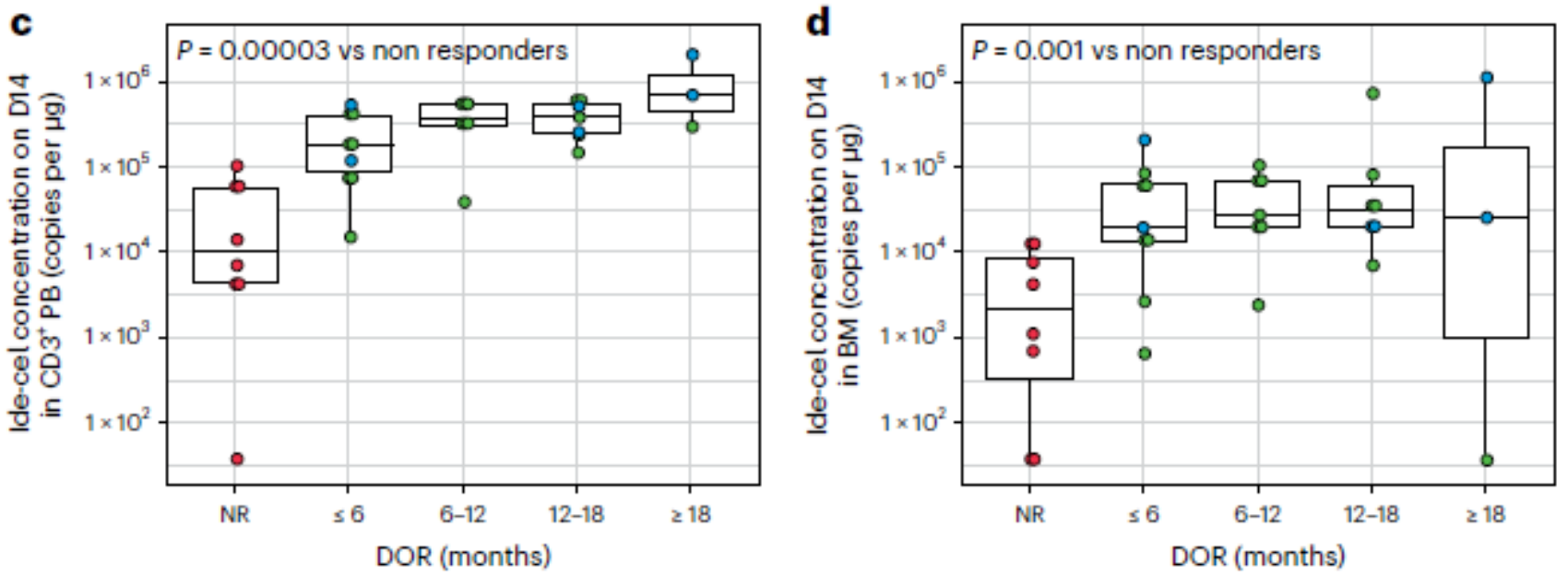
Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.



Raje N et al. *NEJM* 2019

Immune monitoring and anti-BCMA CAR T cell therapy



Article

https://doi.org/10.1038/s41591-023-02496-0

Idecabtagene vicleucel for relapsed and refractory multiple myeloma: post hoc 18-month follow-up of a phase 1 trial

Received: 28 July 2022

Accepted: 11 July 2023

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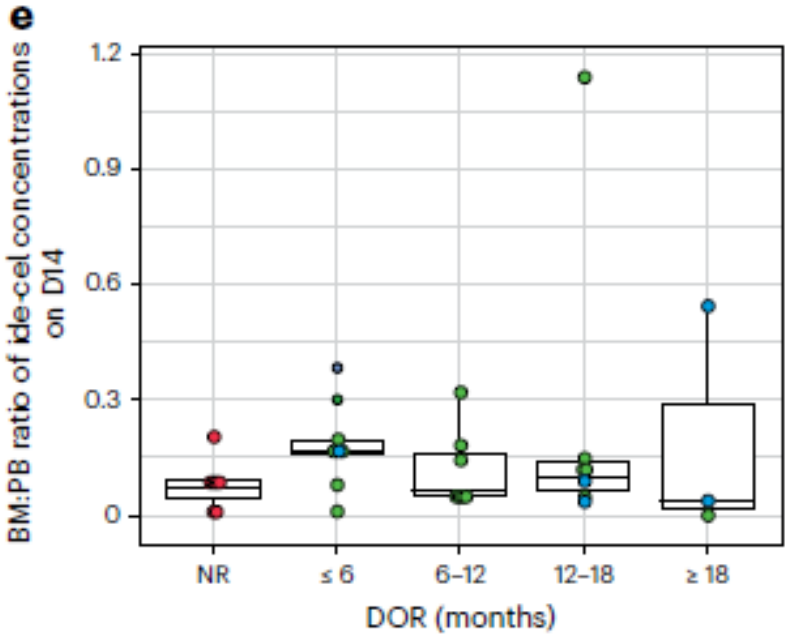
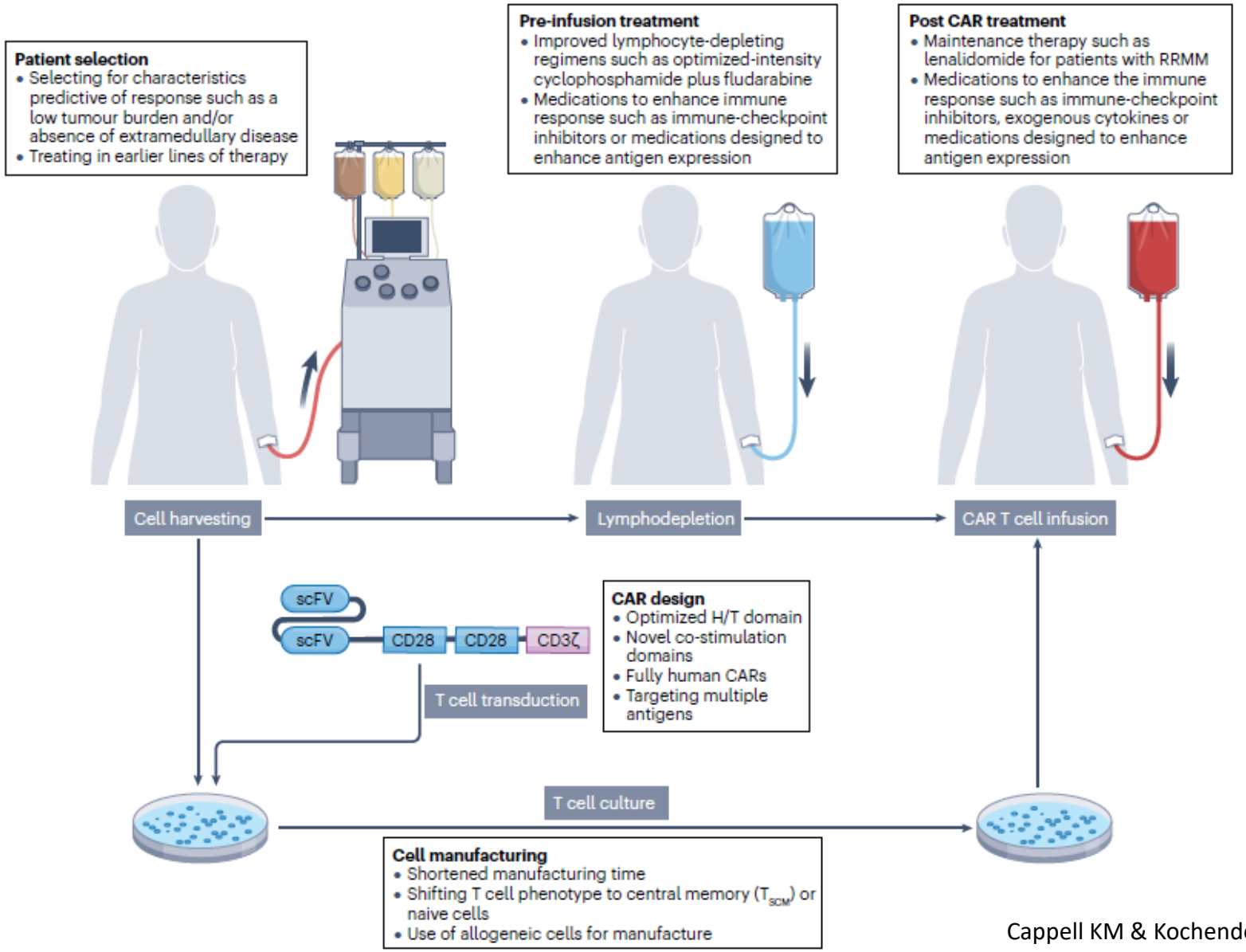
Check for updates

