Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT

14.–17. Juni 2018

KML-Experten berichten vom EHA 2018 in Stockholm

Kompetenznetz Maligne Lymphome

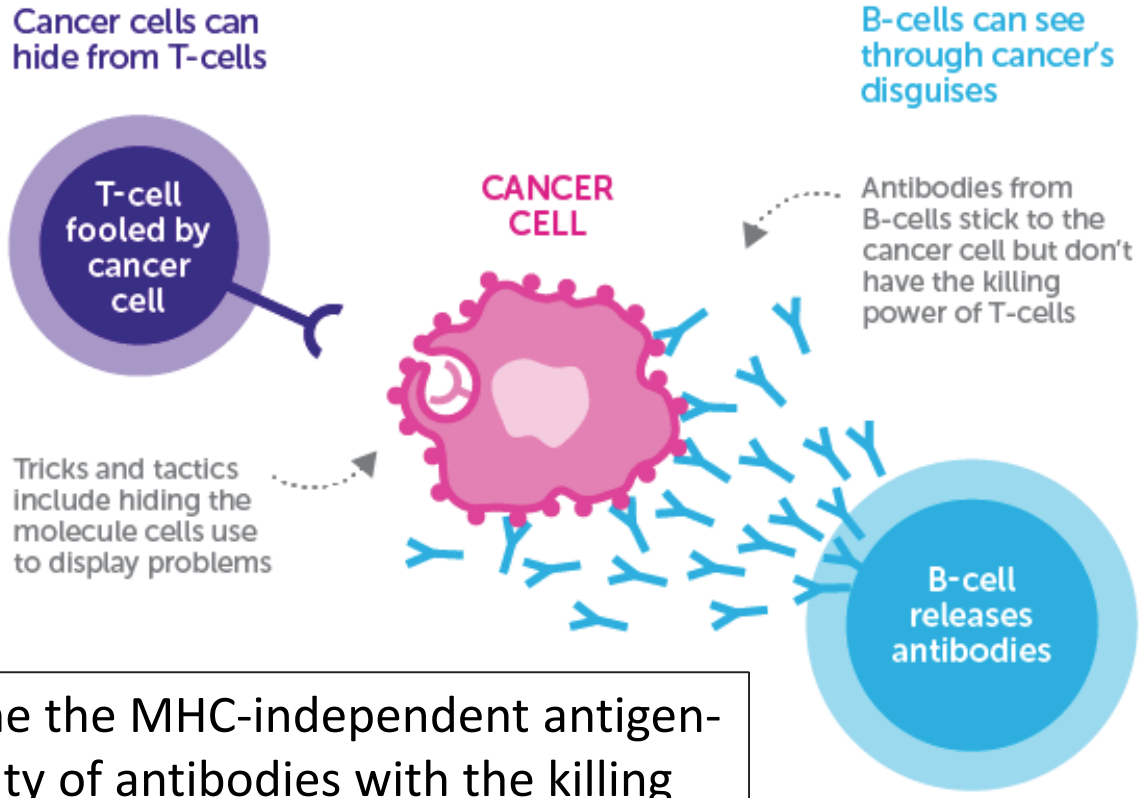
Lymphom Kompetenz KOMPAKT EHA Stockholm 14.–17. Juni 2018

Prof. Dr. med. Peter Borchmann

CAR-T-Zell-Therapien

Oberarzt der Klinik I für Innere Medizin der Uniklinik Köln |
Co-Chairman Deutsche Hodgkin Studiengruppe (GHSG) |
Mitglied Kompetenznetz Maligne Lymphome e.V.

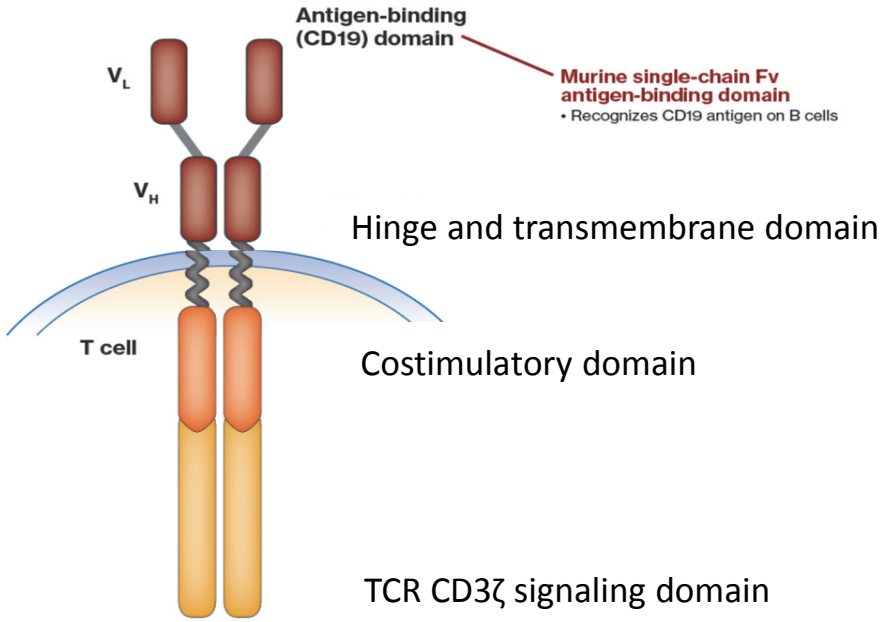
How can we use the adoptive immune system to fight cancer?



How can combine the MHC-independent antigen-binding capacity of antibodies with the killing power of T-cells?

Mears, scienceblog.cancerresearchuk.org, January 19, 2016

Chimeric Antigen Receptor (CAR): structure and function

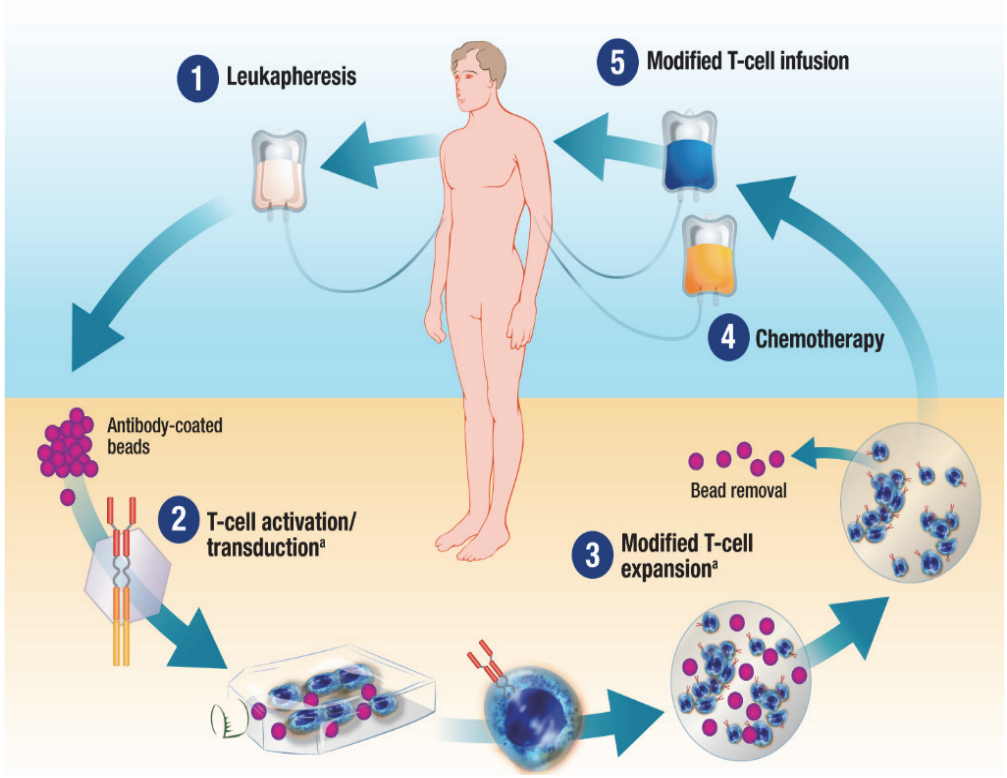


The heavy and light chains of the B cell receptor

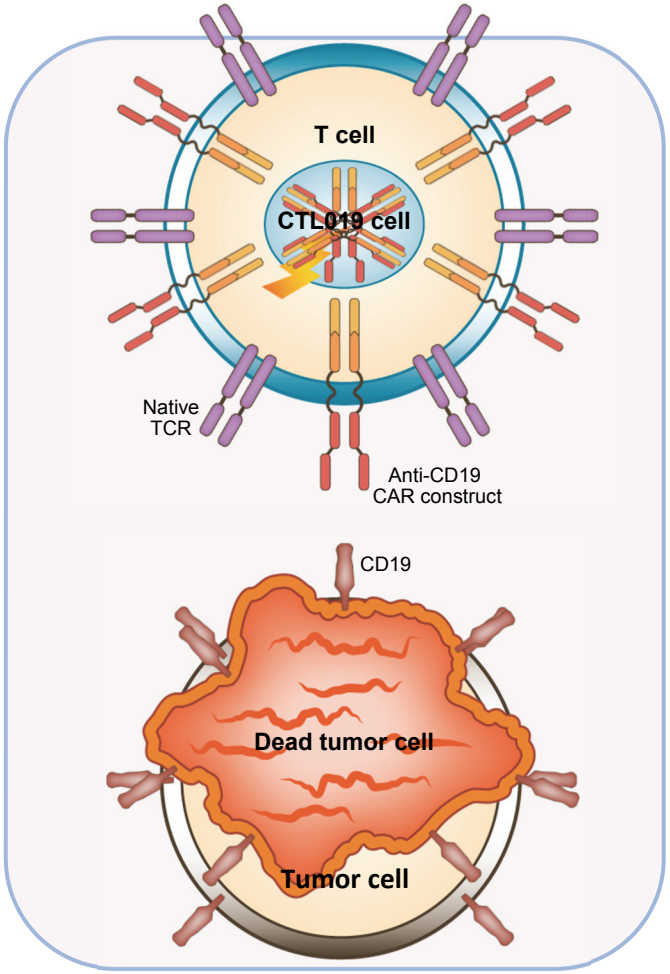
are fused to the T-cell-activating ζ chain of the TCR-associated CD3 complex to **generate non-MHC restricted, activating receptors** capable of redirecting T cell antigen recognition and cytotoxicity.

Figure modified based on 1. Milone MC, et al. *Mol Ther*. 2009;17:1453-1464. 2. Zhang H, et al. *J Immunol*. 2007;179:4910-4918 and 3. Kalos M, et al. *Sci Transl Med*. 2011;3:95ra73.

Implementation of CAR T-cell technology



Cellular reprogramming and *ex vivo* expansion are conducted at a cell processing facility.