Yi Lin[1], Noopur S. Raje[2], Jesús G. Berdeja[3], David S. Siegel[4], Sundar Jagannath[5], Deepu Madduri[5], Michaela Liedtke[6], Jacalyn Rosenblatt[7], Marcela V. Maus[2], Monica Massaro[8], Fabio Petrocca[8], Ashish Yeri[8], Olivia Finney[8], Andrea Caia[9], Zhihong Yang[9], Nathan Martin[9], Timothy B. Campbell[9], Julie Rytlewski[9], Jaymes Fuller[9], Kristen Hege[9], Nikhil C. Munshi[10] & James N. Kochenderfer[11]



Lin Y et al. *Nat Med* 2023

Investigational strategies designed to improve remission duration following CAR T cell therapy



Cappell KM & Kochenderfer JM. *Nat Rev Clin Oncol* 2023

BTKi or CPI in combination with CD19 CAR T cells

Study	Study type	Disease	Target	Number of patients	Agent	ORR	CR	Adverse events
Ibrutinib								
Gauthier et al. [7]	Retrospective	CLL	CD19	17	Ibrutinib	83%	71%	CRS: 76% ≥grade 3: 0%
TRANSCEND CLL 004 [18]	Phase 1/2	CLL	CD19	23	Ibrutinib	82%	45%	CRS: 74% ≥grade 3: 6%
CTL119 UPENN study [40]	Pilot trial	CLL	CD19	19	Ibrutinib	93%	43%	CRS: 95% ≥grade 3: 16%
CPI								
JCAR014 [50]	Phase 1/2	Aggressive B-cell NHL	CD19	13	Durvalumab	50%	42%	CRS: 38% ≥grade 4: 1 Neurotoxicity: 8% >grade 3: 0%
ZUMA-6 [48]	Phase 1	DLBCL	CD19	12	Atezolizumab	90%	60%	CRS: ≥grade 3: 3 Neurotoxicity: ≥grade 3: 6
Chong EA et al. [49]	Phase 1/2	B-cell NHL	CD19	12	Pembrolizumab	27%	9%	CRS: ≥grade 3: 1

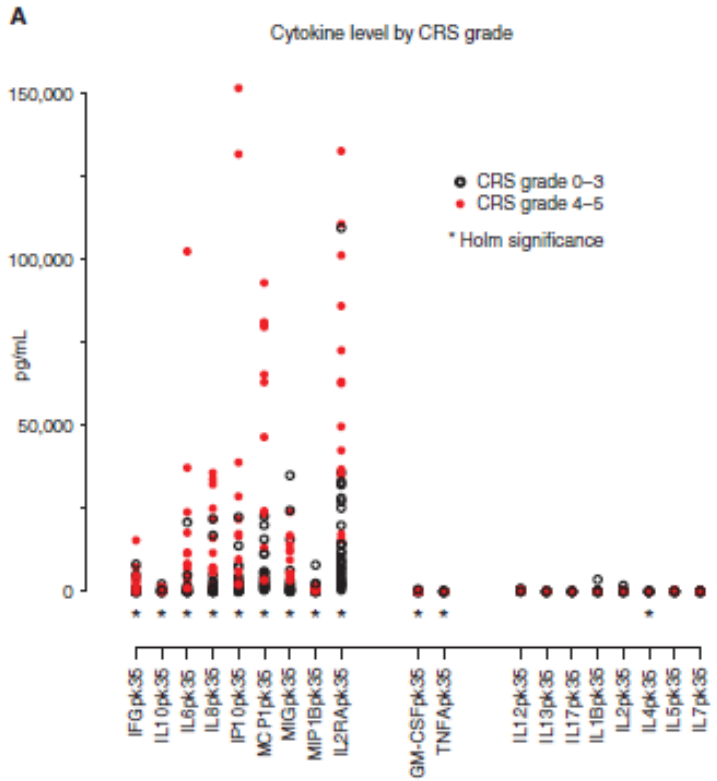
CRS cytokine release syndrome, *NHL* non-Hodgkin lymphoma, *DLBCL* diffuse large B-cell lymphoma, *ALL* acute lymphoblastic leukemia, *BTK* Bruton Tyrosine Kinase, *CLL* chronic lymphocytic leukemia, *CPI* immune checkpoint inhibitor.