1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

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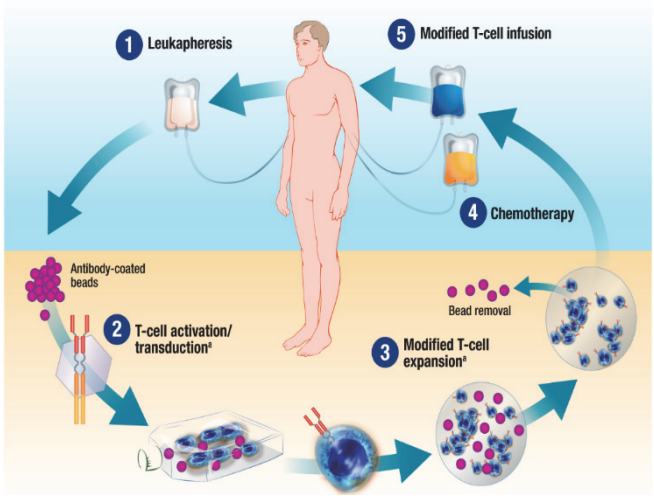

vein-to-vein is frozen-to-frozen

1. Milone MC, et al. *Mol Ther.* 2009;17:1453-1464; 2. Hollyman D, et al. *J Immunother.* 2009;32:169-180; 3. Kalos M, et al. *Sci Transl Med.* 2011;3:95ra73.

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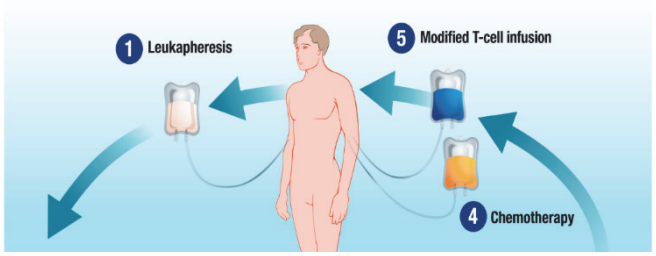
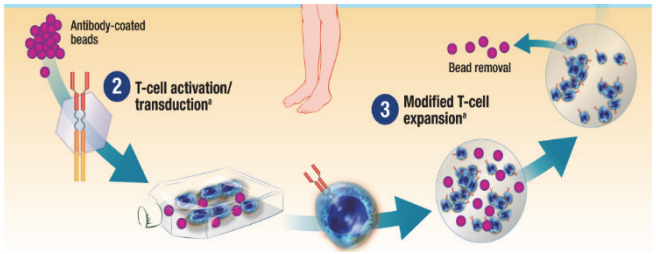


Patient in Sweden

Facility in North-America



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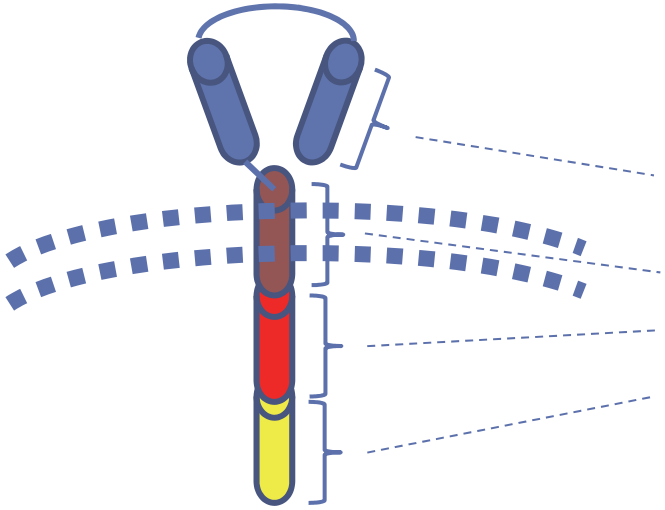
Industry-sponsored constructs

1. KTE-C19, CD19, FMC63-**CD28**-CD3z, Axicabtagene Ciloleucel, **approved 10/17 for r/r aggressive NHL diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.**

2. CTL019, CD19, FMC63-**41BB**-CD3z, Tisagenlecleucel, approved 08/17 for childhood ALL, **approved 4/18 for r/r DLBCL, DLBCL transformed from FL, and high grade B-cell lymphoma**

3. JCAR017, CD19, FMC63-**41BB**-CD3z, Lisocabtagene maraleucel

CD19 CAR T-Cell Constructs for DLBCL



domain	KTE-C19	CTL019	JCAR017
anti-CD19-antibody single chain variable fragment	FMC63	FMC63	FMC63
transmembrane	CD28	CD8	CD28
co-stimulatory	CD28	4-1BB	4-1BB
TCR signaling	CD3ζ	CD3ζ	CD3ζ

(S799) An Updated Analysis of JULIET, a Global Pivotal Phase 2 Trial of Tisagenlecleucel in Adult Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Presenter: Peter Borchmann, *Cologne, Germany*

Autor(s): Peter Borchmann, Constantine S. Tam, Ulrich Jäger, Joseph P. McGuirk, Harald Holte, Edmund K. Waller, Samantha M. Jaglowski, Michael R. Bishop, Charalambos Andreadis, Stephen Ronan Foley, Jason R. Westin, Isabelle Fleury, P. Joy Ho, Stephan Mielke, Gilles Salles, Richard T. Maziarz, Özlem Anak, Lida Bubuteishvili Pacaud, Christopher del Corral, Rakesh Awasthi, Sergei Agoulnik, Feng Tai, Stephen J. Schuster

On behalf of the JULIET study investigators

JULIET: Adverse Events of Special Interest

	Patients (N = 111)		
AESI[a]	All Grades, %	Grade 3, %	Grade 4, %
Cytokine release syndrome[b]	58	14	8
Neurological events	21	7	5
Prolonged cytopenia[c]	44	16	16
Infections	34	18	2
Febrile neutropenia	15	13	2

[a] Occurring within 8 weeks of tisagenlecleucel infusion. [b] Cytokine release syndrome was graded using the Penn scale. [c] At day 28.