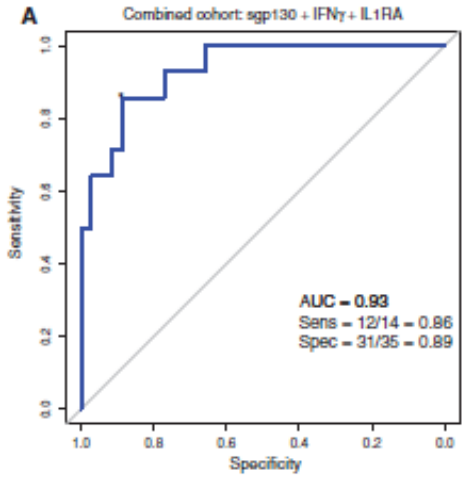
Inclusion not based on immune monitoring criteria…

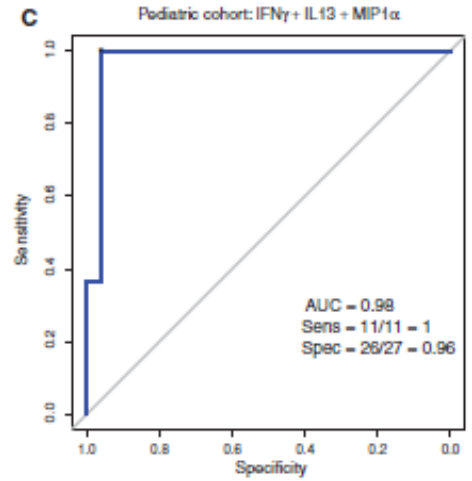
RESEARCH ARTICLE

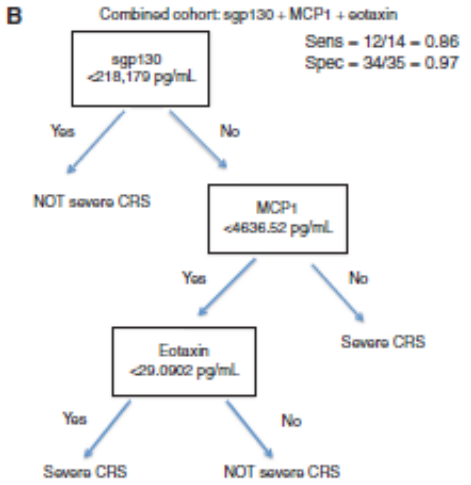
Identification of Predictive Biomarkers for Cytokine Release Syndrome after Chimeric Antigen Receptor T-cell Therapy for Acute Lymphoblastic Leukemia

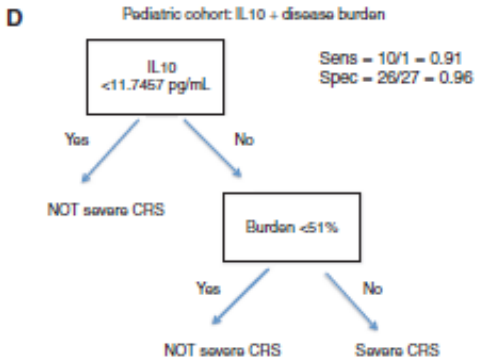
David T. Teachey[1,2,3], Simon F. Lacey[3,4,5], Pamela A. Shaw[6], J. Joseph Melenhorst[3,4,5], Shannon L. Maude[1,2,3], Noelle Frey[3,7,8], Edward Pequignot[3,4,5], Vanessa E. Gonzalez[3,4], Fang Chen[3,4,5], Jeffrey Finklestein[3,4,5], David M. Barrett[1,2,3], Scott L. Weiss[9], Julie C. Fitzgerald[9], Robert A. Berg[9], Richard Aplenc[1,2,3], Colleen Callahan[1], Susan R. Rheingold[1,2,3], Zhaohui Zheng[3,4,5], Stefan Rose-John[10], Jason C. White[11], Farzana Nazimuddin[3,4,5], Gerald Wertheim[3,4], Bruce L. Levine[3,4,5], Carl H. June[3,4,5], David L. Porter[3,7,8], and Stephan A. Grupp[1,2,3,4]

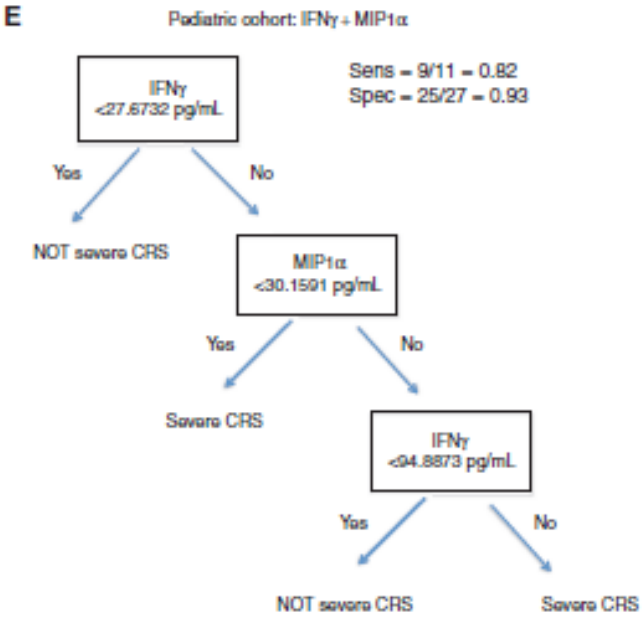












Teachey DT, et al. *Cancer Discov* 2016

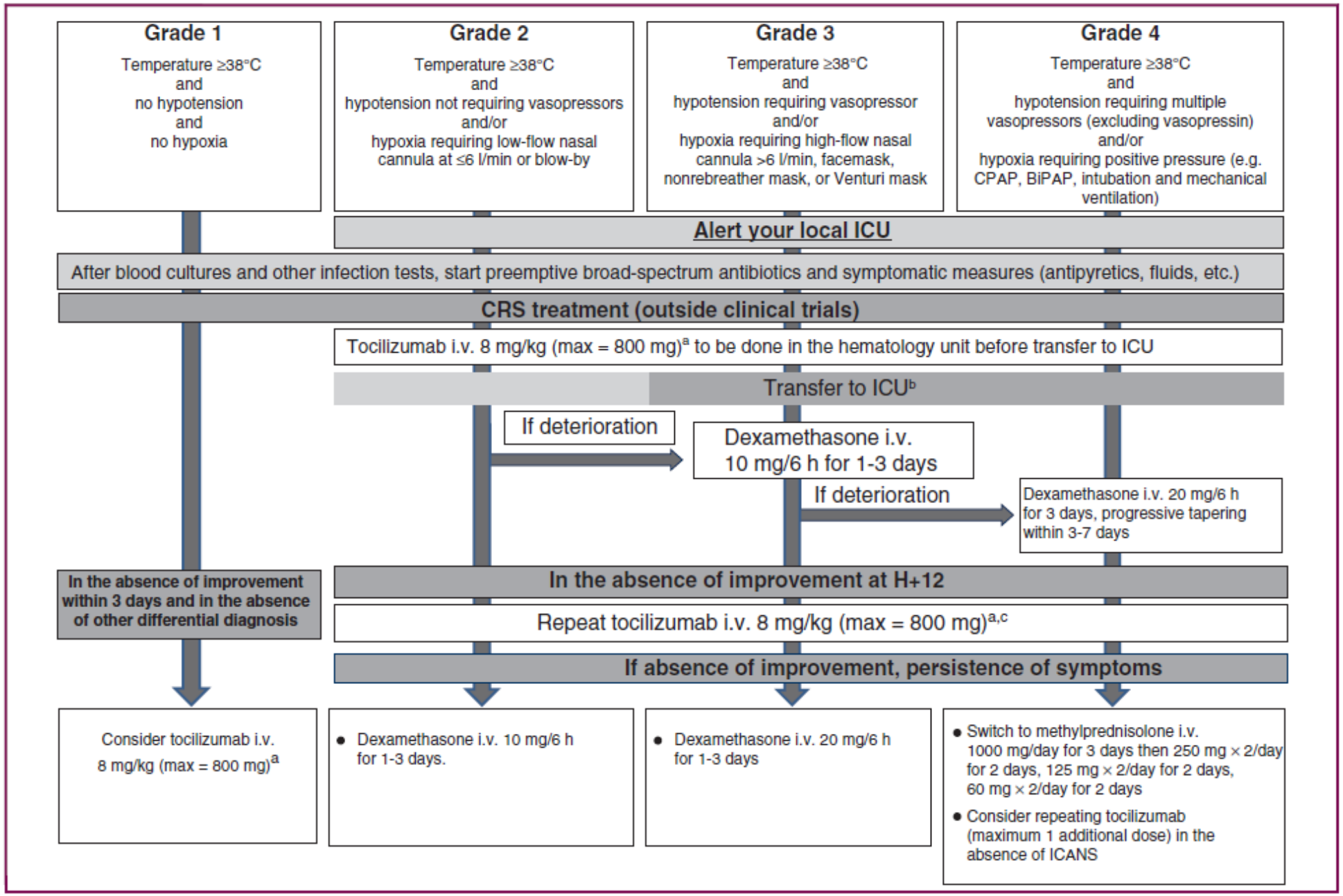
Grading and management of cytokine release syndrome (CRS)

Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)

P. J. Hayden[1], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

Hayden PJ, et al. *Ann Oncol* 2022

Risk factors for high-grade CRS:
- high tumor burden
- infection/comorbidities
- intense lymhphodepletion
- CD28-CAR-T products
- low platelet count
- acute leukemia



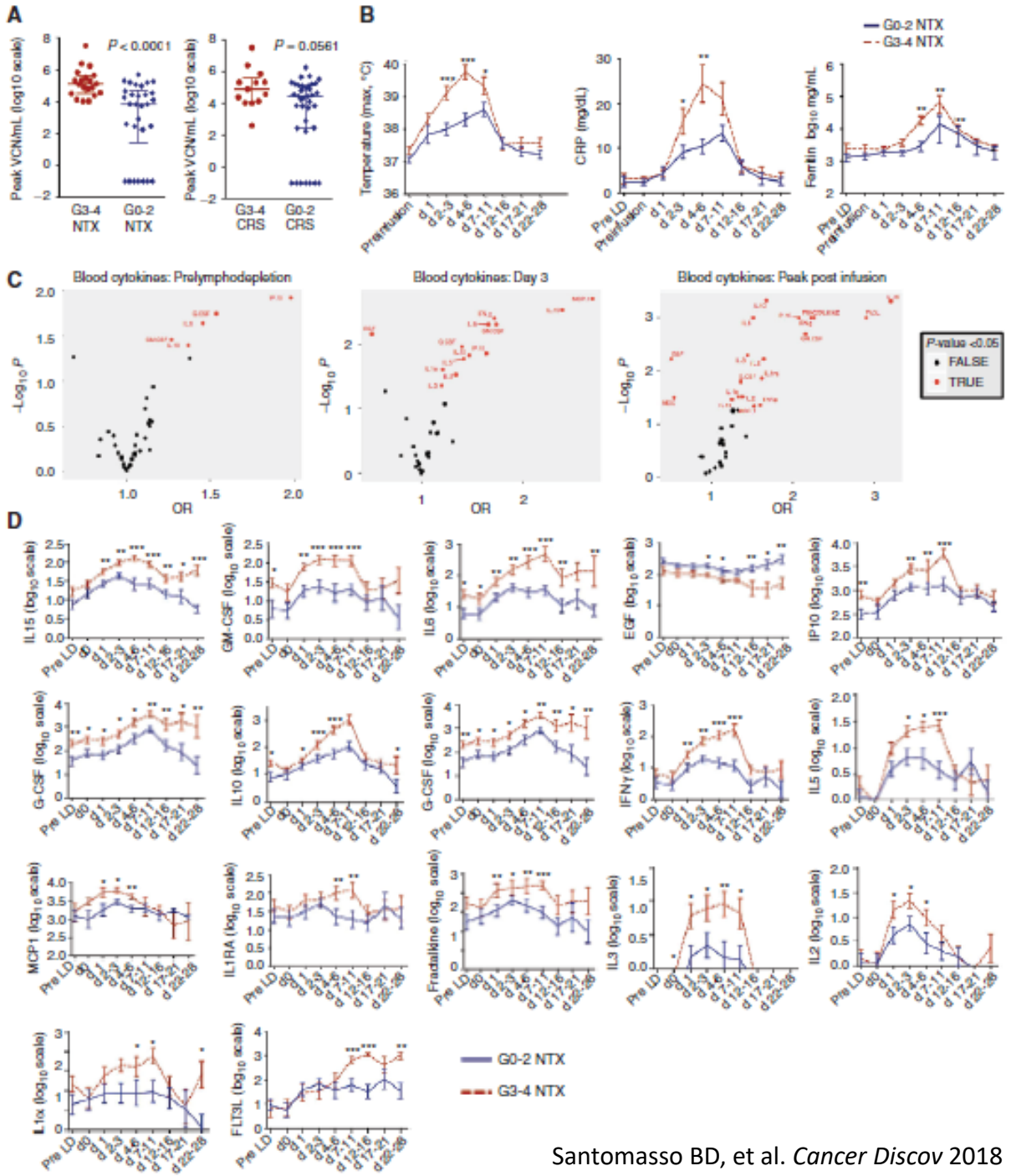
Clinical and Biological Correlates of Neurotoxicity Associated with CAR T-cell Therapy in Patients with B-cell Acute Lymphoblastic Leukemia