No deaths due to tisagenlecleucel, CRS or cerebral edema

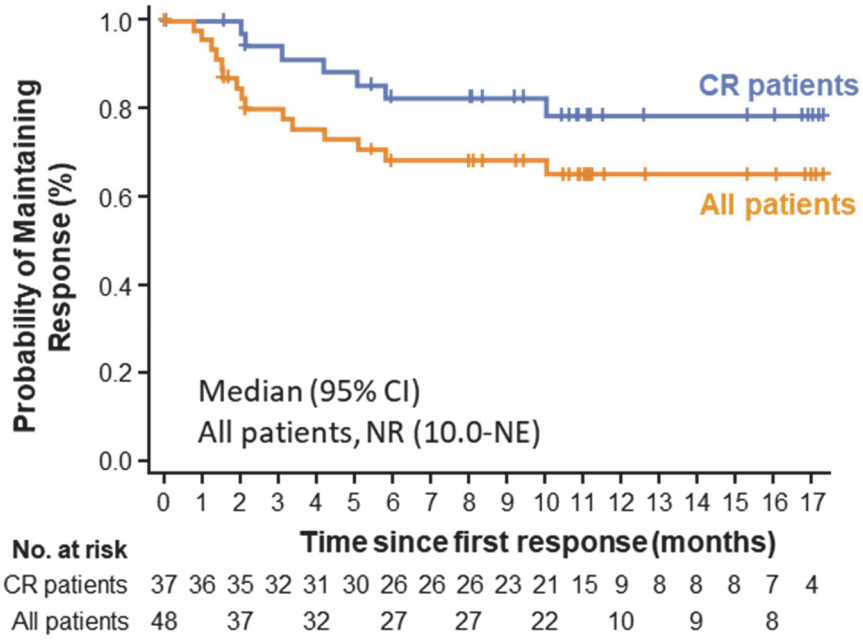
The most common neurological events were

- Confusional state (8% any grade; 2% grade 3)
- Encephalopathy (6% any grade; 1% grade 3 and 4% grade 4)

AESI, adverse events of special interest; CRS, cytokine release syndrome.

JULIET: At 14 Months Median Follow-up, Median DOR Not Reached

ORR, 52% (95% CI, 41%-62%); 40% CR, 12% PR[a]



- **Median DOR has not been reached**
- **12-mo relapse-free survival rate**
  - **78.5% (95% CI, 60%-89%) among CR patients**
  - 65% (95% CI, 49%-78%) among all responders
- **54% (13/24) of patients converted from PR to CR**, including 2 patients 9-12 mo after initial response
- Tisagenlecleucel transgene was detected in peripheral blood for up to 2 years in responding patients
- No patients proceeded to transplant while in response

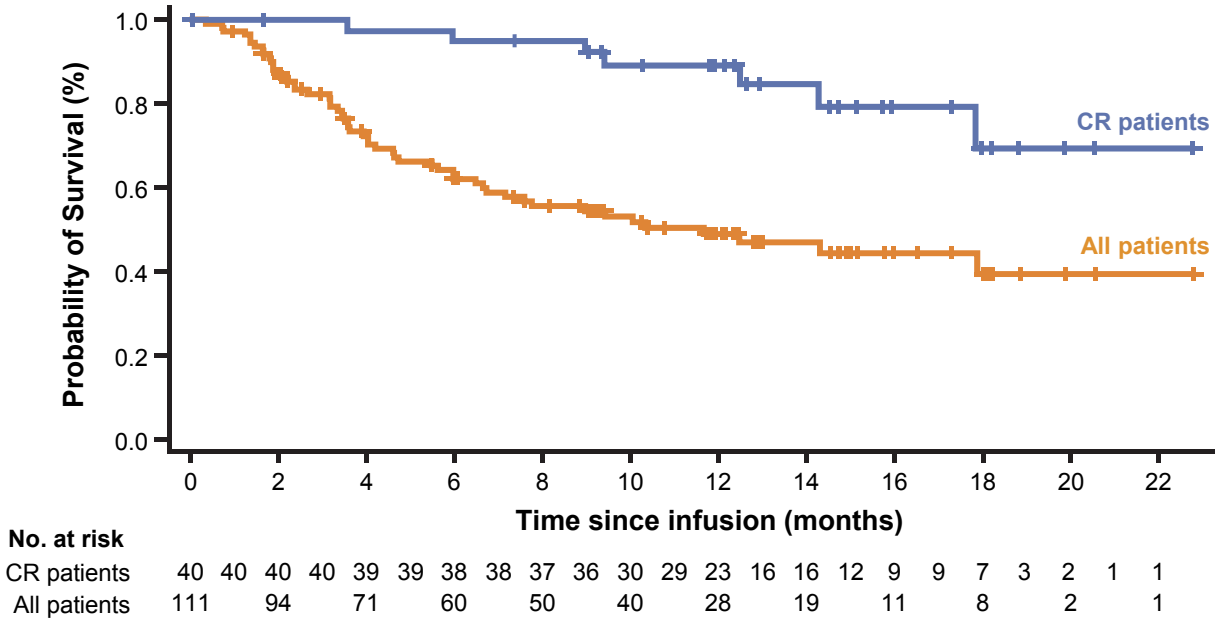
[a] Best ORR within 3 months of infusion.

CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, overall response rate; PR, partial response; SCT, stem cell transplant.