Bianca D. Santomasso[1,2], Jae H. Park[3,4,5,6], Darin Salloum[7], Isabelle Riviere[6,8], Jessica Flynn[9], Elena Mead[10], Elizabeth Halton[5,11], Xiuyan Wang[6,8], Brigitte Senechal[6,8], Terence Purdon[5], Justin R. Cross[12], Hui Liu[12], Behroze Vachha[13], Xi Chen[1], Lisa M. DeAngelis[1], Daniel Li[14], Yvette Bernal[5], Mithat Gonen[9], Hans-Guido Wendel[7], Michel Sadelain[5,6], and Renier J. Brentjens[3,4,5,6]

ABSTRACT

CD19-specific chimeric antigen receptor (CAR) T-cell therapy is highly effective against relapsed or refractory acute lymphoblastic leukemia (ALL), but is hindered by neurotoxicity. In 53 adult patients with ALL, we found a significant association of severe neurotoxicity with high pretreatment disease burden, higher peak CAR T-cell expansion, and early and higher elevations of proinflammatory cytokines in blood. Patients with severe neurotoxicity had evidence of blood–cerebrospinal fluid (CSF) barrier disruption correlating with neurotoxicity grade without association with CSF white blood cell count or CAR T-cell quantity in CSF. Proinflammatory cytokines were enriched in CSF during severe neurotoxicity with disproportionately high levels of IL6, IL8, MCP1, and IP10, suggesting central nervous system–specific production. Seizures, seizure-like activity, myoclonus, and neuroimaging characteristics suggested excitatory neurotoxicity, and we found elevated levels of endogenous excitatory agonists in CSF during neurotoxicity.

SIGNIFICANCE: We detail the neurologic symptoms and blood, CSF, and neuroimaging correlates of neurotoxicity associated with CD19 CAR T cells and identify neurotoxicity risk factors. Our findings implicate cellular components other than T cells and suggest novel links between systemic inflammation and characteristic neurotoxicity symptoms. *Cancer Discov; 8(8); 958–71. ©2018 AACR.*



Santomasso BD, et al. *Cancer Discov* 2018

Grading and management of immune effector cell-associated neurotoxicity syndrome (ICANS)

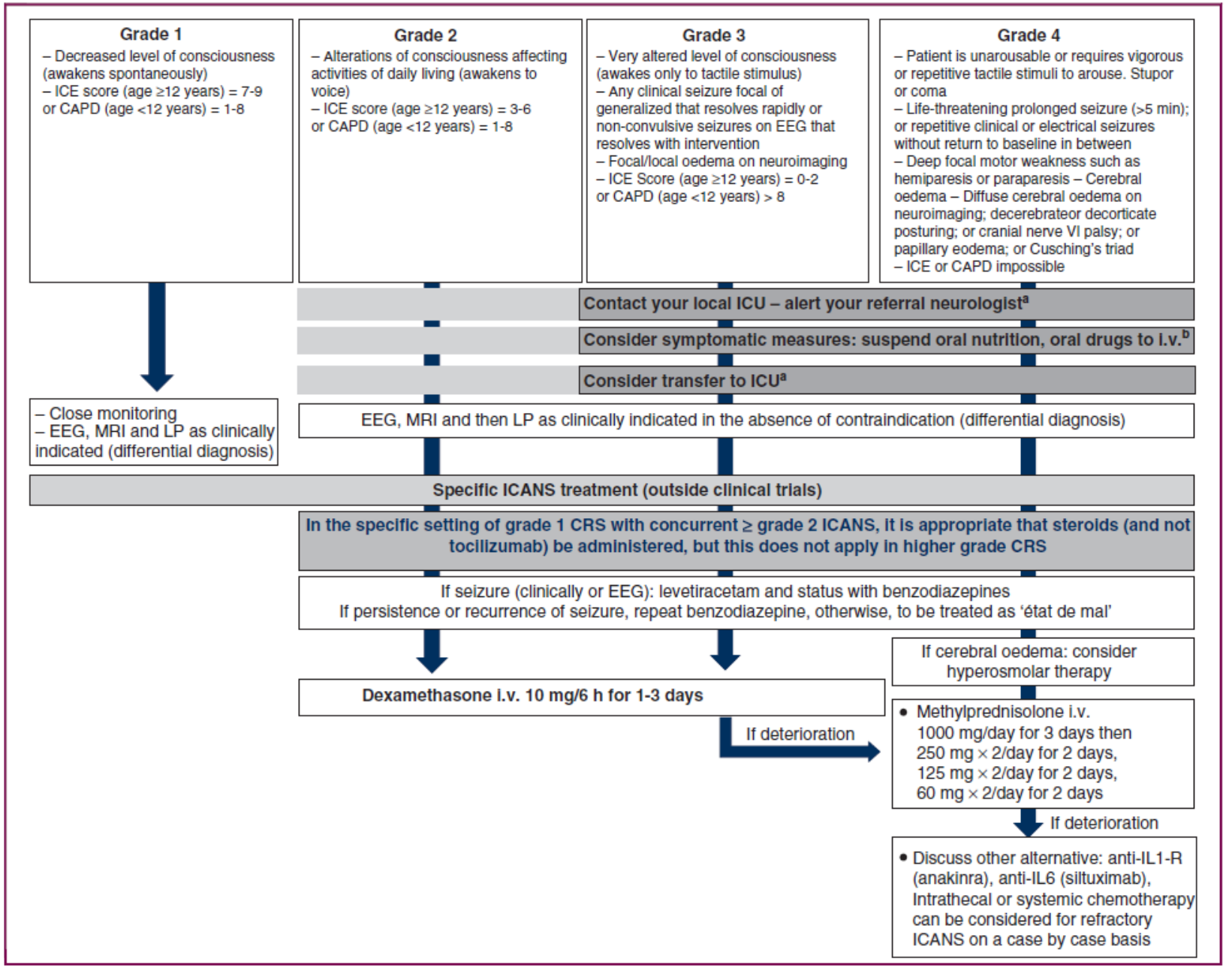
Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA)

P. J. Hayden[1†], C. Roddie[2,3*†], P. Bader[4], G. W. Basak[5], H. Bonig[6], C. Bonini[7], C. Chabannon[8], F. Ciceri[9], S. Corbacioglu[10], R. Ellard[11], F. Sanchez-Guijo[12], U. Jäger[13], M. Hildebrandt[14], M. Hudecek[15], M. J. Kersten[16], U. Köhl[17,18], J. Kuball[19], S. Mielke[20], M. Mohty[21], J. Murray[22], A. Nagler[23], J. Rees[3,24], C. Rioufol[25], R. Saccardi[26], J. A. Snowden[27], J. Styczynski[28], M. Subklewe[29], C. Thieblemont[30], M. Topp[15], Á. U. Ispizua[31], D. Chen[3,32], R. Vrhovac[33], J. G. Gribben[32], N. Kröger[34], H. Einsele[15] & I. Yakoub-Agha[35]

Hayden PJ, et al. *Ann Oncol* 2022

Risk factors for severe ICANS:

- high tumor burden
- aggressive disease
- CD28-CAR-T products
- higher CAR-T doses
- pre-existing neurological conditions
- low platelet count
- early severe CRS.