JULIET: ORR Consistent Across Subgroups

	Null hypothesis of ORR ≤ 20%	ORR n/N (%)	[95% CI]
All patients		48/93 (52)	[41-62]
Age			
<65 years		35/71 (49)	[37-61]
≥65 years		13/22 (59)	[36-79]
Sex			
Female		19/33 (58)	[39-74.5]
Male		29/60 (48)	[35-62]
Prior response status			
Refractory to last line		19/48 (40)	[26-55]
Relapsed to last line		29/45 (64)	[49-78]
IPI at enrollment			
<2 risk factors		14/25 (56)	[35-76]
≥2 risk factors		34/68 (50)	[38-62]
Prior antineoplastic therapy			
≤2 lines		26/49 (53)	[38-67.5]
>2 lines		22/44 (50)	[35-65]
Molecular subtype			
Activated B-cell		21/40 (52)	[36-69]
Germinal cell		24/50 (48)	[34-63]
Prior HSCT therapy			
No		26/52 (50)	[36-64]
Yes		22/41 (54)	[37-69]
Rearranged *MYC/BCL2/BCL6*			
Double/Triple hits		8/16 (50)	[25-75]
Other	0 10 20 30 40 50 60 70 80 90 100	40/77 (52)	[40-63.5]

JULIET: Median Overall Survival Was Not Reached for CR Patients



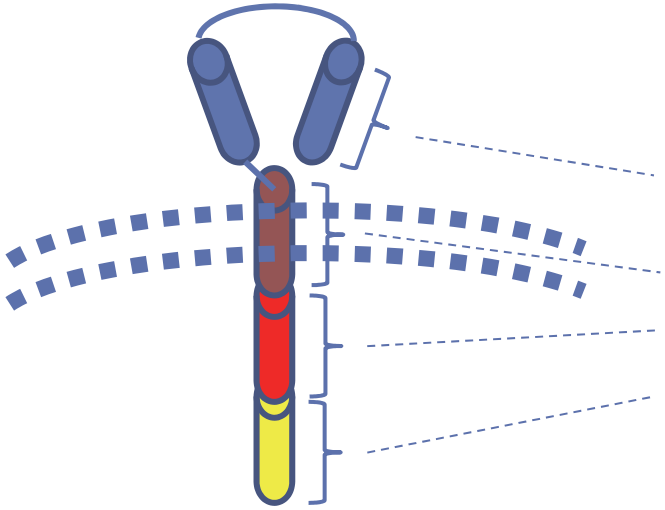
Median, mo (95% CI)
CR patients, NE (17.9-NE)
All patients, 11.7 (6.6-NE)

Overall survival at 12 mo

- **49% among all infused patients**
- **95% among CR patients**

CR, complete response; NE, not evaluable.

CD19 CAR T-Cell Constructs for DLBCL



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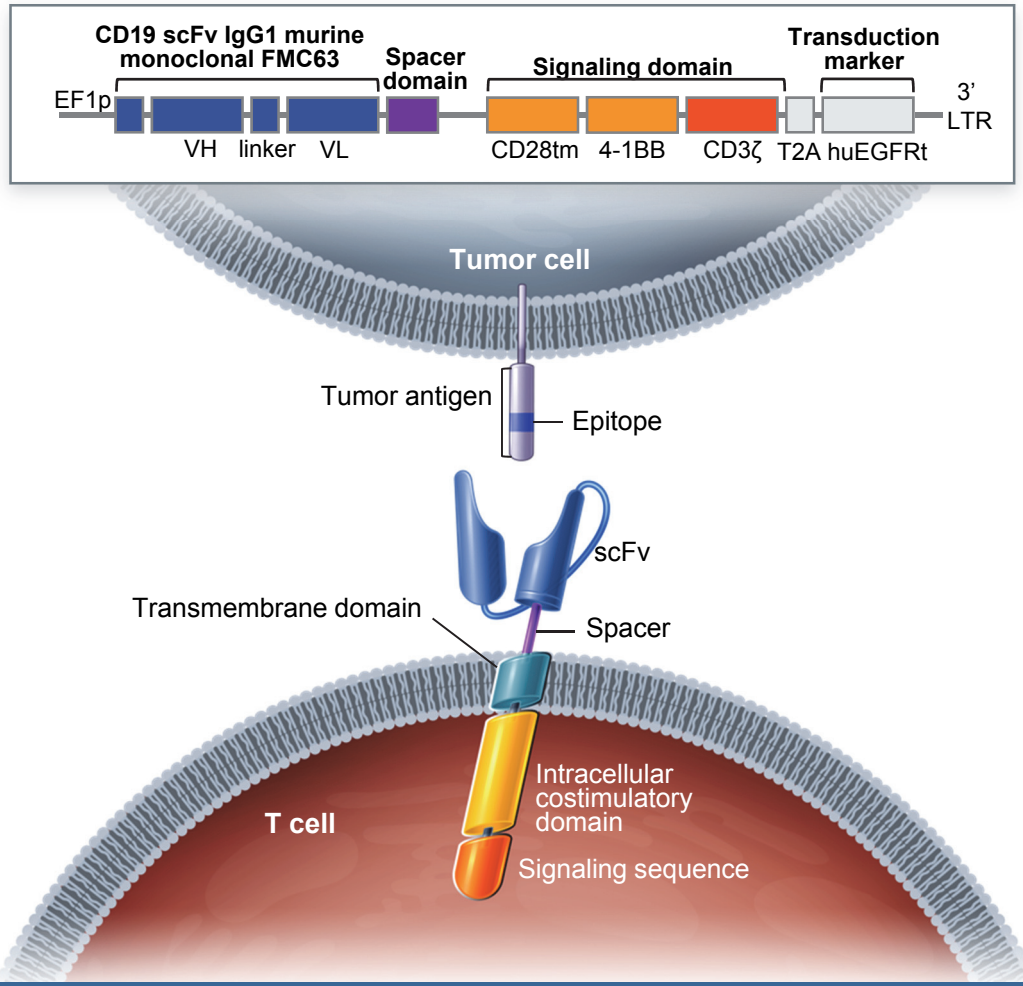
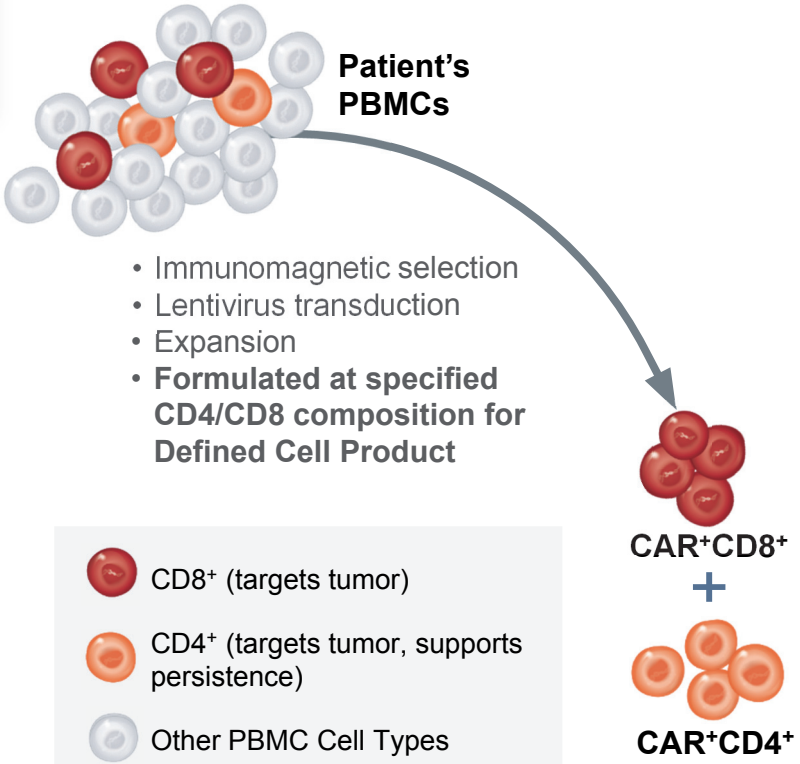
JCAR017: CD19-Targeted Defined Cell Product