Variability in CAR T-cell detection methods and the frequency/intervals of testing

CAR T-cell detection scoping review: an essential biomarker in critical need of standardization

David P Turicek ,[1] Victoria M Giordani,[1,2] Josquin Moraly,[1,3] Naomi Taylor ,[4,5] Nirali N Shah [6]

ABSTRACT

The expansion and persistence of chimeric antigen receptor (CAR) T-cells in patients are associated with response, toxicity, and long-term efficacy. As such, the tools used to detect CAR T-cells following infusion are fundamental for optimizing this therapeutic approach. Nevertheless, despite the critical value of this essential biomarker, there is significant variability in CAR T-cell detection methods as well as the frequency and intervals of testing. Furthermore, heterogeneity in the reporting of quantitative data adds layers of complexity that limit intertrial and interconstruct comparisons. We sought to assess the heterogeneity of CAR T-cell expansion and persistence data in a scoping review using the PRISMA-ScR checklist. Focusing on 21 clinical trials from the USA, featuring a Food and Drug Administration-approved CAR T-cell construct or one of its predecessors, 105 manuscripts were screened and 60 were selected for analysis, based on the inclusion of CAR T-cell expansion and persistence data. Across the array of CAR T-cell constructs, flow cytometry and quantitative PCR were identified as the two primary techniques for detecting CAR T-cells. However, despite apparent uniformity in detection techniques, the specific methods used were highly variable. Detection time points and the number of evaluated time points also ranged markedly and quantitative data were often not reported. To evaluate whether subsequent manuscripts from a trial resolved these issues, we analyzed all subsequent manuscripts reporting on the 21 clinical trials, recording all expansion and persistence data. While additional detection techniques–including droplet digital PCR, NanoString, and single-cell RNA sequencing–were reported in follow-up publications, inconsistencies with respect to detection time points and frequency remained, with a significant amount of quantitative data still not readily available. Our findings highlight the critical need to establish universal standards for reporting on CAR T-cell detection, especially in early phase studies. The current reporting of non-interconvertible metrics and limited provision of quantitative data make cross-trial and cross-CAR T-cell construct comparisons extremely challenging. Establishing a standardized approach for collecting and reporting data is urgently needed and would represent a substantial advancement in the ability to improve outcomes for patients receiving CAR T-cell therapies.

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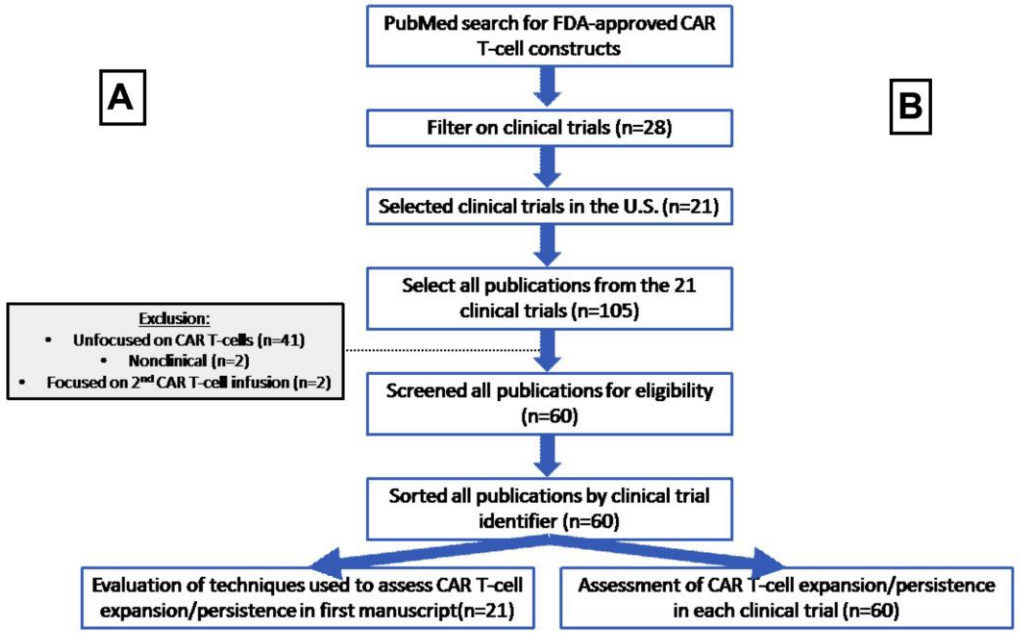

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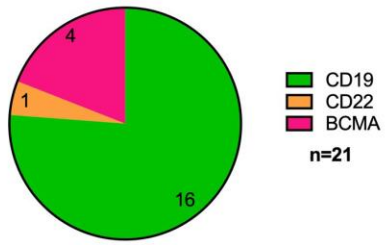

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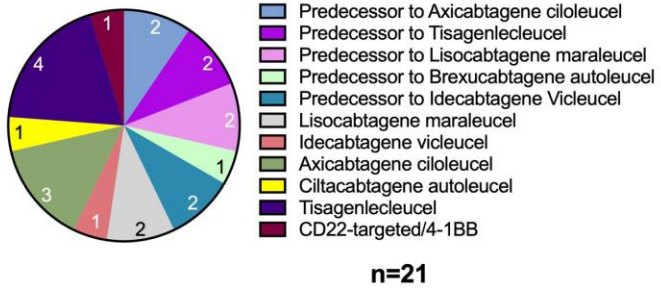