(S800) UPDATED SAFETY & LONG TERM CLINICAL OUTCOMES IN TRANSCEND NHL 001, PIVOTAL TRIAL OF LISOCABTAGENE MARALEUCEL (JCAR017) IN R/R AGGRESSIVE NHL

Presenter: Jeremy Abramson et al., *Boston, USA*

Author(s): Jeremy Abramson, Leo Gordon, M. Lia Palomba, Matthew Lunning, Jon Arnason, Andres Forero-Torres, Michael Wang, David Maloney, Alison Sehgal, Charalambos Andreadis, Enkhtsetseg Purev, Scott Solomon, Nilanjan Ghosh, Tina Albertson, Benhuai Xie, Jacob Garcia, Tanya Siddiqi

(S800) Jeremy Abramson et al., Boston, United States

SAFETY

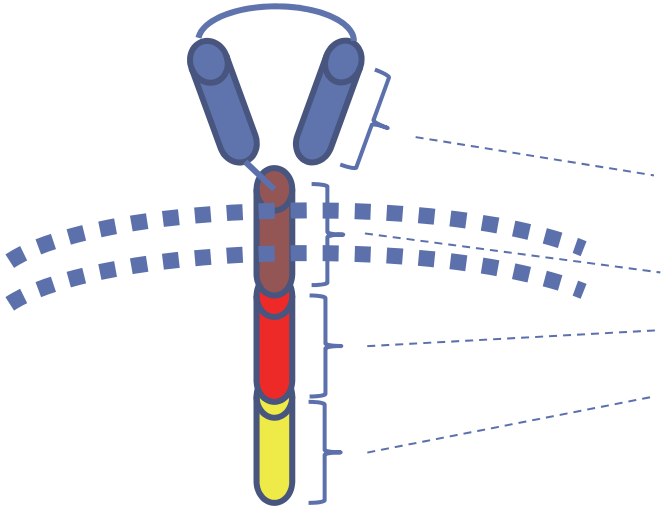
- 91 pts were treated and evaluable for safety
- CRS was seen in 35% of pts; a single pt (1%) developed grade 3-4 CRS.
- Neurotoxicity (NT) developed in 19% of pts including 12% grade 3-4; all but one event resolved at time of data snapshot.
- Nineteen pts (21%) received tocilizumab and/or dexamethasone.