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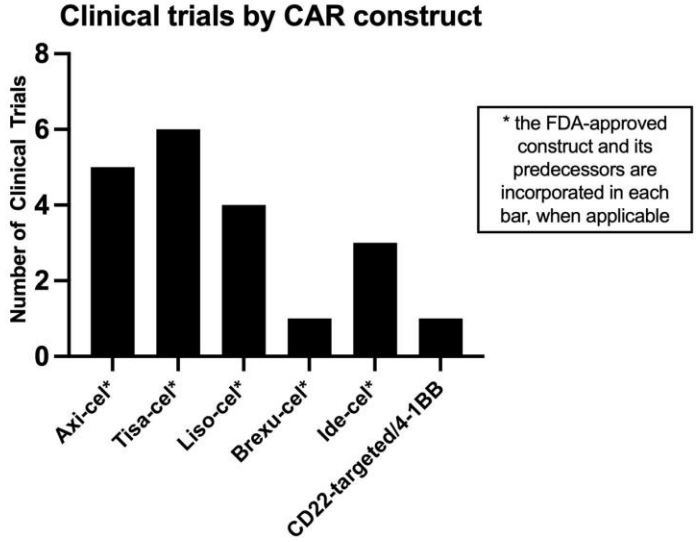

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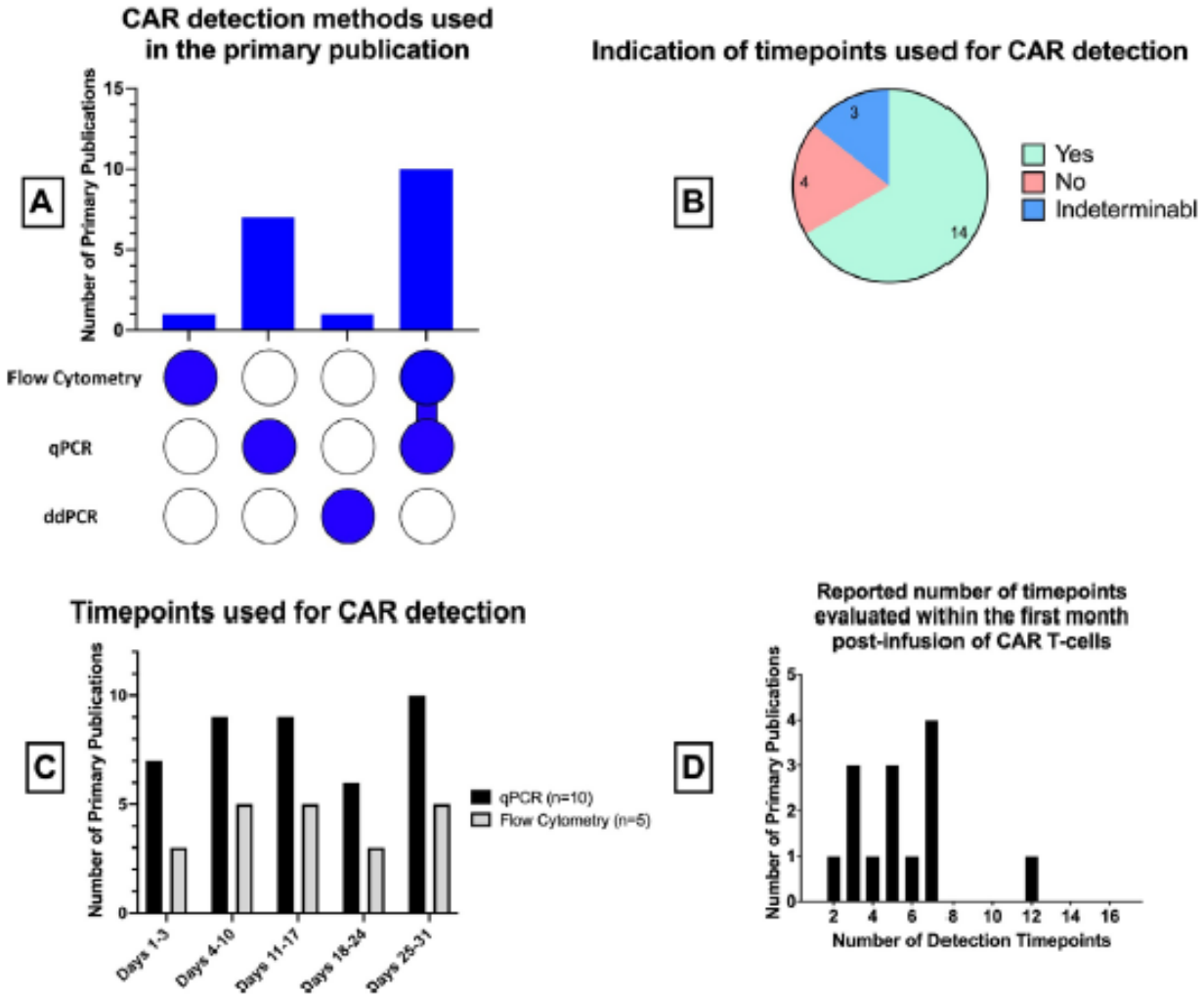

Box 1 Metrics and parameters used to represent CAR T-cell expansion and persistence in clinical trials

$AUC_{0-28\ days}$ (transgene copies/μg DNA×days).
$AUC_{0-28\ days}$ (transgene copies/μL PB×days).
$AUC_{0-63\ days}$ (cells/μL blood).
$AUC_{0-84\ days}$ (transgene copies/μg DNA×days).
$AUC_{0-84\ days}$ (transgene copies/μL PB×days).
$AUC_{28-90\ days}$ (log_{10}(transgene copies)/μg DNA).
C_{last} (transgene copies/μg DNA).
C_{last} (transgene copies/μL PB).
C_{max} (transgene copies/μg DNA).
C_{max} (transgene copies/μL PB).
t_{max} (days).
t_{last} (days).
$t_{1/2}$ (days).
Multilog expansion.
Peak factor change.
AUC fold change.
Peak % of T-cells expressing CAR.
Absolute CAR T-cells at day 28 (cells/μL blood).
Peak CAR T-cells circulating in blood (cells/μL).
$CD4^+$:$CD8^+$ CAR T-cell ratio ($AUC_{0-28\ days}$).
$CD4^+$:$CD8^+$ CAR T-cell ratio (fold change from infusion product to peak expansion).
CAR T-cell counts (log_{10} cells/μL of blood).
AUC, area under the curve; C_{last}, last detectable concentration of cell or transgene; C_{max}, peak level of transgene or cell; t_{max}, time to maximum cell or transgene number; $t_{1/2}$, the half-life associated with the disposition phase slopes of a semilogarithmic concentration-time curve (days) in peripheral blood; t_{last}, time to last quantifiable concentration following dosing).

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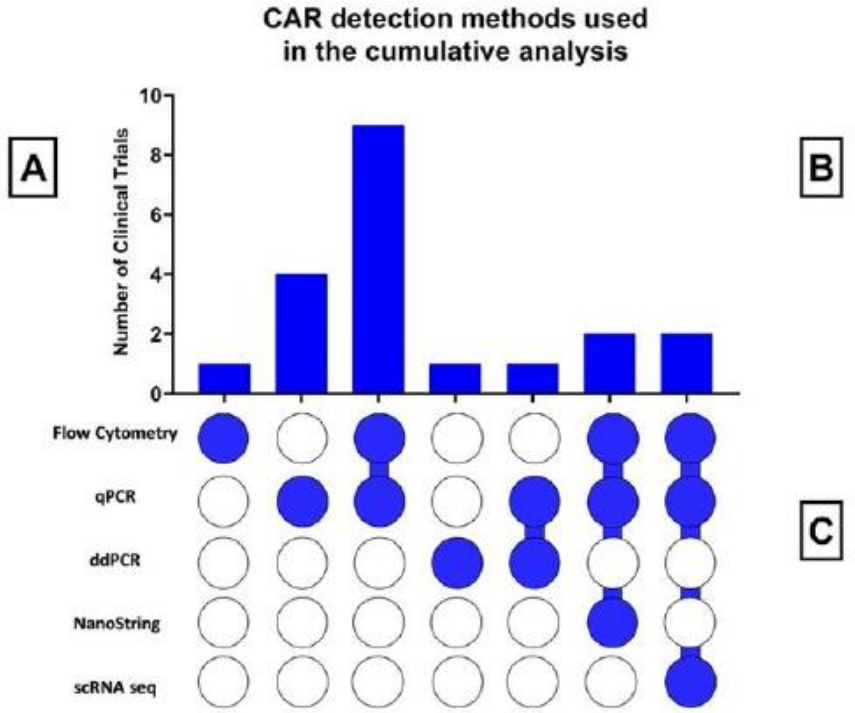
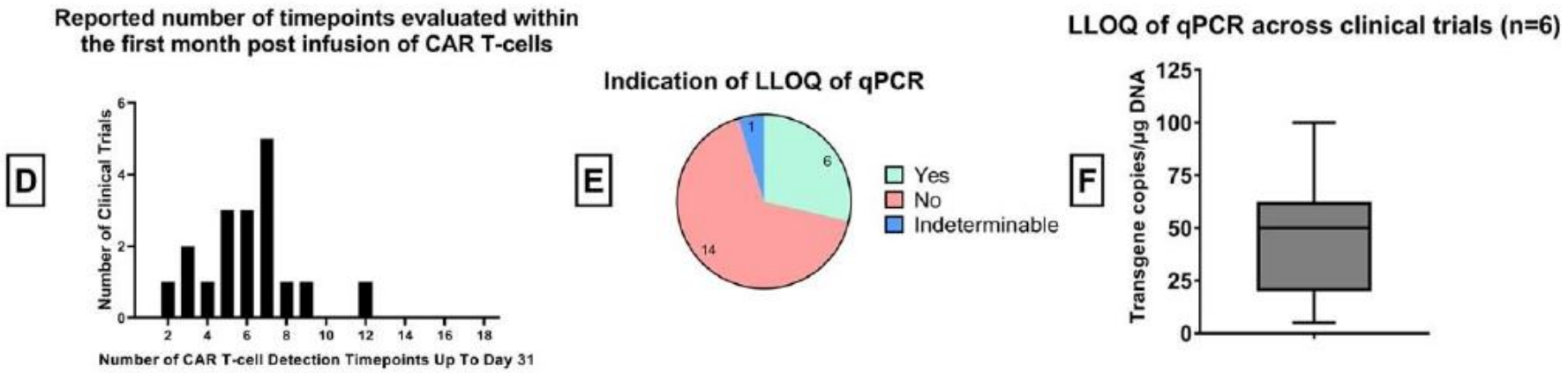
Data from all publications of a given clinical trial





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Il monitoraggio immunologico dopo la reinfusione della terapia cellulare CAR-T è utile nella gestione clinica del paziente?

LE RAGIONI DEL NO

- Nel contesto della leucemia linfoblastica acuta, i criteri che guidano la scelta di procedere o meno a consolidamento mediante allotrapianto sono principalmente indicatori clinici e/o di risposta al trattamento, con la sola eccezione della BCA. Il solo monitoraggio di BCA ed espansione/persistenza delle CAR-T non pone al riparo dal rischio di eventuali ricadute.
- Nel trattamento di linfomi/mielomi, eventuali interventi terapeutici addizionali post CAR-T sono decisi in base a risposta clinica/progressione di malattia. Il principale fattore associato a remissioni durature è la profondità della risposta iniziale, mentre la capacità del monitoraggio immunologico di predire la durata della risposta appare limitata e diversi studi mostrano risposte durature senza necessità di persistenza a lungo termine delle CAR-T (o della BCA).
- Per quanto sia stata chiaramente dimostrata un'associazione tra diversi marcatori immunologici e sviluppo di tossicità severe dopo CAR-T, i principali fattori di rischio per CRS e ICANS rimangono indicatori clinici e al momento né il monitoraggio dell'espansione delle CAR-T né l'analisi del profilo citochinico sono incorporati nei protocolli di gestione di queste due complicanze.
- Una larga parte degli approcci mirati all'ottimizzazione della performance delle CAR-T (miglior preparazione del paziente, rifinitura del costrutto e del manufacturing) è indipendente dal monitoraggio immunologico post-infusione.
- Metodiche di rilevazione, tipologia di parametro da valutare e timepoints non sono ancora standardizzati e possono variare considerevolmente a seconda di patologia e prodotto utilizzato. Il processo di armonizzazione è tutt'altro che semplice.
- L'implementazione di un programma di monitoraggio immunologico estensivo comporta indubbiamente costi aggiuntivi e può non essere estendibile in maniera uniforme a tutti i centri.

Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica, IRCCS Ospedale Pediatrico "Bambino Gesù"

Direttore: Prof. Franco Locatelli

TRAPIANTO EMOPOIETICO E TERAPIE CELLULARI

Marco Becilli
Emilia Boccieri
Roberto Carta
Francesca Del Bufalo
Federica Galaverna
Barbarella Lucarelli
Pietro Merli
Daria Pagliara
Rita Pinto
Francesco Quagliarella
Chiara Rosignoli

Bambino Gesù
OSPEDALE PEDIATRICO

MANIPOLAZIONE CELLULARE

Giusy Li Pira
Elia Girolami
Simone Biagini
Lucia Fresolone

CENTRO TRIAL ONCOEMATOLOGICO

Maria Pia Cefalo
Andrea Dell'Anna
Caterina Laurieri

AFERESI TERAPEUTICA

Giovanna Del Principe
Stefania Lazzaro
Giovanna Leone
Antonella Meschini