(S800) Jeremy Abramson et al., Boston, United States

EFFICACY

- Best ORR in FULL (DLBCL, PMCBL, FL3B) and CORE (DLBCL) was 74% (65/88) and 80% (52/65), respectively;
- best CR was 52% (46/88) in FULL and 55% (36/65) in CORE. Durable response at DL2 was observed in the CORE population, with 6-month ORR and CR of 50% and 50% (7/14)

CD19 CAR T-Cell Constructs for DLBCL



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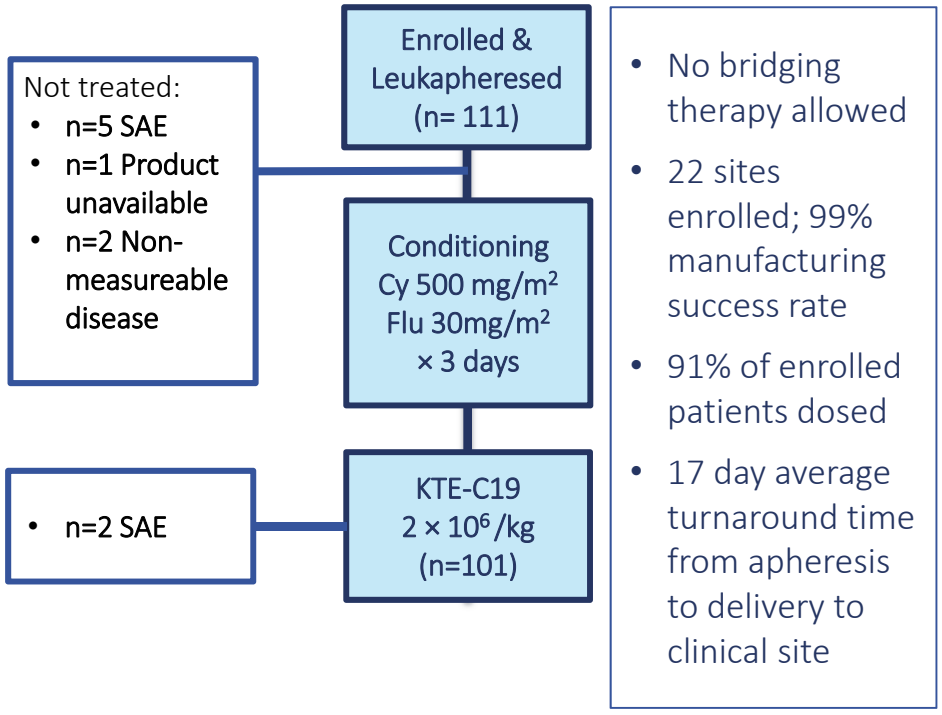
transmembrane	CD28	CD8	CD28
co-stimulatory	CD28	4-1BB	4-1BB
TCR signaling	CD3ζ	CD3ζ	CD3ζ

(S801) AXICABTAGENE CILOLEUCEL (AXI-CEL) IN PATIENTS WITH REFRACTORY LARGE B CELL LYMPHOMA: OUTCOMES BY PRIOR LINES OF THERAPY IN ZUMA-1

Presenter: Olalekan O. Oluwole, *Nashville, USA*

Author(s): Frederick L. Locke, Armin Ghobadi, Lazaros J. Lekakis, David B. Miklos, Caron A. Jacobson, Eric Jacobsen, Ira Braunschweig, Olalekan O. Oluwole, Tanya Siddiqi, Yi Lin, Patrick Reagan, Umar Farooq, Abhinav Deol, Adrian Bot, John M. Rossi, Yizhou Jiang, Allen Xue, William Y. Go, Sattva S. Neelapu

Summary on the approved compound Axicabtagene Ciloleucel in the ZUMA-1 Phase II trial



Characteristic	DLBCL (n=73)
Median age (range), years	59 (25-76)
Age ≥60 years, n (%)	36 (49)
Male, n (%)	47 (64)
ECOG performance status 1, n (%)	48 (66)
Median number of prior therapies (#)	3 (1-7)
IPI 3-4, n (%)	32 (44)
Disease stage III/IV, n (%)	64 (88)
Refractory subgroup, n (%)*	
Refractory to 2nd or later-line	56 (77)
Relapse post-ASCT	15 (21)

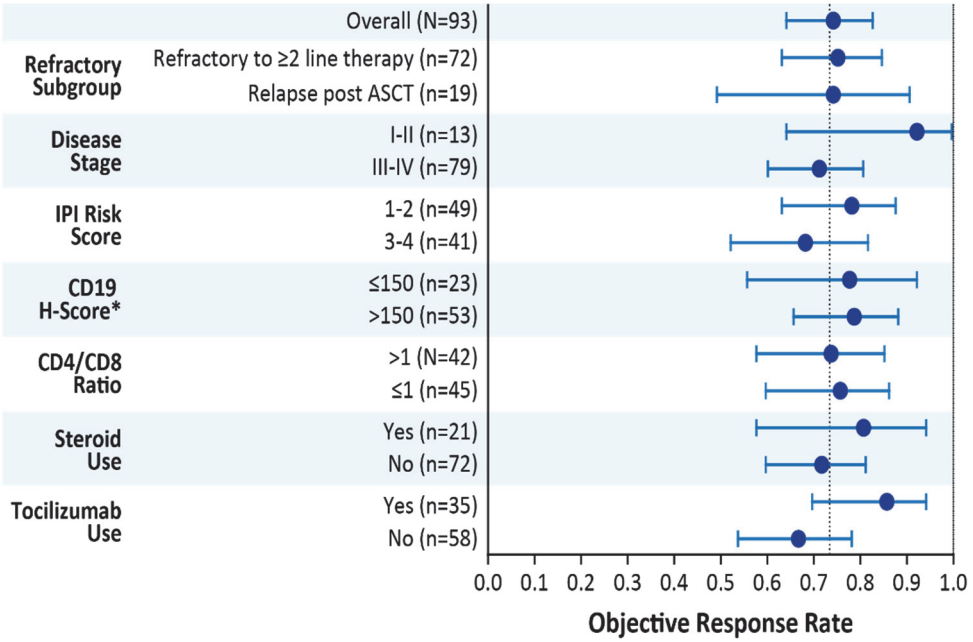
Neelapu et al., N Engl J Med 2017;377:2531-44.

Summary on the approved compound Axicabtagene Ciloleucel in the ZUMA-1 Phase II trial

Best Overall Response

Subgroup	n	ORR	CR
DLBCL	77	82%	38%
TFL / PMBCL	11	83%	71%
Total	101	82%	55%

Consistent Treatment Effect Across Key Covariates

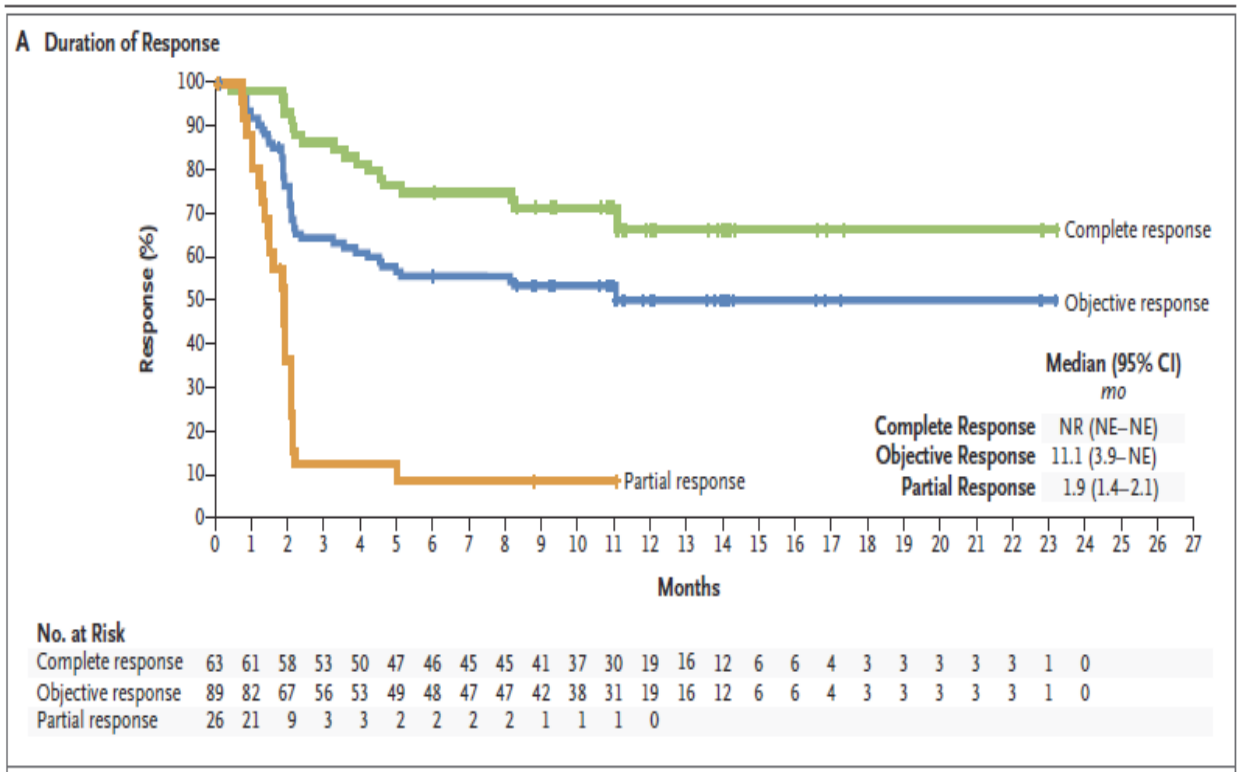


Neelapu et al., N Engl J Med 2017;377:2531-44.

Neelapu et al., LBA, ASH 2016

Summary on the approved compound Axicabtagene Ciloleucel in the ZUMA-1 Phase II trial: DOR and PFS

Duration of response



Neelapu et al., N Engl J Med 2017;377:2531-44.

Summary on the approved compound Axicabtagene Ciloleucel in the ZUMA-1 Phase II trial: DOR and PFS

	LoT	
Response, % (95% CI)	2 – 3 (n = 62)	≥ 4 (n = 43)
ORR	94 (84 – 98)	67 (51 – 81)
CR rate	65 (51 – 76)	53 (38 – 69)
Ongoing ORR	44 (31 – 57)	42 (27 – 58)
6-month PFS[a]	49 (36 – 61)	51 (35 – 65)
12-month OS[a]	65 (51 – 75)	51 (35 – 65)

[a]Kaplan-Meier estimate.

Zusammenfassung EHA 2018

- CAR T-Zell Therapie steht kurz vor der Zulassung in Europa und das Interesse an dieser neuen Therapie war auch auf diesem Meeting sehr groß
- Die drei konkurrierenden Produkte, die alle gegen CD19 gerichtet sind und von denen zwei bereits einen FDA Zulassung haben, wurden hier präsentiert.
- Alle zeigen vergleichbar hohe Ansprechraten, die unabhängig von bekannten Risikofaktoren sind.
- Die Toxizitätsprofile unterscheiden sich nicht grundsätzlich (CRS und NE), jedoch könnte sie quantitativ unterschiedlich sein (CAVE: indirekter Vergleich!)
- Insgesamt sind diese Daten unverändert, also auch mit längerem FU, sehr vielversprechend und die Entwicklung bleibt spannend!

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT EHA Stockholm 14.–17. Juni 2018

Die Kurzpräsentationen sind online unter

www.lymphome.de/eha2018

Für den Inhalt verantwortlich:

Prof. Dr. med. Peter Borchmann

Klinik I für Innere Medizin • Uniklinik Köln

Kompetenznetz Maligne Lymphome

Lymphom Kompetenz KOMPAKT EHA Stockholm 14.–17. Juni 2018

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